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Hemispheric asymmetry of spatial working memory deficit in schizophrenia

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Abstract

Spatial working memory function was assessed in schizophrenia patients, hypothetically 'psychosis-prone' individuals who report unusual perceptual experiences and normal control subjects with an oculomotor delayed response task. Past studies point to the important role of dorsolateral prefrontal system in spatial working memory deficits of schizophrenia patients. In order to better understand the processes precipitating in working memory deficit, two types of working memory errors were examined: *never-corrected* vs. *immediately-corrected* errors. In schizophrenia patients, the loss of spatial representation in working memory, as captured by the presence of never-corrected errors, was much more severe when the target was presented in the right visual hemifield than when the target was presented in the left visual field. The same pattern was observed in healthy, psychometrically ascertained 'psychosis-prone' subjects. Therefore, the observed asymmetry of spatial working memory deficit seems unlikely to be a mere side-effect of medication or hospitalization. Normal control subjects did not show hemispheric asymmetry in error patterns. These results suggest that the loss of spatial representation during a delay period may be more severe in the left hemisphere in patients with schizophrenia and in 'psychosis-prone' individuals.

Keywords: Schizophrenia; Schizotypy; Working memory; Hemispheric asymmetry; Frontal lobe; Oculomotor task

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1. Introduction

The role of dorsolateral prefrontal cortex in spatial working memory function has been studied extensively in animals using the delayed response paradigm (e.g. Jacobsen, 1935; Blum, 1952; Funahashi et al., 1989, 1990; Quintana and Fuster, 1992; Funahashi et al., 1993). Lesions in the prefrontal cortex also result in behaviors that resemble major clinical features of schizophrenia, such as increased distractibility, perseverations and anergia (e.g. see Goldman-Rakic, 1991). Based on neuroanatomical and neurophysiological data, Goldman-Rakic (1991) has proposed that one fundamental deficit of schizophrenia may be conceptualized as a dysfunction of working memory that leads to a disintegration of all behaviors guided by internal representations. In neuroanatomical studies of spatial working memory in the monkey, it is possible to map out the regions of 'mnemonic scotoma' resulting from focal lesions to the area 46 (Funahashi et al., 1993). Funahashi et al. observed that working memory loss is confined to the specific regions corresponding to the site of the lesion in area 46. Therefore, depending on the region of abnormality, the spatial working memory deficit may be precisely localized using the oculomotor delayed response paradigm.

Although occasional cases of initial misdiagnosis of patients with frontal lobe tumors as schizophrenic (e.g. Hall and Young, 1992) are suggestive of structural frontal lobe abnormalities in schizophrenia, it is unclear whether there are apparent, gross structural abnormalities of prefrontal cortex in patients with schizophrenia (see Wible et al., 1995). However, recent studies suggest that there may be a reduced frontal asymmetry (Falkai et al., 1995a) or small frontal volume reductions (Turetsky et al., 1995) in schizophrenia patients. These findings suggest that prefrontal deficits in schizophrenia may involve structurally subtle but functionally significant disturbances in prefrontal cortical cells and circuits (Benes et al., 1991; Breier et al., 1992; Selemon et al., 1995; Daviss and Lewis, 1995). For example, cell density is increased in the area 46 in schizophrenia patients (Daviss and Lewis, 1995; Lewis and Anderson, 1995; Selemon et al., 1995) but it is not known whether these relatively subtle structural abnormalities are lateralized to left or right prefrontal regions.

Behaviorally, patients with schizophrenia show consistent deficits in spatial working memory, regardless of the modality of the response (Park and Holzman, 1992; Spitzer, 1993; Keefe et al., 1995; Carter et al., 1996; McDowell and Clementz, 1996; Spindler et al., 1997). In contrast, bipolar patients show no impairments on the same delayed-response tasks (Park and Holzman, 1992, 1993). Spatial working memory deficit has also been observed in the first-degree relatives of schizophrenia patients (Park et al., 1995a) and in psychometrically ascertained schizotypic subjects (Park et al., 1995b; Park and McTigue, 1997), suggesting that working memory deficit may be a potential marker for schizophrenia.

Given that the delayed response task is deceptively simple, it is not clear why anybody, schizophrenic or not, would make an error on this task. Parsing the spatial delayed response task suggests that successful performance on the delayed response task depends on several hypothetical cognitive components (Park and O'Driscoll, 1996). These components include the ability to maintain the spatial representation of the target during the delay period, inhibition of irrelevant distractors at the response stage, and the initiation and execution of appropriate motor responses (e.g. a saccade or a hand movement). Failure to mediate or facilitate any of these hypothetical components may lead to an error in the delayed response task; not all errors are created equal.

In memory research, *how* an error is elicited and how the subject might attempt to correct a mistake, are rarely examined. We have argued elsewhere that the most informative data on abnormal processes leading to spatial working memory deficits may lie in the patterns of guessing response *after* an error has been made and that it is possible to make inferences about the pathological processes underlying the error response (Park and O'Driscoll, 1996). If the spatial representation was maintained during the delay period but the subject was temporarily disinhibited at the response stage, the subject should be able to make an immediate correction after the

incorrect response has been elicited. In other words, as long as the representation was maintained in working memory, even if an error is produced, it will be corrected if the subject is given a chance to do so. On the other hand, if the spatial representation was disrupted or lost during the delay period, it will be impossible to correct the error response (see Fig. 1).

Park and O'Driscoll (1996) examined spatial working memory errors to see if *subsequent* attempts to correct a mistake were successful. Normal control subjects and bipolar patients made very few errors, but if they did, they were able to correct their mistakes immediately. In addition, the majority of the initial error responses lay within the same quadrant as the correct target position. This pattern of immediate error-correction suggests that normal control subjects and bipolar patients were able to maintain spatial representation of the target during the delay period but they may have been temporarily disrupted at the response stage. Given a chance to correct themselves, they immediately chose the correct target position from memory. If subjects were not able to maintain spatial representation of the target during the delay and that is why they made an error, any subsequent attempts to correct errors would result in random guessing. Normal control subjects and bipolar patients made very few never-corrected errors. In contrast, schizophrenia patients made large numbers of both immediately-corrected and never-corrected errors. Thus, schizophrenia patients seemed to have deficits in the maintenance of representation during the delay, as well as in initiating correct responses at the response stage. The same pattern of deficit was observed in schizotypic subjects. In sum, it is important to bear in mind that what may differentiate schizophrenia patients from the bipolar and normal control subjects, apart from the sheer number of errors, is *how* these errors arise. All subjects are susceptible to making some errors due to distracting or disinhibitory processes at the response stage but only schizophrenia patients and a sub-group of schizotypic subjects seem to lose the spatial representation during the delay period.

In neuroanatomical studies of spatial working memory, 'mnemonic scotomas' and 'mnemonic hemianopoeias', corresponding to the site of the dorsolateral prefrontal lesion, have been described (see Funahashi et al., 1993). For example, a focal lesion in the right principal sulcus area led to the 'mnemonic scotoma' in a small corresponding region of the left visual field but not in any other areas of the visual field. The errors elicited after the focal lesion was made, were not confined to the immediate neighborhood of the correct target position. Instead, these errors tended to be scattered all over the visual field, suggesting the loss of spatial representation of the target. In other words, if the cells which support the maintenance of the internal representation during the delay period are destroyed by lesions, working

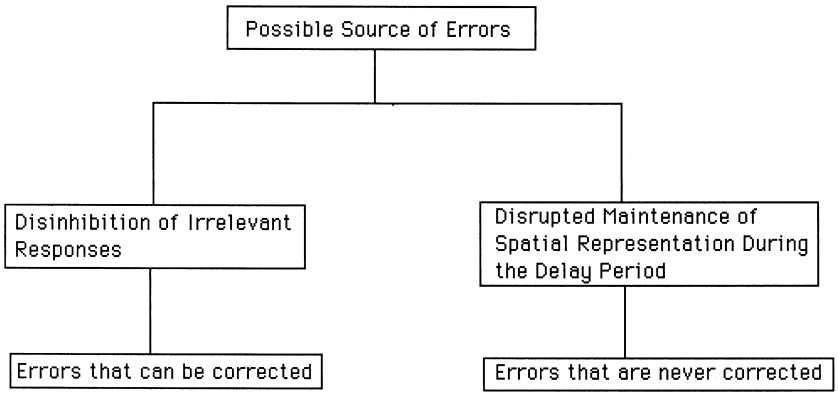

Fig. 1. Types of errors.

memory for a specific spatial region seems to be lost. In addition to the lesion data, Funahashi et al. (1989, 1990, 1993) also showed that incorrect responses on the oculomotor delayed response task were accompanied by an absence of cellular activity in the principal sulcus cells during the delay period. Therefore, any events that disrupt the maintenance of spatial representation during the delay period will result in errors that cannot be corrected. By examining the 'never-corrected' errors, it may be possible to specifically probe the left and right dorsolateral prefrontal functions. This strategy departs from the traditional neuropsychological method of administering tasks that are presumed to tap the left or right hemisphere functions to examine asymmetry (e.g. verbal vs. spatial tasks).

In previous studies of spatial working memory, we did not observe any hemispheric asymmetry in the overall accuracy scores or in reaction times (e.g. Park and Holzman, 1992) but we did not examine asymmetry *in relation to the types of errors*. In this study, immediately-corrected and never-corrected errors in left and right visual fields were examined in schizophrenia patients and normal control subjects. In addition, data from a previous study of psychometric schizotypes (Park et al., 1995b) were re-analyzed to see if there is a hemispheric differences in the incidence of never-corrected errors in individuals who may carry latent liability for schizophrenia.

2. Method

2.1. Subjects

2.1.1. Schizophrenia patients

Thirty-three patients with schizophrenia were recruited from a private psychiatric hospital. These subjects met the criteria for a DSM-III-R diagnosis of schizophrenia, as determined from the SCID (Spitzer and Williams, 1985). The mean age of the patients was 31.5 years (S.E. = 1.4) and they had been ill for an average of 13.2 years (S.E. = 1.5). The mean years of education was 14.7 (S.E. = 0.4) and the mean WAIS score was 110.7 (S.E. = 3.0). All subjects were receiving anti-psychotic medications. No subject had organic brain damage or mental retardation. All subjects were right-handed.

2.1.2. Age-matched normal control subjects for schizophrenia patients

Twenty-nine control subjects who had no history of mental illness in themselves or in the family, were recruited. The mean age was 29.0 (S.E. = 1.6). Average WAIS IQ score was 114.6 (S.E. = 3.4) and the mean years of education was 15.1 (S.E. = 0.7). No control subject was receiving any medications. No subject had organic brain damage or mental retardation. There was no statistical differences between the schizophrenia patients and the normal control subjects in age, WAIS IQ and the educational level. All subjects were right-handed.

2.1.3. High 'perceptual aberration' subjects and younger normal control subjects

The procedure for ascertaining the psychosis-prone subjects and the control subjects were previously described in detail and the overall working memory scores for these subjects have been reported (see Park et al., 1995b). Psychosis-prone subjects were drawn from a sample of first-year university students. Separate group means and standard deviations for males and females on the Perceptual Aberration Scale (PerAb) (Chapman et al., 1978) were computed and served as the basis for subject selection. Hypothetically 'psychosis-prone' subjects were required to have scored at least 2.0 S.D. above the group mean on the PerAb scale, whereas normal control subjects were required to have scored no higher than 0.5 S.D. above the group mean. Study subjects for each of the two groups were selected at random from the two sub-samples of subjects meeting the specified criteria. Testing was conducted blind to the group membership. For the purpose of this study, all left-handers were excluded from error analyses. There were 21 right-handed subjects in the high perceptual aberration group and 15 control subjects. The mean age of the high perceptual aberration group was the same as that of the control subjects (19.0 years, S.E. = 0.1). There was no difference in their WAIS IQ, SAT scores and

the years of education (13 years for all subjects) between the schizotypic and control subjects. [For a detailed description, please see Park et al. (1995b).]

2.2. Procedure

Subjects were seated with their heads on a head rest in front of a stimulus display screen. The fixation point in the center of the screen was a small dot (0.5° of visual angle). The target was a black circle (2° of visual angle). The location of the target varied from trial to trial. There were eight possible target locations, each separated by 45°. The distance between the fixation point and any target location was 12° of visual angle. Target locations were presented in a random order.

Subjects fixated on a dot at the center of the screen. When a subject was ready, the experimenter clicked a mouse to initiate a trial. In the

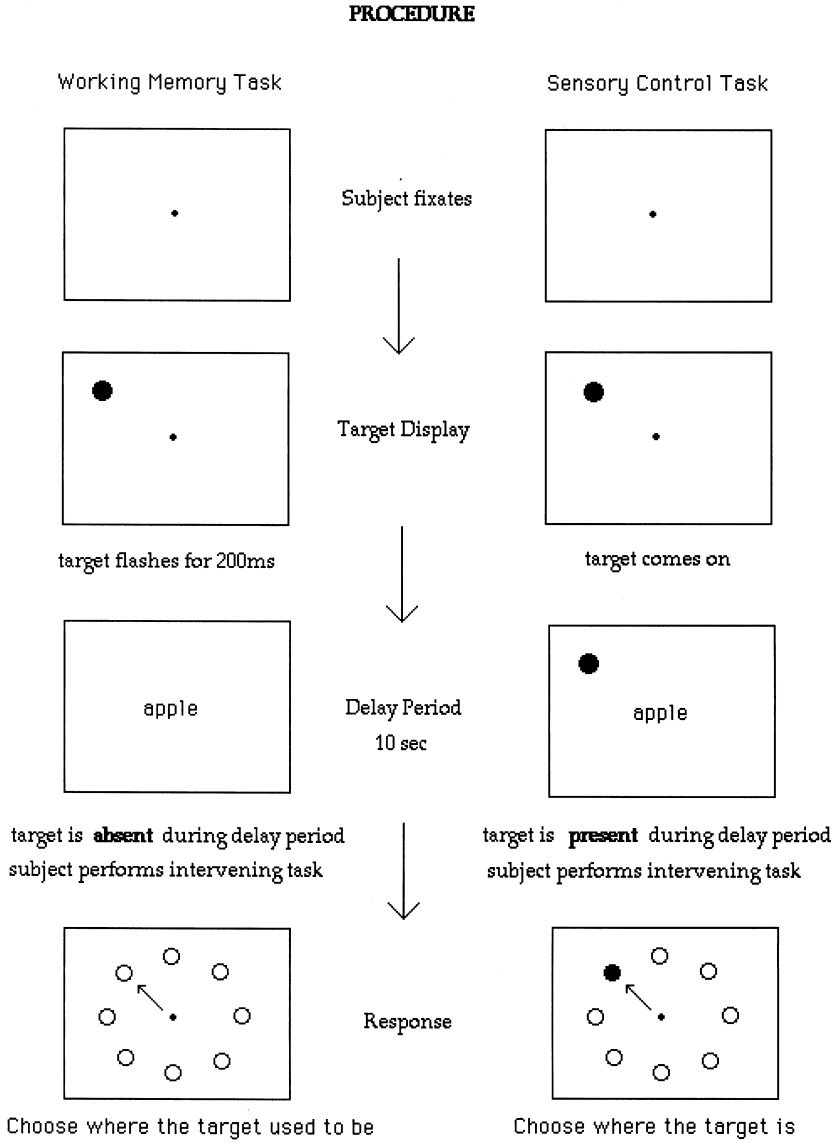

Fig. 2. Procedures for working memory task and sensory control task.

oculomotor working memory task, a target (black circle) was flashed for 200 ms at one of the eight positions. During the target presentation, the subject continued to fixate at the center. Immediately after the target presentation, there was a 10-s delay period, during which the subject performed an intervening task, introduced to prevent rehearsal and to keep the eye fixated at the center [see Park and Holzman (1992) for a detailed description].

After the delay period, eight 'reference' circles (empty, rather than black) appeared on the screen. Subjects were required to move their eyes to the remembered position of the target. If their eyes looked at the correct target position, the screen cleared and the fixation point replaced the reference circles. The next trial could then begin. If the subject did not look at the correct position, the reference circles remained on the screen until the subject looked at the correct position. The eye positions were recorded every 20 ms. If the subject did not look at the correct location within a 9.99-s time limit, the reference circles disappeared and the red fixation point reappeared, indicating that a new trial could begin.

A control for the sensorimotor component of the oculomotor delayed response task was an oculomotor sensory control task. This oculomotor sensory task was identical to the oculomotor memory task except for one aspect: the target remained on the screen at all times. Subjects performed the distractor task for 10 s and then immediately after the appearance of the reference circles, one of which was the black target, they were required to move their eyes to the black target. This task required no memory since the target never disappeared from the screen. Fig. 2 shows the schematic plan of the experiment.

The order of presentation of the oculomotor memory and the oculomotor sensory conditions was counterbalanced across subjects. There were 64 trials on the oculomotor memory task and 64 trials on the oculomotor sensory task. All subjects gave full informed consent, and sufficient time was taken to be certain that each subject understood the task.

2.3. Apparatus

An infrared light source was placed in front of the stimulus display monitor, facing the subject. The reflected infrared light from the right eye of the subject was recorded by a video camera with an infrared filter. The video camera was connected to a pupil/corneal reflection tracking system that records the center of the pupil and a bright corneal reflection moving over the pupil. The spatial difference between the pupil and the corneal reflection remains constant if head movement is small (approx. 1 inch^3) but it changes with eye movement. This method yields a linear representation of the subject's eye position within $\pm 15°$ of visual angle. Within the linear range, the accuracy is better than 1°. The pupil/corneal tracking system was controlled by a Macintosh computer, which recorded and stored the eye position coordinates. To take account of small head movements, the pupil/corneal tracker was connected to an autocalibration system which calculated the subject's point of regard with respect to the stimulus. Calibration was performed by asking subjects to fixate on five experimenter-defined positions on the stimulus display screen, successively: center, upper left, lower left, upper right and lower right. After the calibration, the subjects were given practice trials to be sure all subjects understood the procedure.

2.4. Scoring

2.4.1. Global accuracy score

A response was scored as correct if the eye moved within 1.5° of the center of the target position. If the eye moved to the correct position, the screen cleared and the subject could start a new trial. These responses were computed to form a global accuracy score. This score represents conventional memory testing methods.

2.4.2. Corrected and uncorrected errors

If the eye moved to an incorrect position, the eight possible target positions remained on the screen and the subject was allowed to make as

many eye movements as she could, within 9.99 s. These guesses were recorded. Some errors were easily corrected after one or two incorrect responses but some errors were not corrected within the time limit of 9.99 s. We computed two kinds of errors: those that are corrected after one mistake (E1) and errors that are never corrected within the time limit (En). We hypothesized that subjects make these two types of errors for different reasons. E1 errors may arise due to temporary distraction or disinhibition of irrelevant response tendencies. En errors, on the other hand, may be due to a loss of spatial representation of the target during the delay period. We examined both E1 and En errors in left and right visual fields.

3. Results

3.1. Schizophrenia patients and age-matched control subjects

Multifactorial, repeated measures ANOVA was conducted to compare the differences between the diagnostic groups in the types of errors made in the two visual hemifields. There was a main effect of diagnostic group ($F_{1,60} = 29.4$, $P < 0.0001$). Schizophrenia patients made more working memory errors than did the normal control subjects but the two groups did not differ on the sensory control task. There was also a main effect of the type of errors ($F_{1,60} = 6.2$, $P < 0.02$). Immediately-corrected errors were much more frequently elicited than were the never-corrected errors. There was no main effect of the hemifield of the target presentation ($F_{1,60} = 0.63$, $P > 0.40$). But there was a three-way interaction between the diagnostic group, hemifield of the target and the type of errors made ($F_{1,60} = 3.95$, $P < 0.05$).

Schizophrenia patients made more E1 than did the control subjects ($F_{1,60} = 24.7$, $P < 0.0001$). For immediately-corrected errors (E1), there was no group × hemifield interaction ($F_{1,60} = 1.6$, $P > 0.21$). Schizophrenia patients made more E1 than the normal control subjects in both hemifields.

Schizophrenia patients also made more En ($F_{1,60} = 18.4$, $P < 0.0001$) than did the normal control subjects. There was an interaction between the hemifield of the target presentation and the diagnostic group ($F_{1,60} = 4.23$, $P < 0.05$) such that schizophrenia patients made more En when the target had been presented in the right visual field. This result implicates a disruption or loss of spatial representation in the left frontal system in schizophrenia patients. Normal control subjects showed no asymmetry in En.

Paired *t*-tests for schizophrenia patients show that for E1 there was no difference in the visual field ($t = 1.03$, $P > 0.31$) but there was a significant difference for the En ($t = -2.0$, $P < 0.05$). Paired *t*-tests for the control subjects show that for E1 there was no difference in the visual field ($t = -0.96$, $P > 0.34$) and similarly there was no

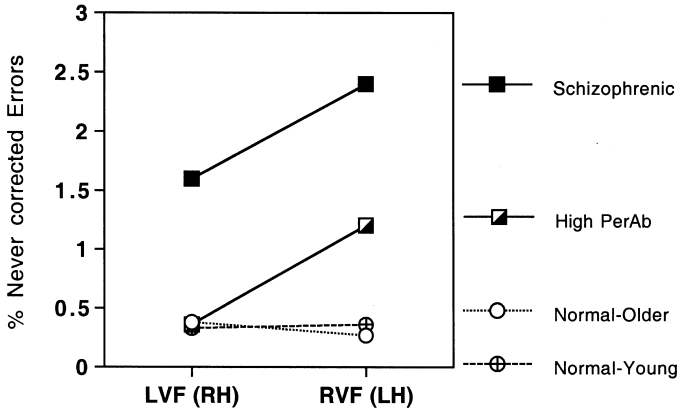

Fig. 3. Never-corrected errors in left and right visual hemifields.

significant difference for the En ($t = 1.36$, $P > 0.18$).

3.2. High perceptual aberration subjects and age-matched control subjects

The main results of the presence of spatial working memory deficit in these subjects have been reported in a previous paper (Park et al., 1995b). However, error patterns in the left and right visual fields have not been examined before. There was a group × visual field interaction for never-corrected errors ($F_{1,34} = 3.9$, $P < 0.05$). Subjects in the high PerAb group made more never-corrected errors (En) when the target had been presented in the right visual field than in the left visual field, whereas the control subjects showed no visual field differences. But there was no group × visual field interaction in the number of immediately-corrected errors ($F_{1,34} = 0.16$, $P > 0.68$). This pattern of errors is similar to that seen in schizophrenia patients (see Fig. 3).

Paired *t*-tests for high PerAb subjects show that for E1 there was no difference in the visual field ($t = -1.6$, $P > 0.12$) but there was a significant difference for the En ($t = -2.75$, $P < 0.01$). Paired *t*-tests for the age-matched control subjects show that for E1 there was no difference in the visual field ($t = 0.46$, $P > 0.64$) and similarly there was no significant difference for the En ($t = -0.44$, $P > 0.66$).

4. Discussion

Spatial working memory function in schizophrenia patients may be characterized, not only by the sheer number of errors, but also by the nature of the errors. Loss of spatial representation, mediated by the dorsolateral prefrontal system, features prominently in the way schizophrenia patients and high PerAb subjects forget. When normal control subjects make errors, they are able to correct their errors immediately. This pattern of errors suggests that the control subjects are able to maintain spatial representation during the delay, even when they make errors at the response stage, presumably due to temporary disinhibition. Thus, spatial working memory errors of schizophrenia patients seem to be qualitatively and quantitatively different from the errors made by non-schizophrenic subjects.

Never-corrected errors were elicited more often by schizophrenia patients (and high PerAb subjects) when the target was presented in the right visual field. This pattern may reflect the loss of spatial representation by the left prefrontal system. However, Carter et al. (1996) suggest that never-corrected errors may also arise from a failure to attend to the target and hence a failure to encode the target. Although, the *encoding deficit hypothesis* has not been directly tested in the present study, for this particular group of patients, the *maintenance deficit hypothesis* may suffice, because indirect evidence may be obtained from their performance on the sensory control task. Schizophrenia patients did not show any asymmetry in accuracy or reaction times on the sensory control task. This suggests that they were able to attend to the target in all parts of the visual field with equal accuracy and speed when no working memory is required.

4.1. Limitations of the study

Although the increased frequency of the never-corrected errors in the RVF suggests that the left frontal system may be compromised in schizophrenia, there are caveats. All schizophrenia patients were medicated and chronically ill. No patient was acutely psychotic at the time of testing. Therefore it is possible that the functional deficit implicating the left prefrontal system is a reflection of the chronic, deficit state, with predominantly negative symptoms. The fact that the high PerAb subjects also showed the same pattern renders support for the hypothesis that the observed left frontal deficit is not solely due to medication or chronicity. It is, nevertheless, interesting to note that the high PerAb subjects scored significantly higher than the control subjects on the Beck's Depression Inventory and the State and Trait Anxiety measures (see Park et al., 1995b). The high PerAb subjects, selected on the basis of their experiences of perceptual aberration (Chapman et al., 1978), do resemble, at least

on one level, the anhedonic, anergic, deficit state displayed by chronic schizophrenia patients in this study. In other words, they displayed signs of the 'Withdrawn' syndrome in schizotypy (Gruzelier, 1996) even though they were selected on the basis of their unusual perceptual experiences.

Growing evidence point to the important role of hemispheric imbalance in the syndromes of psychosis proneness and schizotypal personality (Gruzelier and Richardson, 1994; Gruzelier et al., 1995; Gruzelier, 1996; Gruzelier and Doig, 1996). Gruzelier's model of schizotypal personality consists of three factors: the 'withdrawn' factor is related to reduced left hemisphere activation; the 'active' factor is associated with the left > right hemispheric asymmetry; and the 'unreality factor' (corresponding to the perceptual aberration) is inconsistently associated with hemispheric asymmetry. Our high PerAb subjects were selected on the basis of Gruzelier's 'unreality' factor but they also showed significant signs of the 'withdrawn' factor. The left hemisphere deficit that we observe in these individuals may arise from the 'withdrawn' factor, the 'unreality' factor or both. From our data, it is not possible to separate these two syndromal factors. This issue leads to a more general problem. What might be the most appropriate way to interpret cognitive deficits such as the 'mnemonic hemianopoeia' of the left frontal region observed in the schizophrenia patients (hypothesized dorsolateral prefrontal deficit) in the context of the negative affect associated with left frontal hypoactivation (e.g. Henriques and Davidson, 1991)? At present, we do not know how the frontal lobe systems mediate affective and working memory functions, and how these systems interact in normal and pathological states.

To summarize, the role of prefrontal cortex in schizophrenia has been extensively studied since Kraepelin (1971) first observed in 1919 the similarities between cardinal features of schizophrenia and those of frontal lobe syndrome. Growing evidence from both psychological and anatomical data render support for the frontal lobe hypothesis of schizophrenia. Further analyses of spatial working memory errors indicate that left prefrontal system may be especially problematic in schizophrenia patients with predominantly negative features. Structural or functional hemispheric asymmetry has been most frequently observed in the temporal areas in schizophrenia (see Crow, 1990; Shenton et al., 1992; Falkai et al., 1995b), but the presence of never-corrected errors in the right visual field suggests that the functional asymmetry may extend to the frontal systems.

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