Dysfunction in different phases of working memory in schizophrenia: Evidence from ERP recordings

Yan Li Zhao a,1, Shu Ping Tan a,1, Fu De Yang a, Li Li Wang b, Wen Feng Feng c, Raymond C.K. Chan d,e, Xiao Gao f,g, Dong Feng Zhou h, Bin Bin Li a, Chong Sheng Song a, Feng Mei Fan a, Yun Long Tan a, Jin Guo Zhang a, Yun Hui Wang a, Yi Zhuang Zou a,⁎

a Center for Psychiatric Research, Beijing Huiliouguan Hospital, Beijing 100096, China
b State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China
c Department of Neurosciences, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0608, USA
d Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China
e Neuropsychology and Applied Cognitive Neuroscience Laboratory, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China
f Key Laboratory of Cognition and Personality (SWU), Ministry of Education 400715, China
g School of Psychology, Southwest University, Chong Qion 400715, China
h Institute of Mental Health, Peking University, Beijing 100091, China

ARTICLE INFO

Article history:
Received 3 December 2010
Received in revised form 5 September 2011
Accepted 17 September 2011
Available online xxxx

Keywords:
Working memory
Schizophrenia
Event-related potentials
Sternberg

ABSTRACT

The present study combined a time-locked paradigm and high-time-resolution event-related potential (ERP) recordings to examine different phases of working memory, including early visual processing and late memory-related processes of encoding, maintenance, and retrieval, in 67 adults with schizophrenia and 46 healthy controls. Alterations in ERP components were correlated with task performance. Patients performed significantly worse in the working memory task than healthy subjects, although all subjects' accuracy exceeded 80%. During encoding, the N1 and P2 component amplitudes were lower while the P300 amplitude was higher in schizophrenic patients compared to healthy controls. There were no differences between groups with respect to the mean amplitudes of the negative slow waves in the early stage (the first 400 ms) of the maintenance phase. However, in the next 500-ms time window, the patients exhibited a more negative deflection in the middle fronto-central region than the control group. Likewise, a similar pattern was observed in the second 500-ms period in the middle fronto-central region, although the effect was marginally significant. There were no differences between groups in the remaining 1000 ms. During retrieval, the P1, N1 and P2 amplitudes were lower while the P300 amplitude and latency were higher in schizophrenic patients. The present results indicate early visual deficits in the working memory task in adults with schizophrenia. Impairments in the maintenance phase were confined to the late rehearsal stage. The increased P300 amplitude at the fronto-central electrode sites along with the poorer behavioral performance suggests that schizophrenic patients have an inefficient working memory system.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

In the working memory system, information is represented, maintained, and updated for a short period (Lee and Park, 2005). Working memory has 3 stages: encoding, maintenance, and retrieval. Working memory deficits are a major cognitive dysfunction in schizophrenia (Silver et al., 2003). However, the specific stages of working memory that are specifically impaired in schizophrenia and the neuronal substrates underlying such abnormalities are not well understood (Hashimoto et al., 2010).

Behavioral (Hill et al., 2010; Mazhari et al., 2010; Zilles et al., 2010) and functional magnetic resonance imaging (fMRI) studies have found deficits in the maintenance stage of working memory in schizophrenic patients (Driesen et al., 2008; Henseler et al., 2009). Smith and Jonides (1998) propose a visual-verbal working memory maintenance process involving multiple cognitive processes. First, visual stimulus representations are translated into corresponding phonological representations; these phonological representations remain active and are rehearsed subvocally and refreshed. The phonological translation process is mediated by the posterior parietal area, inferior frontal cortex, and superior temporal cortex; storage of phonological representations is mediated by the posterior parietal areas, whereas rehearsal is mediated by the frontal speech areas (Smith and Jonides, 1998). At present, it remains unclear which component(s) of the maintenance stage are impaired in schizophrenic patients. While some studies suggest that the
impairment exists in the early part of maintenance (Lee and Park, 2005), others suggest there may also be deficits in the late rehearsal process (Hashimoto et al., 2010). The recording of event-related potentials (ERPs) is a high-time-resolution method that can be used to study the time course of maintenance processes. ERP studies in normal subjects detect ERP slow waves from 200 ms to several seconds post-stimulus that are specific to information maintenance in working memory (Ruchkin et al., 1994; Mecklinger and Pfeifer, 1996). However, to our knowledge, no similar ERP studies have been performed in schizophrenic patients.

Behavioral (Hartman et al., 2003; Badcock et al., 2008) and fMRI studies (Cairo et al., 2006; Johnson et al., 2006) also indicate impairments during information encoding in schizophrenic patients. In addition, several ERP studies report impairments during encoding and retrieval. For example, Haenschel et al. (2007) found abnormal P300 amplitude and latency during both the encoding and retrieval stages in schizophrenic adolescents. Moreover, a growing body of evidence demonstrates that schizophrenic patients exhibit significant deficits in early visual processing (e.g., Chen et al., 1999a,b; Butler et al., 2009); these deficits mainly affect the subcortical magnocellular pathway (Luck et al., 2006; Martinez et al., 2008; Yeap et al., 2008). Furthermore, these deficits can be detected according to reduced P1 amplitude (Luck et al., 2006; Haenschel et al., 2007; Yeap et al., 2008). Early visual processing deficits contribute to working memory dysfunction in adolescents with early-onset schizophrenia (Haenschel et al., 2007) as well as individuals with schizotypal features (Koychev et al., 2010).

The main goal of the present study was to investigate which aspects of working memory are impaired in schizophrenic patients. Specifically, we examined whether patients were impaired in early visual processing by using a task involving working memory. Also, if deficits existed in the maintenance phase, we determined which parts of the maintenance process were impaired. In addition, the present study aimed to test whether impaired ERP components were correlated with behavioral performance. To achieve the goals stated above, we used ERPs generated by the modified Sternberg's short-term memory scanning task (SMST) (Manoach et al., 1999) in which participants were instructed to remember a set of unique digits in short-term memory (encoding phase); several seconds later (maintenance phase), a probe stimulus was presented (retrieval phase) and the participants answered whether the probe was part of the initial sample or not. With this task, the distinct phases of working memory can be distinguished and examined.

2. Materials and methods

2.1. Subjects

Sixty-seven adult inpatients of Beijing HuiIongguan Hospital in China with a DSM-IV diagnosis of schizophrenia (American Psychiatric Association, 1994) were recruited in the present study. Patients with a history of substance abuse in the last 6 months or additional neuropsychiatric diagnoses were excluded. Current clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). An additional 46 normal control participants were recruited from the surrounding community through poster advertisements. Control subjects with a history of mental illness or substance abuse were excluded. There were no significant differences between the 2 groups with respect to age, sex, handedness, or education (Table 1). All participants had normal or corrected to normal vision. All participants provided written informed consent, and the protocol was approved by the ethics committee of Beijing HuiIongguan Hospital.

2.2. SMST procedure

The SMST paradigm is described in previous studies (Pelosi et al., 1998; Pelosi and Blumhardt, 1999). Subjects were presented sets of 5 digits from 0 to 9 and were asked to memorize them. In each trial, an initial fixation was presented for 2 s; then, the 5 digits were presented for 1 s each (encoding phase) (Fig. 1). Following a 3-s delay (maintenance phase), a probe stimulus was presented for 2.5 s (retrieval phase). Participants were asked to indicate whether or not the probe number was in the previous set of digits by pressing buttons. Probe digits that were present or absent from the encoding phase were presented 50 times each. The reaction time and probe identification accuracy were recorded. Trials in which the reaction time was less than 200 ms (precipitate responses) were excluded from analysis (Pelosi and Blumhardt, 1999).

2.3. ERP recording

An electrode cap (NeuroScan Inc.) with 64 channels was fitted to a participant's head with the ground electrode at AFz and the reference electrodes physically linked at the left and right mastoid. The vertical electrooculogram (EOG) was recorded with electrodes placed above and below the left eye. The horizontal EOG was recorded as the left versus right orbital rim. Recording, digitization, and processing of electroencephalography (EEG) data were performed with a Brain Amp amplifier and Brain Vision Recorder software (Brain Products, Munich, Germany). The EEG and EOG signals were amplified with a 0.01–100 Hz bandpass filter and were continuously sampled at 500 Hz/channel. Impedance was kept below 5 kΩ. The EEG data were analyzed for ERPs with the Brain Vision Analyzer software (Brain Products). Epochs were computed off line. ERPs were filtered with a high-frequency cutoff of 30 Hz (roll-off, 24 dB per octave) before further processing. Trials containing blinks, eye movements, or

Please cite this article as: Zhao, Y.L., et al., Dysfunction in different phases of working memory in schizophrenia: Evidence from ERP recordings, Schizophr. Res. (2011), doi:10.1016/j.schres.2011.09.017
other artifacts (EEG sweeps with amplitudes exceeding ±100 μV) were excluded from averaging. Only correctly performed trials were included in the analysis.

2.4. Data measure and analysis

Data were analyzed according to the topographical distribution of grand averaged ERP activity as well as the methods of previous studies (Bosch et al., 2001; Bledowski et al., 2006; Haenschel et al., 2007). The averaged epoch of ERPs of both encoding and retrieval was 1000 ms including a 200-ms prestimulus baseline. Peak latencies (from stimulus onset to the peak of each component) and amplitudes (N1, P1, and P2: baseline to peak; P300: peak to peak) were measured and analyzed at both phases. To assess encoding, we analyzed ERPs elicited by the 5 sample stimuli; at this stage, P2 (130–260 ms) was analyzed at the F3, F4, Fz, C3, C4, and Cz electrode sites and P300 (346–450 ms) was measured at the Fz, FCz, Cz, CPz, and Pz sites. During retrieval, P2 over the F3, F4, and Fz electrode sites was analyzed from 110 to 220 ms, and P300 at the Fz, FCz, Cz, CPz, and Pz electrode sites was measured from 230 to 450 ms. The P1 component was measured at O1, Oz, and O2 (50–160 ms), and the N1 component was measured at PO7 and PO8 (100–250 ms) during both encoding and retrieval. Repeated measures ANOVA was used to assess differences in all dependent measurements (P1, N1, P2, and P300 amplitudes and latencies) in a single participant (i.e., between electrode sites) and between groups (i.e., controls versus patients).

Negative slow waves were found over the entire scalp during the maintenance period. The averaged ERP epoch for this phase was 3000 ms, and the baseline was corrected from −300 ms before the onset of the 5th number stimulus. To avoid a loss of statistical power, electrode sites were pooled to form 10 topographical regions of interest (ROIs) (Bosch et al., 2001). ROIs were defined as follows (see Fig. 2): left frontal: F7 and F5; middle frontal: F1, Fz, and F2; right frontal: F6 and F8; left fronto-central: FT7, FC5, and T7; middle fronto-central: FC1, FC2, C1, Cz, and C2; right fronto-central: FC6, FT8, and T8; left centro-parietal: TP7, CP5, P7, and F5; middle centro-parietal: CP1, CPz, CP2, P1, Pz, and P2; right centro-parietal: CP6, TP8, P6, and P8; and middle parieto-occipital: PO3, POz, PO4, O1, Oz, and O2. Five time epochs were selected: 1600–2000, 2000–2500, 2500–3000, 3000–3500, and 3500–4000 ms. Repeated measures ANOVA was conducted with 2 factors: scalp location (10 levels) and time window (5 levels); the dependent variables were the mean voltages within ROIs restricted to predefined time epochs.

P-values were corrected using the Greenhouse–Geisser correction. Pearson’s correlation coefficients were calculated to assess the relationships between impaired ERP components and behavioral performance.

Fig. 1. SMST paradigm.

Fig. 2. Regions of interest.

Please cite this article as: Zhao, Y.L., et al., Dysfunction in different phases of working memory in schizophrenia: Evidence from ERP recordings, Schizophr. Res. (2011), doi:10.1016/j.schres.2011.09.017
3. Results

3.1. Behavioral measurements

Table 2 shows the mean response times and performance accuracy in both groups. The accuracy of all participants was above 80%. The independent samples test revealed slower reaction time \( t(111) = -5.043, p < 0.001 \) and poorer accuracy \( t(111) = 2.990, p = 0.003 \) in the patients compared to the controls.

3.2. ERP data analysis

3.2.1. Encoding

3.2.1.1. P1. The latency and amplitude of the P1 component were submitted separately to ANOVA with 2 factors: electrode site (P1/P2/P3) and group (control/patient). The results revealed that the P1 latency did not exhibit a significant main effect with respect to electrode site or group \( F(2, 110) = 2.261, p = 0.120; F(1, 111) = 0.278, p = 0.599 \). The relationship between electrode site and group was also insignificant \( F(2, 110) = 0.060, p = 0.903 \). The ANOVA of P1 amplitude indicated that the main effect of group was not statistically significant \( F(1, 111) = 1.918, p = 0.169 \).

3.2.1.2. N1. Two-way ANOVA with the factors of electrode site (PO7/PO8) and group (control/patient) was performed separately for the latency and amplitude of the N1 component. The main effect of group in latency was not significant \( F(1, 111) = 0.775, p = 0.381 \). The N1 latency exhibited a significant main effect on group \( F(1, 111) = 23.988, p < 0.001 \), indicating a more negative deflection in the control group than in the patient group (Fig. 3).

3.2.1.3. P2. Three-way ANOVA [laterality (left/midline/right) according to anterior–posterior electrode site (F/C) by group (control/patient)] of the P2 latency revealed no effect of group \( F(1, 111) = 1.564, p = 0.214 \) and no significant interactions. ANOVA for the P2 amplitude indicated a significant main effect of group \( F(1, 111) = 4.165, p = 0.044 \). This indicates that the control group had significantly larger P2 amplitudes than the patient group (Fig. 3).

3.2.1.4. P300. ANOVA for P300 latency and amplitude were conducted separately with 2 factors: electrode site (Fz/FCz/Cz/CPz/Pz) and group (control/patient). The results revealed that the P300 latency did not exhibit a significant main effect of group \( F(1, 111) = 0.016, p = 0.900 \). The P300 amplitude indicated a significant interaction effect of electrode site by group \( F(4, 108) = 5.776, p = 0.010 \). Simple effect analyses found that the patients had larger P300 amplitudes than controls at the Fz, FCz, and Cz electrode sites \( p = 0.074, 0.012, \) and 0.020, respectively (Fig. 3).

3.2.2. Maintenance

3.2.2.1. Negative slow waves. The mean amplitudes of the negative slow waves measured at the 10 ROIs indicated main effects of time window \( F(4,108) = 63.257, p < 0.001 \) and scalp location \( F(9,103) = 32.273, p < 0.001 \), an interaction effect between time window and scalp location \( F(36, 76) = 39.883, p < 0.001 \), and a marginally significant group interaction effect between time window and scalp location \( F(36, 76) = 2.063, p = 0.059 \). Simple effect analyses found that there were no differences between the 2 groups during the first 400 ms (1600–2000 ms). From 2000 to 2500 ms, the patients exhibited more negative deflection in the middle fronto-central region than the control group \( p = 0.045 \). A similar pattern was observed in the middle fronto-central region from 2500 to 3000 ms, although this effect was marginally significant \( p = 0.065 \). There were no significant differences between groups in the remaining 1000 ms \( p > 0.05 \), Fig. 4).

3.2.3. Retrieval

3.2.3.1. P1. ANOVA for P1 latency and amplitude measured at the O1, O2, and OZ electrode sites revealed a nonsignificant main effect by group with respect to latency \( F(1, 111) = 0.269, p = 0.605 \). P1 amplitude exhibited a significant main effect of group \( F(1, 111) = 5.163, p = 0.025 \) and an interaction effect between electrode site and group \( F(2, 110) = 3.808, p = 0.028 \). Simple effects analyses showed that P1 amplitudes were smaller in patients than in controls at the O2 and OZ sites \( p = 0.006; p = 0.043 \), Fig. 5).

3.2.3.2. N1. No significant differences in latency \( F(1, 111) = 0.694, p = 0.406 \) were found between groups. The N1 amplitude was more negative in controls than in patients \( F(1, 111) = 35.413, p < 0.001 \), Fig. 5).

3.2.3.3. P2. P2 latency measured at the F3, F4, and Fz electrodes indicated a nonsignificant main effect of group \( F(1, 111) = 0.593, p = 0.443 \). P2 amplitude showed a significant interaction effect of electrode site by group \( F(2, 110) = 3.470, p = 0.036 \). Simple effects analyses found that P2 amplitudes were smaller at F3 in patients than in controls \( p = 0.006 \), Fig. 5).

3.2.3.4. P300. The ANOVA of the P300 latency revealed a significant main effect of group \( F(1, 111) = 60.827, p < 0.001 \). The latencies were significantly longer in patients than in controls (Fig. 5). In addition, P300 amplitude showed a significant interaction effect of electrode site by group \( F(4, 108) = 8.971, p < 0.001 \). Simple effects analyses demonstrated that P300 amplitudes were larger in patients than controls at Fz, FCz, and Cz \( p = 0.045, 0.058, \) and 0.048, respectively (Fig. 5).

3.3. Effect of illness duration

Considering that our sample included patients with a wide range of illness duration \( 0.2–36 \) years, we assigned patients to 1 of 2 groups according to mean illness duration \( M = 16.31 \) and assessed whether illness duration affected the results. The independent samples test suggested that there were no differences between the 2 patient groups with respect to either reaction time \( t(64) = -1.581, p = 0.119 \) or accuracy \( t(64) = -0.322, p = 0.749 \). Repeated measures ANOVA of the amplitudes and latencies of all ERP components during early visual processing and the late memory-related processes (encoding, maintenance, and retrieval; age was controlled as a covariate) demonstrated that there were no significant differences between the ERP results of the 2 patient groups except for a significant difference in the latency of the N1 component at the encoding phase. Longer latencies were observed in the longer disease duration patient group than in the shorter duration group \( p = 0.01 \).

3.4. Correlation between impaired ERP components and behavioral performance

To better elucidate the potential role of neuronal substrates in working memory performance, the amplitudes and latencies of the ERP components (P1/N1/P2/P3/negative slow wave) that exhibited

<table>
<thead>
<tr>
<th>Group</th>
<th>RT (ms)</th>
<th>ACC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Patients with schizophrenia</td>
<td>1157.62</td>
<td>211.77</td>
</tr>
<tr>
<td>Controls</td>
<td>967.24</td>
<td>173.48</td>
</tr>
</tbody>
</table>

Table 2 The mean response times and the proportion of correct responses (accuracy) of both groups.
a main effect of group or an interaction effect between electrode site and group were subjected to correlational analyses separately assessing accuracy and response time in the working memory task in the patient and control groups. No significant correlations were found in either group.

4. Discussion

The present study found performance deficits and ERP abnormalities during various stages of the working memory process in schizophrenic patients. Thus, the results indicate inefficiency in the neuronal substrates underlying working memory in a sample of adult patients with schizophrenia.

4.1. Early visual processing impairments

The results in the present study show reductions in both P1 and N1 amplitudes in schizophrenic patients. The observed reduced P1 amplitude adds to the growing body of evidence that early visual processing is impaired in schizophrenic patients. Although the majority of previous studies do not report a reduced N1 component, our finding is not unprecedented. Butler et al. (2007) found that both P1 and N1 amplitudes are reduced in response to magnocellular visual pathway-biased stimuli in schizophrenic patients, while responses to parvocellular pathway-biased stimuli are normal. The results suggest that deficits in early visual processing affect the subcortical magnocellular pathway; this leads to secondary impairment in the activation of cortical visual structures within both the dorsal and ventral stream pathways. Furthermore, reduced P1 and N1 amplitudes are observed since the P1 ERP component arises from generators in both dorsal and ventral streams, and the N1 component arises from generators in ventral streams (Butler et al., 2007). The discrepancy between most previous results and the present results is most likely due to the use of different tasks and stimuli. For example, some studies use complex visual shapes as stimuli (Haenschel et al., 2007; Koychev et al., 2010); meanwhile, we used accessible digits—information input that may be more dependent on magnocellular pathway activity. Moreover, the present study also demonstrates that the secondary impairments in the activation of the ventral stream visual pathway are more serious in patients with longer illness duration, as these patients had longer N1 latencies than those with shorter illness duration. Finally, no direct correlations were observed between the P1/N1 amplitudes, and working memory accuracy. One of the potential reasons for this is that we used accessible stimuli that require less detailed processing to establish perceptual representations for subsequent working memory encoding.

4.2. Maintenance phase impairments

There were no differences between the 2 groups regarding maintenance phase impairments in the early stage (the first 400 ms). However, in the next 500-ms time window, the patients exhibited a more negative deflection in the middle fronto-central region than the control group. Likewise, a similar pattern was observed in the second 500-ms period in the middle fronto-central region, although this effect was marginally significant. In the remaining 1000 ms, there were no significant differences between the 2 groups. Since frontal speech areas mediate rehearsal processes (Smith and Jonides, 1998), these results may suggest that patients with schizophrenia have impairments in the late rehearsal stage. This impairment most likely results from deficits in sustained attention in schizophrenic patients (Bergman et al., 1995). However, with longer durations (>2 s), normal subjects may be equally...
vulnerable to interference (Lee and Park, 2005) such that the difference between groups becomes insignificant.

4.3. Encoding and retrieval impairment

Compared to the controls, schizophrenic patients had significantly greater P300 amplitudes during both encoding and retrieval at the fronto-central electrode sites. These findings contradict those of previous studies that found decreased P300 amplitudes in schizophrenic patients in response to various tasks and stimuli (Jeon and Polich, 2003). Many factors may contribute to this difference, including task demand. Schizophrenic patients performed the task with lower accuracy and longer reaction times compared to the normal controls; the increased P300 amplitudes may reflect the increased task demand in the patients. However, in the present study, the accuracy of all participants exceeded 80%, suggesting that the task demand was within capacity. However, increased amplitudes and poorer performance may be observed when the demand exceeds capacity. This hypothesis was advocated by Manoach et al. (1999) and Callicott et al. (2003) to clarify divergent findings in fMRI studies in which both decreases (e.g., Volz et al., 1999) and increases (e.g., Manoach et al., 2000) were observed in the dorsolateral prefrontal cortex in schizophrenic patients. We believe this hypothesis can explain the differences in P300 between patients and controls. Furthermore, the poorer performance in addition to the increased P300 amplitude suggests an inefficient working memory system in schizophrenic patients (e.g., Manoach et al., 1999). Previous research shows that treatment with second-generation antipsychotics is associated with improvements in working memory deficits in schizophrenia (Bertolino et al., 2004; Galletly et al., 2005; Kebir and Tabbane, 2008). Most patients (90.9%) in our sample were taking atypical antipsychotics. In the future, ERP recordings during the performance of working memory in antipsychotics-naive patients or in patients with first-episode schizophrenia should be investigated to minimize the confounding effects of long-term medication use. Finally, we incorporated only one working memory load, which made it impossible to study load effects. Moreover, the task demand in the present study was low, resulting in a high overall degree of accuracy that may account for the lack of a correlation between the impaired ERP components and behavioral performance. In future studies, task demand should be varied to investigate these issues.

4.4. Limitations

First, while we interpret the results of the present study as providing evidence for the neural source of the working memory deficits in schizophrenia, it is arguable that there are significant behavioral differences between schizophrenic patients and healthy controls that make ERP interpretation difficult. Although the patients’ overall performance was poorer, their accuracy exceeded 80%, which indicates active participation and feasible task demand. In addition, we only analyzed the results from successful trials. Given these arguments, we believe that the ERP impairments found in the present study cannot be attributed solely to differences in engagement. Furthermore, the poorer performance in addition to the increased P300 amplitude suggests an inefficient working memory system in schizophrenic patients (e.g., Manoach et al., 1999). Previous research shows that treatment with second-generation antipsychotics is associated with improvements in working memory deficits in schizophrenia (Bertolino et al., 2004; Galletly et al., 2005; Kebir and Tabbane, 2008). Most patients (90.9%) in our sample were taking atypical antipsychotics. In the future, ERP recordings during the performance of working memory in antipsychotics-naive patients or in patients with first-episode schizophrenia should be investigated to minimize the confounding effects of long-term medication use. Finally, we incorporated only one working memory load, which made it impossible to study load effects. Moreover, the task demand in the present study was low, resulting in a high overall degree of accuracy that may account for the lack of a correlation between the impaired ERP components and behavioral performance. In future studies, task demand should be varied to investigate these issues.

4.5. Conclusions and implications

The present study combined a time-locked paradigm and a high-time-resolution ERP technique to investigate the underlying mechanisms of working memory deficits in adults with schizophrenia. First, early visual and late memory-related processes of encoding, maintenance, and retrieval were all impaired in schizophrenic patients. We believe this hypothesis can explain the differences in impaired ERP components and behavioral performance. In future studies, task demand should be varied to investigate these issues.
patients. Moreover, the impairments during maintenance were limited to the late rehearsal process. Finally, the increased P300 amplitude at fronto-central electrode sites in addition to poorer behavioral performance suggests that schizophrenic patients have inefficient working memory systems.

The results of the present study have important implications for future clinical therapy and research. While early visual processing deficits in schizophrenic patients play an important role in high-order dysfunctions, current medications for schizophrenia are relatively ineffective in treating these deficits; therefore, new medications that positively affect sensory deficits are needed (Javitt, 2009). Moreover, previous studies demonstrate that conventional cognitive remediation therapy can only improve working memory deficits in schizophrenic patients to a certain extent (Wykes et al., 2007; Sartory, 2008). The present results suggest that we can provide more training for visual sensory processing and maintaining mental representations, and that the effects may be more apparent. A novel neuroplasticity-based cognitive training regimen specifically aimed at restoring degraded early perceptual processes was recently developed (Fisher et al., 2010); this training regimen resulted in significant durable gains in measures of verbal memory. This strongly supports our opinion regarding future cognitive training for improving working memory performance. Finally, our finding of an increased P300 amplitude in schizophrenic patients corroborates other evidence that abnormalities in prefrontal cortical functioning in schizophrenic patients are not simply due to too much or too little activity, but are related to task parameters (Callicott et al., 2003).

Role of funding source
This study was partially supported by Beijing Municipal Science & Technology Commission grant (No. D0906001000091), Beijing Natural Science Foundation grant (No. 7102086), Fund of Capital Medical Development and Research grant (No. 2007–3059), and Beijing Municipal Training Programme Foundation for the Talents (No. 2007d0301400101). This work was supported by the major project of Beijing science and technology (D0906001000091).

Fig. 5. Grand averaged waveforms for the retrieval conditions in the control group (black line) and the patient group (red line). P1 can be seen at Oz, N1 can be seen at P07, P2 at Fz, and P300 at Cz.

Contributors
Yan Li Zhao executed the analyses, interpreted the data and wrote the first draft of the manuscript. Shu Ping Tan and Yi Zhuang Zou designed the study, supervised the project and gave suggestions in data analysis and interpretation. Fu De Yang gave important suggestions for the study designing and the revision of the manuscript. Li Li Wang provided important technical support. Wen Feng Feng, Raymond C.K. Chan, Xiao Cao, Dong Feng Zhou and Yun Long Tan gave suggestions for the revision of the manuscript. Chong Sheng Song collected the clinical data. Bin Bin Li, Feng Mei Fan, Jin Guo Zhang and Yun Hui Wang aided with EEG recording.

Conflict of interest
All authors have no conflicts of interest.

Acknowledgment
The authors are grateful to Nan Chen, Hong Zhen Fan, Xiao Yan Cao and Lun Zhao, for their technical and statistical assistance. Appreciation is also owed to the patients, clinical psychiatrists and nursing staff in Beijing HuiLong Guan Hospital for their participation and collaboration. The authors also thank the anonymous reviewers for helpful comments.

References

Please cite this article as: Zhao, Y.L., et al., Dysfunction in different phases of working memory in schizophrenia: Evidence from ERP recordings, Schizophr. Res. (2011), doi:10.1016/j.schres.2011.09.017


