Contribution of Impaired Early-Stage Visual Processing to Working Memory Dysfunction in Adolescents With Schizophrenia

A Study With Event-Related Potentials and Functional Magnetic Resonance Imaging

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Context: Working memory (WM) deficits in patients with schizophrenia have mainly been associated with prefrontal dysfunction. However, the contribution of perceptual deficits and abnormalities in sensory areas has not been explored. The present study closes this important gap in our understanding of WM dysfunction in schizophrenia by monitoring neural activity during WM encoding and retrieval with event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI).

Objective: To investigate the neurophysiological changes that contribute to WM impairment in early-onset schizophrenia at perceptual and cognitive stages using the ERP components P1, P3a, P370, and P570 and fMRI data from extrastriate visual areas.

Design: We conducted the study between June 1, 2003, and December 20, 2006. Electroencephalographic and fMRI data were acquired separately during a visual delayed discrimination task. Participants encoded up to 3 abstract shapes that were presented sequentially for 600 milliseconds each and decided after a 12-second delay whether a probe matched 1 of the sample stimuli.

Setting: Between-group study at an inpatient psychiatric hospital and outpatient psychiatric facilities.

Participants: Seventeen adolescents with early-onset schizophrenia according to DSM-IV criteria and 17 matched controls participated in the study.

Main Outcome Measures: Amplitude of the ERP components P1, P3a, P370, and P570 and the fMRI signal from extrastriate visual areas.

Results: The P1 amplitude was reduced in patients during encoding and retrieval. The P1 amplitude increased with WM load during encoding only in controls. In this group, a stronger P1 amplitude increase predicted better WM performance. The P1 reduction was mirrored by reduced activation of visual areas in patients in fMRI. The P370 amplitude during encoding and retrieval was also reduced in patients.

Conclusions: The P1 amplitude reduction indicates an early visual deficit in adolescents with schizophrenia. Our findings suggest that P1 is of particular relevance for successful WM encoding. Early visual deficits contribute to impaired WM in schizophrenia in addition to deficits in later memory-related processes.

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Early visual processing is related to the P1 component. It indexes the suppression of irrelevant information, a mechanism that seems to be necessary for efficient WM encoding. It is also sensitive to spatial attention, which is required for subsequent processing of object features. Although the perceptual and cognitive processes probed by the P1 are thus highly relevant in the context of WM, most previous studies have shown no WM-related P1 amplitude effects. Conversely, the classic ERP component associated with memory processes is the P3. The P3 can be divided into a frontocentral P3a and a parietocentral P3b. The P3a has been regarded as an index of the novelty of information and may be the neurophysiological correlate of the orienting response, whereas the P3b is elicited by expected (but rare) task-relevant stimuli. The P3b during retrieval.23,33

Consolidation during encoding and template matching reflecting stimulus evaluation and the second reflecting a WM task can be divided into 2 peaks: the first most likely increased with WM load in delayed discrimination tasks and the second P3b peak. Furthermore, we assess whether analogous impairments are also present during retrieval.

We were specifically interested in the possible contribution of early visual-processing deficits. Given that combined EEG-fMRI analyses have consistently reported P1 generators in the middle occipital gyrus, fusiform gyrus, and posterior temporal areas, we used fMRI to provide complementary information about group differences in these areas.

### METHODS

#### STUDY PARTICIPANTS

Seventeen patients with early-onset schizophrenia according to DSM-IV criteria and 17 controls (Table 1) participated in the study. Patients were recruited from the Clinic for Child and Adolescent Psychiatry of Frankfurt University and associated outpatient facilities. A DSM-IV diagnosis of schizophrenia was established with the German version of the Structured Clinical Interview for DSM-IV and thorough medical record review. Current clinical symptoms were assessed with the Positive and Negative Syndrome Scale. Patients with a history of substance abuse in the 6 months preceding the study or those with additional neuropsychiatric diagnoses were excluded from the study. Seventeen controls matched for age, sex, handedness, and premorbid IQ were recruited through local advertisements. Controls with a history of mental illness or substance abuse were excluded. All participants and, for participants younger than 18 years, parents provided informed consent before the study. Approval was obtained from the local ethics committee. The study was conducted between June 1, 2003, and December 20, 2006.

#### STIMULI AND TASK

A delayed discrimination task that probes load effects in visual WM was implemented on a personal computer using the Experimental-Run-Time-System software (www.berisoft.com). Thirty-six nonnatural visual objects were presented in the center of the computer monitor (visual angle, 1.34°). The WM load was manipulated by presenting 1, 2, or 3 sample stimuli for 600 milliseconds each, with an interstimulus interval of 400 milliseconds (encoding phase). After a delay of 12 seconds (maintenance phase), a probe stimulus was presented for 3 seconds (retrieval phase). Participants had to indicate whether it was part of the initial sample set by pressing a button. The intertrial interval was 12 seconds. The 3 WM load conditions were randomly intermixed within each run. The experiment was preceded by a training session that allowed participants to complete as many trials as necessary to familiarize themselves with the structure and timing of the task. Participants took part in 2 EEG sessions on consecutive days, each comprising three 10-minute blocks, and 1 fMRI session, comprising two 12-minute blocks.

#### ERP DATA ACQUISITION, PROCESSING, AND ANALYSIS

An electrode cap with 64 channels was fitted to the participant's head with the ground electrode at the middle anterior frontal electrode, the reference at the middle frontocentral electrode, and an additional vertical electro-oculogram electrode below the right eye. For analysis, data were re-referenced to
Averaged ERPs were filtered with a high-frequency cutoff at 30 Hz (roll-off, 12 dB per octave) before further processing. Peak amplitudes and latencies of P1 at electrode O1, O2 (centrooccipital electrode), and O2 were defined in the interval between 80 and 160 milliseconds and of P3a at C1, Cz (vertex electrode), and C2 were defined in the time window between 200 and 400 milliseconds. We defined the first and the second P3b peaks according to peak latency: P370 and P570. The P370 component at P3, Pz, and P4 was defined in the time window between 200 and 400 milliseconds and the second P3b peak, the P570 component at P3, Pz, and P4, was defined as between 450 and 750 milliseconds.

Repeated-measures multivariate analysis of variance was used to test the effects within participants (electrode and WM load) and between groups on all dependent measures (P1, P3a, P370, and P570 amplitude and latency). The WM load × group interactions were reported only if significant. In cases of significant group effects, we correlated amplitudes with accuracy for each load condition. We used polynomial contrasts to determine linear or quadratic trends to measure if the increase in amplitude. In cases of significant linear effects of WM load, we used linear regression to measure if amplitudes in addition to WM load can predict accuracy.

**IMR DATA ACQUISITION, PROCESSING, AND ANALYSIS**

Images were acquired with a 1.5-T Magnetom Vision MRI scanner (Siemens, Erlangen, Germany) using an echoplanar imaging sequence (16 axial sections; repetition time, 2000 milliseconds; echo time, 60 milliseconds; field angle, 90°; field of view, 220 × 220 mm²; voxel size, 3.43 × 3.43 × 5 mm³; gap, 1 mm; 350 volumes). Data analysis was performed with BrainVoyager QX 1.8.6 (Brain Innovation, Maastricht, the Netherlands). The first 4 volumes of functional runs were discarded to allow for T1 equilibration. Temporal offsets of the acquisition of each section were

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**Table 1. Demographic and Clinical Characteristics of Patients With Schizophrenia and Controls**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients With Schizophrenia (n=17)</th>
<th>Controls (n=17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>17.9 (15.2-20.4)</td>
<td>17.5 (15.1-19.9)</td>
<td>.48 (t_{15}=0.87)</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td>&gt;.99 (χ²=0)</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Handedness, No.</td>
<td></td>
<td></td>
<td>&gt;.99 (χ²=0)</td>
</tr>
<tr>
<td>Right</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) premorbid IQ⁴</td>
<td>96 (16)</td>
<td>97 (9)</td>
<td>.83 (t_{15}=-0.21)</td>
</tr>
<tr>
<td>Mean (SD) length of illness, y</td>
<td>1.4 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age at disease onset</td>
<td>16.5 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) PANSS score</td>
<td>44.9 (18.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroleptic medication use, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine fumarate</td>
<td>10</td>
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<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) chlorpromazine equivalents, mg/d⁵</td>
<td>188.7 (166.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PANSS, Positive and Negative Syndrome Scale.⁵⁵

⁴Premorbid IQ was measured with the Mehrfachwahl-Wortschatz-Intelligenztest,⁵⁴ the German equivalent of the National Adult Reading Test.
corrected for by sinc interpolation to the first section of each scanning volume. Data preprocessing further included 3-dimensional motion correction, spatial smoothing with a gaussian kernel (full width at half maximum, 8 mm), linear trend removal and temporal high-pass filtering (3 cycles per functional run), manual alignment to a high-resolution anatomy, and transformation into Talairach coordinate space. Multisubject statistical analysis was performed by voxelwise multiple linear regression of the blood oxygenation level-dependent signal. For each of the 3 WM load conditions, 4 boxcar predictors were defined, representing the different phases of the task: encoding, early delay, late delay, and retrieval. They were adjusted for the hemodynamic delay by convolution with a canonical hemodynamic response function. The 3-dimensional group statistical maps were generated by associating each voxel with the $F$ value corresponding to the specific set of predictors and calculated on the basis of the least mean squares solution of the general linear model with a mixed-effects model. The obtained $\beta$ weights were entered into a second-level, random-effects analysis. To detect areas with a significant group difference, we computed the following t test: load 1–controls + load 2–controls + load 3–controls > load 1–patients + load 2–patients + load 3–patients thresholded at $P < .000005$ (minimum cluster size, 10 mm$^3$). We searched for areas that showed this effect during encoding or retrieval within a 15-mm radius of the P1 coordinates reported by Noeschelt et al$^{39}$ (left hemisphere: $−39, −74, 4$; right hemisphere: $32, −75, 6$; Talairach space$^{38}$).

**RESULTS**

**BEHAVIOR**

Figure 2 shows the mean response times and the proportion of correct responses (accuracy) across both groups. Reaction time increased with WM load for both groups ($F_{2,31} = 111.96$, $P < .001$). The interaction between WM load and group showed a trend toward statistical significance ($F_{2,31} = 2.56$, $P = .09$), which is attributable to the control group demonstrating a greater increase from WM load 1 to WM load 2 than patients. The linear contrasts confirmed the monotonic increase in both groups with WM load (controls: $F_{1,15} = 114.32$, $P < .001$; patients: $F_{1,15} = 59.47$, $P < .001$).

The overall accuracy was lower in patients than controls ($F_{1,32} = 24.98$, $P < .001$). With an increase in WM load, the accuracy decreased in both groups ($F_{2,31} = 10.06$, $P = .003$). The linear contrast confirmed a trend toward a significant interaction between WM load and group ($F_{2,31} = 3.32$, $P = .08$), showing that the decrease in accuracy was more pronounced in patients. No correlation was seen between chlorpromazine equivalents and accuracy or reaction time.

**BROADBAND ERPs**

Because no interaction between group and electrode location was significant for the amplitudes of the various ERP components during encoding (P1: $F_{2,31} = 1.61$, $P = .21$; P3a: $F_{2,31} = 1.04$, $P = .36$; P370: $F_{2,31} = 0.17$, $P = .83$; P570: $F_{2,31} = 0.36$, $P = .09$) and only for P3a during retrieval (P1: $F_{2,31} = 1.56$, $P = .22$; P3a: $F_{2,31} = 4.14$, $P = .02$; P370: $F_{2,31} = 0.5$, $P = .59$; P570: $F_{2,31} = 0.4$, $P = .95$), results are reported only for midline electrodes (for P1 electrode Oz, for P3a electrode Cz, for P370 and P570 electrode P2). No correlation was found between chlorpromazine equivalents and any of the amplitude or latency measures in patients.

**ENCODING**

**P1 Component**

The grand mean ERPs to WM loads 1, 2, and 3 during encoding in controls and patients are illustrated in Figure 3. The sample stimuli evoked a P1 component with a mean (SD) latency of 132 (17) milliseconds in controls and 140 (24) milliseconds in patients at the central occipital electrode (Oz) (Figure 3 and Figure 4). No significant effect of group ($F_{1,32} = 2.09$, $P = .16$) or WM load ($F_{2,31} = 0.32$, $P = .73$) was found on latency. The P1 amplitude was significantly reduced in patients compared with controls ($F_{1,32} = 5.53$, $P = .02$) and increased with WM load ($F_{2,31} = 3.43$, $P = .04$; Table 2). Post hoc tests indicated that this increase was explained by a linear amplitude increase with WM load from 1 to 3 in controls ($r = 0.52$, $P = .02$). Conversely, patients showed neither a linear ($F_{1,15} = 0.94$, $P = .35$) nor a significant quadratic trend ($F_{1,15} = 1.4$, $P = .25$).

In addition, P1 amplitude correlated with accuracy for WM load 3 in controls ($r = 0.52$, $P = .03$), but no correlation was found for any of the WM load conditions in patients. Stepwise linear regression analyses were then computed to test if accuracy could be predicted by WM load and by P1 amplitude. We found a significant effect of both variables ($F_{2,48} = 8.38$, $P < .001$) in controls but not in patients. Although accuracy was negatively correlated with WM load ($\beta = −0.51$, $P < .001$), it was positively correlated with P1 amplitude ($\beta = 0.26$, $P = .046$). A higher P1 amplitude increase with increasing WM load predicted better performance.
Figure 3. Event-related potentials (ERPs) during working memory (WM) encoding. The ERP responses after the first sample stimulus for WM load 1 (black line), the second stimulus for WM load 2 (green line), and the third stimulus for WM load 3 (red line) are shown at the central occipital electrode (Oz), the central parietal electrode (Pz), the vertex electrode (Cz), and the central frontal electrode (Fz) for controls (A) and patients with early-onset schizophrenia (B). The P1 can be seen at Oz, P3a at Cz, and P370 and P570 at Pz. The ERPs at Fz are shown for illustrative purposes.

Figure 4. Peak and mean event-related potential (ERP) amplitudes. The P1 peak amplitude at the central occipital electrode (Oz) (A), P3a mean amplitude at the vertex electrode (Cz) (B), and P370 (C) and P570 (D) mean amplitude for the central parietal electrode (Pz) in response to working memory load 1, 2, or 3 for encoding and retrieval in controls and patients are shown. Error bars represent standard error.

**P3a Component**

The sample stimuli evoked a P3a component measured between 200 and 450 milliseconds, with a mean (SD) latency of 280 (40) milliseconds in controls and 288 (57) milliseconds in patients at the midline central electrode (Cz). The P3a mean amplitude did not differ between groups ($F_{1,32}=0.81, P=.37$) (Figures 3 and 4 and Table 2).
The mean amplitude increased with WM load (Cz: main effect load: $F_{1,31}=9.49, P<.001$). Post hoc tests showed that this increase was explained by a linear increase with WM load in patients ($F_{1,15}=5.01, P=.04$) and a quadratic increase in controls ($F_{1,13}=9.46, P=.04$). No difference was found in latency at the midline central electrode (group: $F_{1,32}=0.7, P=.41$; WM load: $F_{2,31}=2.24, P=.12$). No significant correlation was found between P3a and accuracy. In the linear regression model with WM load and P3a amplitude, P3a did not predict accuracy.

### P370 Component

The P370 component measured between 200 and 450 milliseconds and peaked with a mean (SD) latency of 372 (53) milliseconds in controls and 359 (44) milliseconds in patients at the central parietal electrodes (Pz) (Figures 3 and 4). Latency did not differ across groups ($F_{1,32}=0.99, P=.33$), but a statistically significant difference was found in latency with WM load ($F_{2,31}=3.48, P=.05$; Table 2). The mean P370 amplitude was significantly smaller in patients ($F_{1,32}=6.36, P=.02$; Figure 4) but did not increase with WM load ($F_{2,31}=1.9, P=.16$). A positive correlation between P370 amplitude and accuracy was significant for WM load 2 ($r=0.58, P=.01$) and WM load 3 ($r=0.8, P<.001$) in controls, but no correlation was found for any of the WM load conditions in patients.

### P570 Component

The sample stimuli evoked a P570 component with a mean (SD) latency of 568 (75) milliseconds in controls and 568 (73) milliseconds in patients at the central parietal electrodes (Pz) (Figure 3 and Table 2). Latency did not differ significantly between groups ($F_{1,32}=0.001, P=.98$) or across load conditions ($F_{2,31}=0.81, P=.44$). No effects of group were found on amplitude ($F_{1,32}=2.68, P=.11$). The P570 mean amplitude (measured between 450 and 750 milliseconds) showed a statistically significant decrease with WM load ($F_{2,31}=28.24, P<.001$; Figure 4). This quadratic decrease was statistically significant in controls ($F_{1,15}=45.59, P<.001$) and patients ($F_{1,15}=15.92, P=.001$). In addition, we found a significant correlation between P570 amplitude and accuracy in WM load 3 ($r=0.67, P=.003$) in controls.

### RETRIEVAL

#### P1 Activity

The grand mean ERPs to WM loads 1, 2, and 3 during retrieval in controls and patients are illustrated in Figure 5. The probe-related P1 activity peaked at a mean (SD) of 135 (16) milliseconds in controls and 129 (23) milliseconds in patients. The P1 peak amplitude approached a significant reduction in patients relative to controls ($F_{1,32}=3.8, P=.06$; Figures 4 and 5 and Table 3). No effect of WM load was found on P1 peak amplitude ($F_{2,31}=1.44, P=.25$) or latency ($F_{2,31}=1.1, P=.89$). No significant correlation was found between P1 amplitude and accuracy in any of the WM load conditions.

#### P3a Activity

The P3a component peaked with a mean (SD) latency of 291 (51) milliseconds in controls and 293 (72) milliseconds in patients. No significant difference in latency ($F_{1,32}=0.005, P=.94$) or mean amplitude ($F_{1,32}=1.16, P=.29$) was found between groups. The mean amplitude decreased significantly with WM load ($F_{2,31}=4.9, P=.01$) (Figures 4 and 5 and Table 3). A trend toward a load × group interaction was found for P3a during retrieval ($F_{2,31}=2.72, P=.07$). Post hoc tests showed that this interaction was explained by a quadratic decrease with

<table>
<thead>
<tr>
<th>Encoding</th>
<th>Mean (SE) Amplitude, µV</th>
<th>Mean (SE) Latency, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WM Load 1</td>
<td>WM Load 2</td>
</tr>
<tr>
<td>P1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>3.55 (0.53)</td>
<td>4.32 (0.44)</td>
</tr>
<tr>
<td>Patients</td>
<td>2.32 (0.59)</td>
<td>3.3 (0.59)</td>
</tr>
<tr>
<td>Effect size (d)</td>
<td>0.53</td>
<td>0.51</td>
</tr>
<tr>
<td>P3a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>2.15 (0.37)</td>
<td>1.53 (0.41)</td>
</tr>
<tr>
<td>Patients</td>
<td>1.27 (0.37)</td>
<td>1.57 (0.56)</td>
</tr>
<tr>
<td>Effect size (d)</td>
<td>0.70</td>
<td>0.72</td>
</tr>
<tr>
<td>P370</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>4.59 (0.47)</td>
<td>4.24 (0.55)</td>
</tr>
<tr>
<td>Patients</td>
<td>3.59 (0.37)</td>
<td>2.63 (0.55)</td>
</tr>
<tr>
<td>Effect size (d)</td>
<td>0.53</td>
<td>0.51</td>
</tr>
<tr>
<td>P570</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>7.28 (0.7)</td>
<td>4.6 (0.42)</td>
</tr>
<tr>
<td>Patients</td>
<td>6.3 (0.7)</td>
<td>3.42 (0.73)</td>
</tr>
<tr>
<td>Abbreviation: WM, working memory.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a Data are peak amplitude and latency for P1 at the central occipital electrode, mean amplitude and latency for P3a at the vertex electrode, and P370 and P570 at the central parietal electrode to loads 1, 2, and 3 sample stimuli during encoding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b Effect sizes were calculated for significant group differences.</td>
<td></td>
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</tbody>
</table>
Figure 5. Event-related potential (ERPs) during working memory (WM) retrieval. The ERP responses after the test stimulus for WM load 1 (black line), WM load 2 (green line), and WM load 3 (red line) are shown at the central occipital electrode (Oz), the central parietal electrode (Pz), the vertex electrode (Cz), and the central frontal electrode (Fz) in controls (A) and patients with schizophrenia (B). The P1 can be seen at Oz, P3a at Cz, and P370 and P570 at Pz. The ERPs at Fz are shown for illustrative purposes.

Table 3. Amplitudes and Latencies During Retrievala

<table>
<thead>
<tr>
<th>Retrieval</th>
<th>Mean (SE) Amplitude, µV</th>
<th>Mean (SE) Latency, ms</th>
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<tbody>
<tr>
<td></td>
<td>WM Load 1</td>
<td>WM Load 2</td>
</tr>
<tr>
<td>P1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>4.15 (0.41)</td>
<td>3.81 (0.47)</td>
</tr>
<tr>
<td>Patients</td>
<td>2.39 (0.40)</td>
<td>2.86 (0.55)</td>
</tr>
<tr>
<td>Effect size (d)b</td>
<td>1.10</td>
<td>0.45</td>
</tr>
<tr>
<td>P3a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>2.9 (0.47)</td>
<td>2.81 (0.42)</td>
</tr>
<tr>
<td>Patients</td>
<td>2.68 (0.63)</td>
<td>1.62 (0.49)</td>
</tr>
<tr>
<td>P370</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>5.64 (0.63)</td>
<td>5.27 (0.49)</td>
</tr>
<tr>
<td>Patients</td>
<td>4.46 (0.51)</td>
<td>3.37 (0.45)</td>
</tr>
<tr>
<td>Effect size (d)b</td>
<td>0.47</td>
<td>0.99</td>
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<tr>
<td>P570</td>
<td></td>
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<tr>
<td>Controls</td>
<td>7.67 (0.85)</td>
<td>7.24 (0.80)</td>
</tr>
<tr>
<td>Patients</td>
<td>7.75 (0.80)</td>
<td>6.99 (0.83)</td>
</tr>
</tbody>
</table>

Abbreviation: WM, working memory.

a Data are peak amplitude and latency for P1 at the central occipital electrode, mean amplitude and latency for P3a at the vertex electrode, and P370 and P570 at the central parietal electrode to loads 1, 2, and 3 test stimuli during retrieval.

b Effect sizes are calculated for significant group differences.

WM load in patients ($F_{1,15}=7.07$, $P=0.02$) but not in controls ($F_{1,15}=0.01$, $P=0.92$). No significant correlation was found between P3a amplitude and accuracy in any of the WM load conditions.

**P370 Activity**

The P370 component peaked with a mean (SD) latency of 375 (49) milliseconds in controls and 369 (62) milliseconds in patients. This difference was not statistically significant ($F_{1,32}=0.17$, $P=0.08$). The mean amplitude was significantly smaller in patients than in controls ($F_{1,32}=4.12$, $P=0.05$). The mean amplitude decreased significantly with increasing WM load ($F_{2,31}=5.78$, $P=0.006$) (Figures 4 and 5 and Table 3). The load-dependent decrease was only statistically significant in patients (quadratic contrast: $F_{1,15}=10.09$, $P=0.006$; linear contrast: $F_{1,15}=3.62$, $P=0.08$) but not in controls (quadratic contrast: $F_{1,15}=0.05$, $P=0.82$; linear contrast: $F_{1,15}=2.64$, $P=0.12$). A significant correlation was found between P370 amplitude and accuracy at WM load 3 ($r=0.7$, $P=0.002$).
Figure 6. Functional magnetic resonance imaging (fMRI) group differences in visual areas during encoding and retrieval. Visual areas with a significant group difference during encoding or retrieval (P < .000005, minimum cluster size of 10 mm³) in the fMRI analysis depicted on the average brain of all participants. Only brain areas within a 15-mm radius of the P1 coordinates derived from an established dipole model²⁹ (left hemisphere: −39, −74, 4; right hemisphere: 32, −75, 6; Talairach space) are shown.

P570 Activity

The P570 component peaked significantly later in patients than in controls ($F_{1,32}=6.48, P=.02$), with a mean (SD) latency of 533 (63) milliseconds in controls and 574 (59) milliseconds in patients. In contrast to P370, the P570 amplitude was not significantly different between groups ($F_{1,32}=0.001, P=.98$). The P570 at Pz decreased in mean amplitude with increasing WM load ($F_{2,31}=12.43, P<.001$) (Figures 4 and 5, Table 3). Post hoc tests showed that this linear decrease was statistically significant in both groups (controls: $F_{1,15}=10.12, P=.006$; patients: $F_{1,15}=15.92, P=.001$). No significant correlation was found between P570 and accuracy in any of the WM load conditions. In the linear regression model with WM load and P570 amplitude, P570 did not predict accuracy.

fMRI Data

Behavioral parameters closely matched those acquired during EEG recordings. For encoding, significant group differences were observed in the middle occipital gyrus bilaterally, in the left middle and superior temporal gyrus, and in the right inferior temporal gyrus (Figure 6A and Table 4). For retrieval, clusters in the middle occipital gyrus bilaterally, the left middle temporal gyrus, and the right inferior temporal gyrus were found (Figure 6B and Table 4). Group differences during retrieval were more confined in terms of the number of voxels than during encoding. However, 49% of voxels showing a significant group difference during retrieval also showed a significant group difference during encoding. Post hoc 2-tailed $t$ tests were computed to examine group differences for each WM load condition within individual clusters (Table 4). For encoding, all clusters showed significantly greater activation for WM loads 2 and 3 for controls. For retrieval, greater activation for controls was found in all clusters. Differences in activation were most pronounced for WM load 1 and declined toward the highest WM load conditions.

COMMENT

We examined the neural substrates of visual WM encoding and retrieval in patients with early-onset schizophrenia and compared the results with those obtained from healthy controls. Accuracy was significantly lower and decreased more steeply with WM load in patients than in controls. Reaction times increased with WM load but were not slowed in our sample of adolescent patients in contrast to findings in older chronically ill patients.

Compared with controls, the patients showed reduced amplitudes in P1 and P370 components during encoding. During retrieval, P1 showed a strong trend toward a reduction in patients with a large effect size for WM load 1. The P370 was again reduced in patients. No correlation was found between individual chlorpromazine equivalents and any of the dependent measures, in line with evidence that both P1 and P3 deficits occur irrespective of medication status.²⁴,²⁵ Several of the investigated ERP components were sensitive to WM load. During encoding, P1 and P3a amplitude increased and P570
Table 4. Functional Magnetic Resonance Imaging Group Differences in Visual Areas

<table>
<thead>
<tr>
<th>ROI</th>
<th>BA</th>
<th>Cluster Size, mm³</th>
<th>WM Load 1</th>
<th>WM Load 2</th>
<th>WM Load 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encoding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left GOm</td>
<td>19</td>
<td>-25</td>
<td>1010</td>
<td>3.12d</td>
<td>2.68e</td>
</tr>
<tr>
<td>Right GOm</td>
<td>19</td>
<td>-26</td>
<td>1585</td>
<td>3.26d</td>
<td>2.74e</td>
</tr>
<tr>
<td>Left GTi/GTm</td>
<td>22/59</td>
<td>-47</td>
<td>5726</td>
<td>3.10d</td>
<td>3.59d</td>
</tr>
<tr>
<td>Right GTi</td>
<td>37</td>
<td>-42</td>
<td>658</td>
<td>-0.03</td>
<td>2.25e</td>
</tr>
<tr>
<td>Retrieval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left GOm</td>
<td>18/19</td>
<td>-28</td>
<td>224</td>
<td>2.79d</td>
<td>2.44e</td>
</tr>
<tr>
<td>Left GOm</td>
<td>19</td>
<td>-35</td>
<td>135</td>
<td>2.48e</td>
<td>2.06e</td>
</tr>
<tr>
<td>Right GOm</td>
<td>19</td>
<td>-26</td>
<td>1102</td>
<td>4.13d</td>
<td>3.01d</td>
</tr>
<tr>
<td>Left GTi</td>
<td>37</td>
<td>-44</td>
<td>3716</td>
<td>3.98d</td>
<td>2.64e</td>
</tr>
<tr>
<td>Right GTi</td>
<td>37</td>
<td>-40</td>
<td>679</td>
<td>3.19d</td>
<td>3.67d</td>
</tr>
</tbody>
</table>

Abbreviations: BA, Brodmann area; GOm, middle occipital gyrus; GTi, inferior temporal gyrus; GTm, middle temporal gyrus; GTs, superior temporal gyrus; ROI, region of interest; WM, working memory.

a Visual areas with a significant group difference during encoding or retrieval (P<.000005, minimum cluster size of 10 mm³) in the functional magnetic resonance imaging analysis.

b Indicates standard brain space as defined by Talairach and Tournoux (x, y, z).58

c The t values are listed for ROI-based 2-tailed t tests comparing group differences for individual WM load conditions.

d P<.01.
e P<.05.

...
types 3,82,83 overlap with each other and whether their in- 
address the extent to which these putative endopheno- 
tics 7,8 have been found in unaffected first-degree rela-
tives. These operations have been associated with the P1 com-
ponent 2,7,8,70-72 and seem to be necessary for further ob-
ject processing and encoding into WM. The rapid pre-
sentation of up to 3 objects makes these processes par-
icularly demanding, which should increase the like-
lihood that deficits in patients reflected by reduced P1 
amplitude contribute to disturbed WM encoding. How-
ever, because the P1 is modulated by spatial selective at-
tention only to a small degree, it is unlikely that im-
paired spatial attention in patients is at the root of their 
marked P1 deficit.

Finally, the increase in the P1 with presenting stimuli 
in succession could reflect the sequential buildup of a 
sensory memory trace. Future studies need to investi-
gate if the WM load–dependent P1 increase is due to sen-
sitization of sensory processes. 73

In summary, adolescents with early-onset schizophre-
ния demonstrated an attenuated P1 component, an ab-
sence of a P1 WM load modulation, and reduced blood oxy-
genation level–dependent activation in early visual areas 
during WM. This finding highlights the relevance of early 
sensory deficits for higher-level cognitive dysfunction in 
schizophrenia. These early processing deficits might also 
reduce encoding efficiency for other forms of memory, such 
as long-term visual memory 74 and auditory sensory 
memory. 75 Although sufficient stimulus presentation time 
may facilitate encoding and normalize WM perform-
ance, 17 impairments in WM maintenance still persist when 
encoding difficulty is adjusted for by reducing stimulus com-
plexity. 12 The influence of impaired encoding on WM ma-
intenance may be further illuminated by analyzing slow po-
tentials 79 or time frequency patterns. 77,78 An integration of 
the present ERP approach with anatomical connectivity 50,70,80 and EEG measures of functional connectivity 2,81 will be paramount to further elucidate the underlying neu-
ral deficits.

Both impaired P1 generation 82 and WM dysfunc-
tion 78 have been found in unaffected first-degree rela-
tives of patients with schizophrenia. Future studies should 
address the extent to which these putative endophenotypes 3,82,83 overlap with each other and whether their in-
tegration into a composite endophenotype might pro-
vide a more robust marker of genetic vulnerability for 
schizophrenia. 88

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