

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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WORKING MEMORY (WM) deficits are a core feature of schizophrenia¹⁻³ that often develop before the first clinical symptoms^{4,6} and affect first-degree relatives of patients.^{7,8} Most studies have focused on maintenance and executive processes and prefrontal cortex dysfunction, which has consistently been reported in functional magnetic resonance imaging (fMRI) studies of patients⁹⁻¹¹ and their first-degree relatives.¹²

However, recent behavioral^{3,13-17} and fMRI^{18,19} evidence indicates that abnormal

encoding also contributes to WM impairment in patients with schizophrenia. Parallel neurophysiological evidence from steady-state visual evoked potentials and time frequency analysis of electroencephalographic (EEG) signals also indicates dysfunctional early-stage visual processing.²⁰⁻²² In this study, we use event-related potentials (ERPs) to distinguish among the mechanisms that reflect different stages of visual WM, using the temporal resolution of ERPs to probe the early perceptual stages and the later, memory-related operations.²³

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Early visual processing is related to the P1 component.²⁴ It indexes the suppression of irrelevant information,^{25,26} a mechanism that seems to be necessary for efficient WM encoding.²⁷ It is also sensitive to spatial attention,^{25,26,28-30} which is required for subsequent processing of object features.³¹ Although the perceptual and cognitive processes probed by the P1 are thus highly relevant in the context of WM, most previous studies³² have shown no WM-related P1 amplitude effects. Conversely, the classic ERP component associated with memory processes is the P3.^{23,33} The P3 can be divided into a frontocentral P3a and a parietocentral P3b.³⁴ The P3a has been regarded as an index of the novelty of information and may be the neurophysiological correlate of the orienting response,³⁵ whereas the P3b is elicited by expected (but rare) task-relevant stimuli.³⁶ The P3b complex is similar during encoding and retrieval in its latency and duration.³⁷ Several studies^{23,33,38} have found that the P3b amplitude decreased and the P3 latency increased with WM load in delayed discrimination tasks like the one used in the present study. In contrast to the P3b evoked with oddball paradigms, the P3b elicited by a WM task can be divided into 2 peaks: the first most likely reflecting stimulus evaluation and the second reflecting consolidation during encoding and template matching during retrieval.^{23,33}

The classic view that only late components such as the P3 are abnormal in schizophrenia, whereas early visual processing is unimpaired,^{39,40} has recently been challenged.⁴¹⁻⁴⁴ A growing body of evidence indicates abnormalities in schizophrenia of the P3⁴⁵⁻⁴⁷ and changes in early potentials, such as the auditory P50⁴⁸ and the visual P1.⁴¹⁻⁴⁴

To minimize the confounders of chronic illness and long-term medication use, we investigated ERP changes during the performance of a WM task in adolescents with a recent onset of schizophrenia (mean illness duration, 1.4 years). Compared with adult-onset schizophrenia, early-onset schizophrenia, the manifestation of the illness by the age of 18 years,^{49,50} seems to represent a rarer, more homogeneous form of the disorder with a higher genetic loading⁵¹ and a more severe and unremitting outcome.⁵² Its study might thus lead to more salient and consistent findings.

We investigated ERP responses related to early visual and subsequent memory-related processes during WM encoding and retrieval in adolescent patients with early-onset schizophrenia. We designed a delayed discrimination task using abstract visual shapes as stimuli and manipulated WM load by varying the number of sample stimuli in the encoding period. We focused on the following components: P1, P3a, and the early and late P3b peaks (P370 and P570). We aimed to identify ERP components sensitive to increasing WM load and group differences and to clarify which processing stages are disrupted.

If early perceptual dysfunction contributes to WM deficits, we expect reduced P1 responses to the sample stimuli. If switching from the encoding of the already presented stimuli (ie, the first stimulus of load 2 and the first and second stimuli of load 3) to that of the subsequently presented stimuli (ie, the second stimulus of load 2 and the second and third stimuli of load 3) is impaired, we would expect a reduced P3a to the subsequently presented stimuli

in the patient group. If stimulus evaluation or consolidation is abnormal, we expect a reduction in the first or 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,^{24,28-30} 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-IV⁵⁶ and thorough medical record review. Current clinical symptoms were assessed with the Positive and Negative Syndrome Scale.⁵⁵ 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 WM⁵⁷ was implemented on a personal computer using the Experimental-Run-Time-System software (www.berisoft.com) (**Figure 1**). 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

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

Characteristics	Patients With Schizophrenia (n=17)	Controls (n=17)	P Value
Mean age (range), y	17.9 (15.2-20.4)	17.5 (15.1-19.9)	.48 ($t_{32}=0.87$)
Sex, No.			>.99 ($\chi^2=0$)
Male	11	11	
Female	6	6	
Handedness, No.			>.99 ($\chi^2=0$)
Right	13	13	
Left	4	4	
Mean (SD) premorbid IQ ^a	96 (16)	97 (9)	.83 ($t_{32}=-0.21$)
Mean (SD) length of illness, y	1.4 (0.9)		
Mean (SD) age at disease onset	16.5 (1.2)		
Mean (SD) PANSS score	44.9 (18.4)		
Neuroleptic medication use, No.			
Quetiapine fumarate	10		
Risperidone	2		
Clozapine	1		
Olanzapine	1		
Aripiprazole	2		
Perphenazine	1		
Mean (SD) chlorpromazine equivalents, mg/d ⁵³	188.7 (166.0)		

Abbreviation: PANSS, Positive and Negative Syndrome Scale.⁵⁵

^aPremorbid IQ was measured with the Mehrfachwahl-Wortschatz-Intelligenztest,⁵⁴ the German equivalent of the National Adult Reading Test.

the average reference. Recording, digitization, and processing of the EEG data were performed with a BrainAmp amplifier and the BrainVision Recorder software (Brain Products, Munich, Germany). The EEG was recorded at a sampling rate of 500 Hz with a system bandpass between 0 and 100 Hz. Impedance was kept below 5 k Ω .

The EEG data during encoding and retrieval were analyzed for ERPs with the BrainVision Analyzer software (Brain Products). The EEG data were averaged in intervals from -300 milliseconds before to 1000 milliseconds after stimulus onset and baseline corrected from -100 milliseconds to stimulus onset. Epochs were excluded automatically if the amplitudes exceeded a threshold of ± 100 μ V. Only correct trials were entered into the analysis. To assess encoding, we analyzed the final sample stimulus in each WM load condition (ie, the first stimulus for a load of 1, the second stimulus for a load of 2, and the third for a load of 3). This approach ensured an equal number of stimuli for each condition and, more important, maximized the effect of prior processing in the WM load conditions.

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, Oz (central occipital 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 (central parietal electrode), 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 \times 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 WM load resulted in a monotonic increase in the component

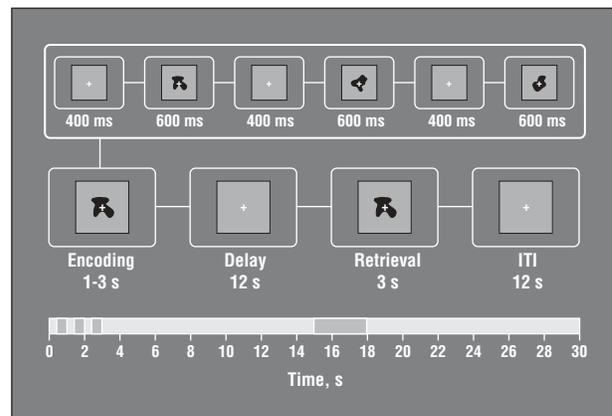


Figure 1. Working memory paradigm. The visual delayed discrimination task used abstract shapes. The working memory load was varied by presenting 1, 2, or 3 objects for encoding for 600 milliseconds each, with an interstimulus interval of 400 milliseconds (ms). After a 12-second delay, a probe stimulus was presented for 3 seconds. Participants had to judge whether or not it was part of the initial sample set by pressing a button. This was followed by an intertrial interval (ITI) of 12 seconds.

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.

fMRI 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 \times 220 mm²; voxel size, 3.43 \times 3.43 \times 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

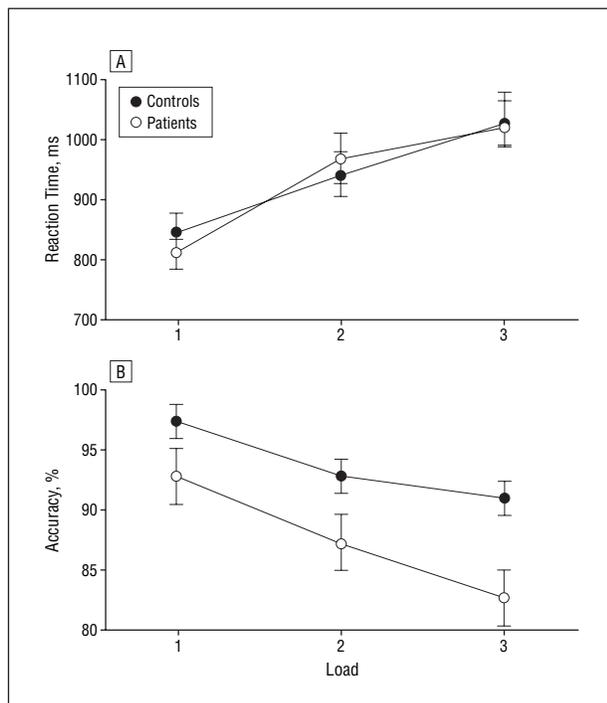


Figure 2. Mean reaction time (A) and mean accuracy (B) (percentage of correct answers) in response to working memory loads 1, 2, or 3 in controls and patients with schizophrenia. Error bars represent standard error.

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.⁵⁸

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.⁵⁹ 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 β 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 mm³). We searched for areas that showed this effect during encoding or retrieval within a 15-mm radius of the P1 coordinates reported by Noesselt et al²⁹ (left hemisphere: –39, –74, 4; right hemisphere: 32, –75, 6; Talairach space⁵⁸).

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 be-

tween 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: $F_{2,31} = 0.36$, $P = .69$) 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 Pz). 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 ($F_{1,15} = 6.42$, $P = .02$). 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.

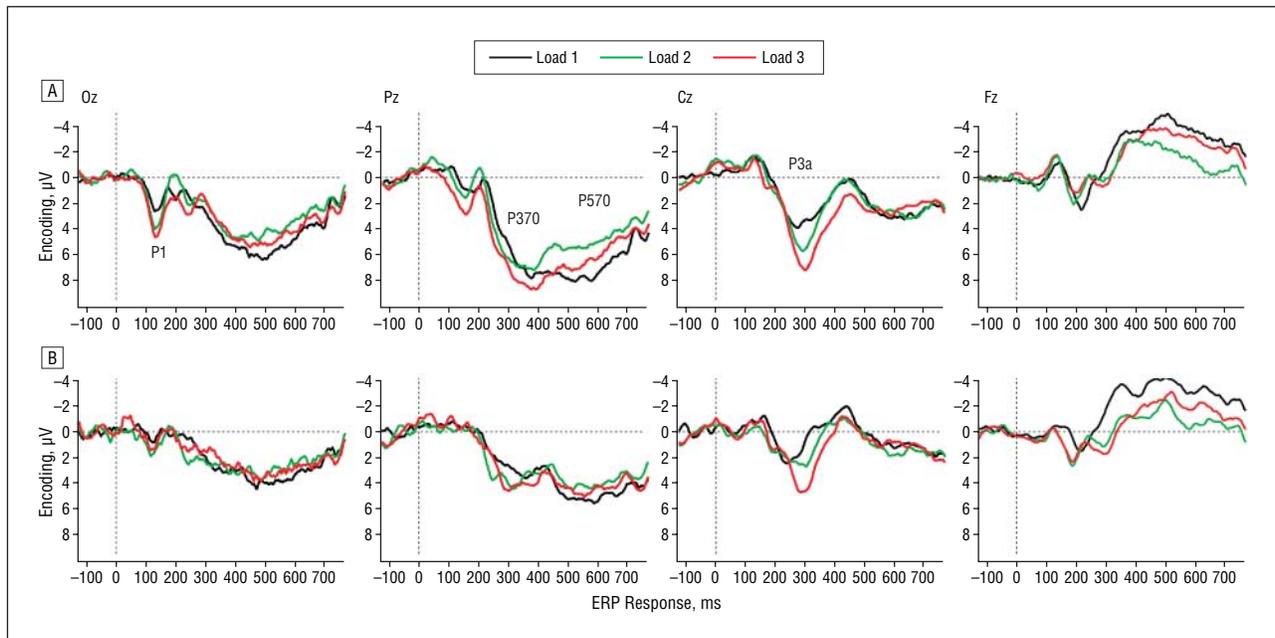


Figure 3. Event-related potentials (ERPs) during working memory (WM) encoding. The ERP responses after the first sample stimulus for WM load 1 (black line), the second stimulus for WM load 2 (green line), and the third stimulus for WM load 3 (red line) are shown at the central occipital electrode (Oz), 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.

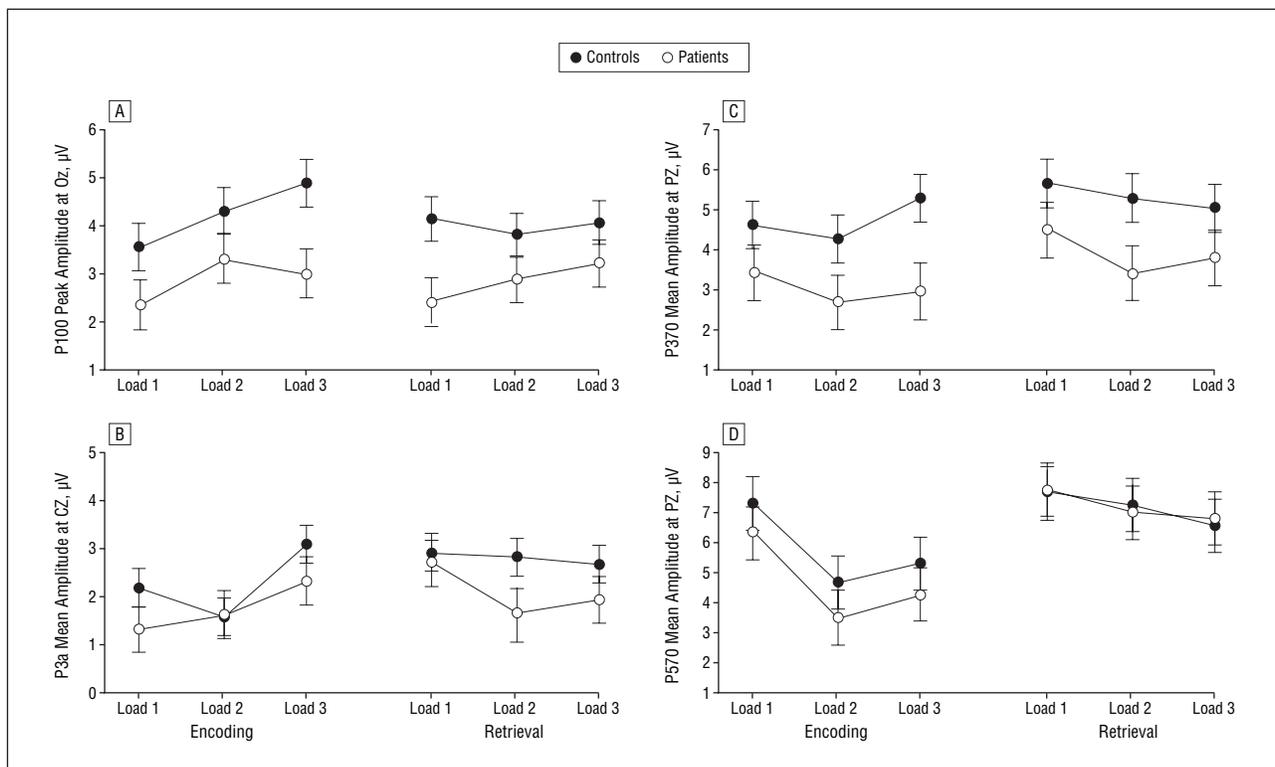


Figure 4. Peak and mean event-related potential (ERP) amplitudes. The P1 peak amplitude at the central occipital electrode (Oz) (A), P3a mean amplitude at the vertex electrode (Cz) (B), and P370 (C) and P570 (D) mean amplitude for the central parietal electrode (Pz) in response to working memory load 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) la-

tency 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).

Table 2. Amplitudes and Latencies During Encoding^a

Encoding	Mean (SE) Amplitude, μ V			Mean (SE) Latency, ms		
	WM Load 1	WM Load 2	WM Load 3	WM Load 1	WM Load 2	WM Load 3
P1						
Controls	3.55 (0.53)	4.32 (0.44)	4.91 (0.51)	125 (5)	132 (3)	137 (5)
Patients	2.32 (0.59)	3.3 (0.59)	2.99 (0.56)	149 (6)	136 (5)	134 (6)
Effect size (d) ^b	0.53	0.51	0.87			
P3a	2.15 (0.37)	1.53 (0.41)	3.07 (0.45)	282 (14)	264 (10)	292 (5)
Controls						
Patients	1.27 (0.37)	1.57 (0.56)	2.31 (0.64)	285 (15)	277 (16)	302 (11)
P370						
Controls	4.59 (0.47)	4.24 (0.55)	5.26 (0.73)	387 (12)	353 (13)	374 (14)
Patients	3.39 (0.37)	2.63 (0.55)	2.9 (0.65)	399 (11)	320 (10)	360 (11)
Effect size (d) ^b	0.70	0.72	0.81			
P570						
Controls	7.28 (0.7)	4.6 (0.42)	6.37 (0.63)	556 (13)	555 (17)	593 (24)
Patients	6.3 (0.7)	3.42 (0.73)	4.21 (0.87)	555 (14)	596 (23)	552 (17)

Abbreviation: WM, working memory.

^aData 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.

^bEffect sizes were calculated for significant group differences.

The mean amplitude increased with WM load (Cz: main effect load: $F_{2,31}=9.49$, $P<.001$). 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 ($F_{1,15}=9.46$, $P=.04$). 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 \times 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

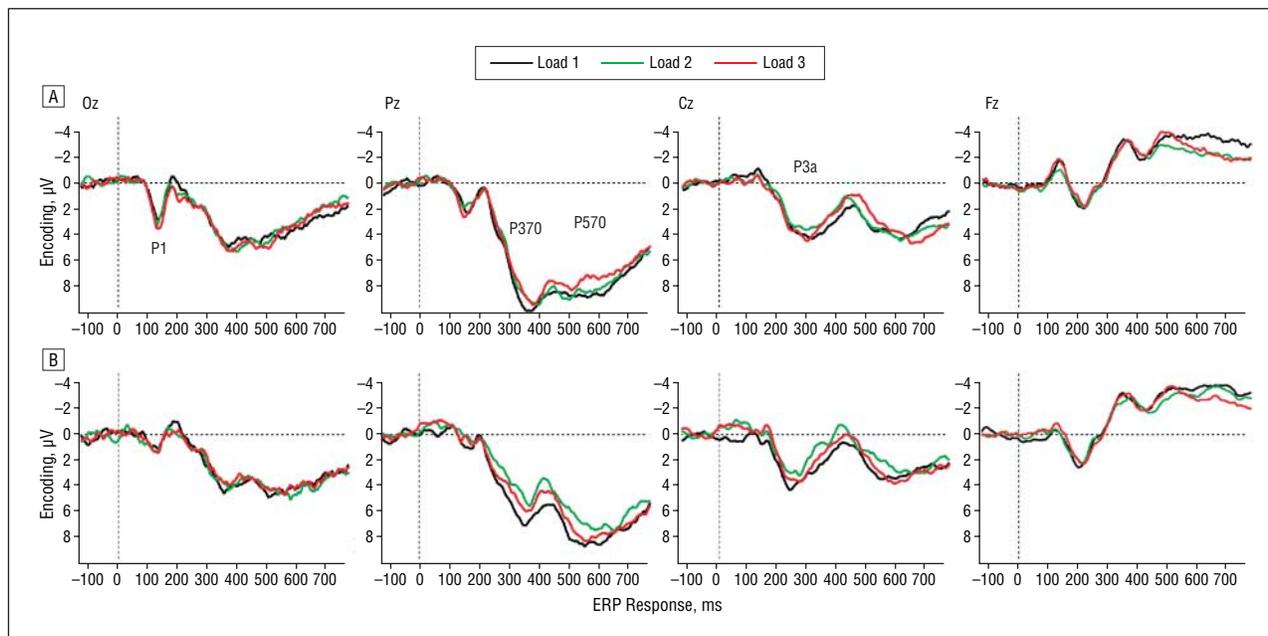


Figure 5. Event-related potential (ERPs) during working memory (WM) retrieval. The ERP responses after the test stimulus for WM load 1 (black line), WM load 2 (green line), and WM load 3 (red line) are shown at the central occipital electrode (Oz), the central parietal electrode (Pz), the vertex electrode (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 Retrieval^a

Retrieval	Mean (SE) Amplitude, μ V			Mean (SE) Latency, ms		
	WM Load 1	WM Load 2	WM Load 3	WM Load 1	WM Load 2	WM Load 3
P1						
Controls	4.15 (0.41)	3.81 (0.47)	4.07 (0.41)	128 (5)	139 (4)	137 (2)
Patients	2.39 (0.40)	2.86 (0.55)	3.20 (0.55)	133 (5)	125 (6)	130 (6)
Effect size (d) ^b	1.10	0.45	0.47			
P3a						
Controls	2.9 (0.47)	2.81 (0.42)	2.66 (0.50)	297 (12)	298 (14)	282 (11)
Patients	2.68 (0.63)	1.62 (0.49)	1.90 (0.50)	279 (17)	314 (20)	280 (14)
P370						
Controls	5.64 (0.63)	5.27 (0.49)	5.02 (0.61)	375 (13)	376 (12)	372 (11)
Patients	4.46 (0.51)	3.37 (0.45)	3.76 (0.52)	376 (14)	364 (16)	364 (15)
Effect size (d) ^b	0.47	0.99	0.55			
P570						
Controls	7.67 (0.85)	7.24 (0.80)	6.53 (0.79)	534 (15)	533 (15)	532 (15)
Patients	7.75 (0.80)	6.99 (0.83)	6.79 (0.83)	559 (12)	583 (18)	581 (14)

Abbreviation: WM, working memory.

^aData 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.

^bEffect sizes are calculated for significant group differences.

WM load in patients ($F_{1,15}=7.07$, $P=.02$) but not in controls ($F_{1,15}=0.01$, $P=.92$). 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 ($F_{1,32}=0.17$, $P=.68$). The mean amplitude

was significantly smaller in patients than in controls ($F_{1,32}=4.12$, $P=.05$). The mean amplitude decreased significantly with increasing WM load ($F_{2,31}=5.78$, $P=.006$) (Figures 4 and 5 and Table 3). The load-dependent decrease was only statistically significant in patients (quadratic contrast: $F_{1,15}=10.09$, $P=.006$; linear contrast: $F_{1,15}=3.62$, $P=.08$) but not in controls (quadratic contrast: $F_{1,15}=0.05$, $P=.82$; linear contrast: $F_{1,15}=2.64$, $P=.12$). A significant correlation was found between P370 amplitude and accuracy at WM load 3 ($r=0.7$, $P=.002$).

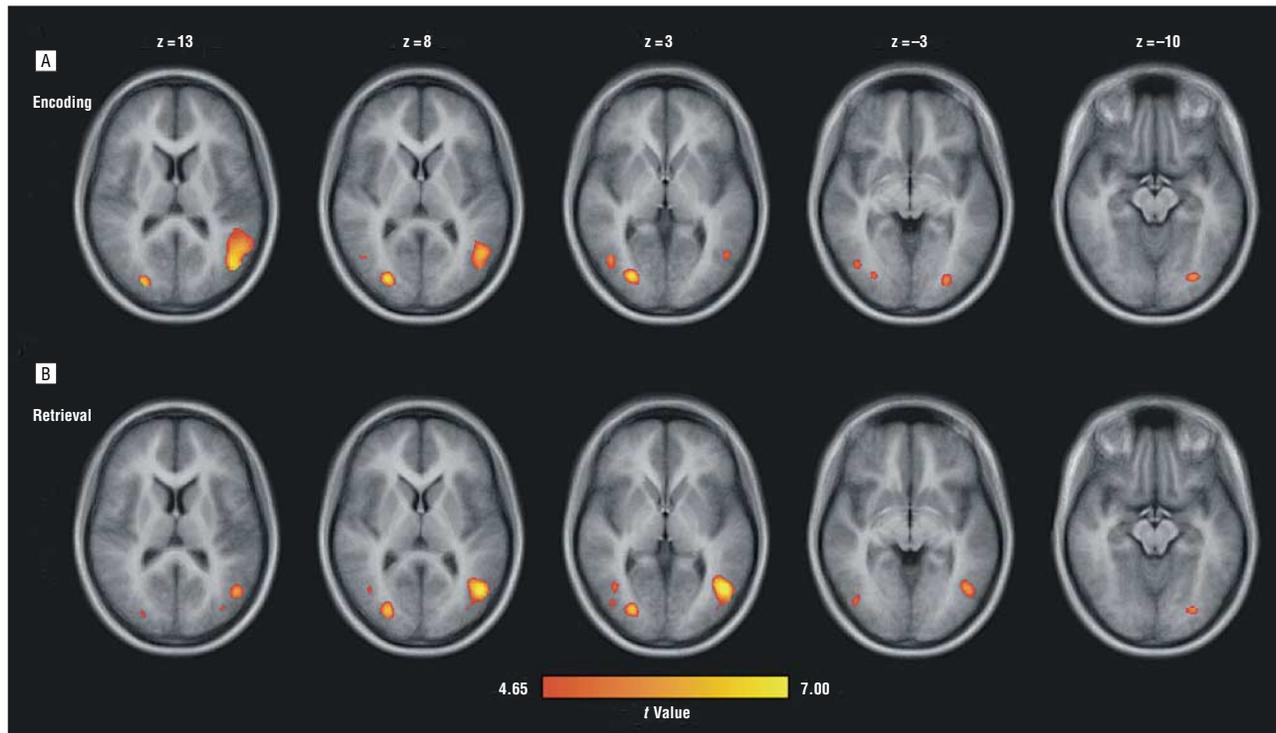


Figure 6. Functional magnetic resonance imaging (fMRI) group differences in visual areas during encoding and retrieval. Visual areas with a significant group difference during encoding or retrieval ($P < .000005$, minimum cluster size of 10 mm³) in the fMRI analysis depicted on the average brain of all 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.^{42,47} 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^a

ROI	BA	Talairach ^b			Cluster Size, mm ³	ROI-Based Group Contrasts (<i>t</i>) ^c		
		x	y	z		WM Load 1	WM Load 2	WM Load 3
Encoding								
Left GOM	19	-28	-78	-8	1010	0.01	3.12 ^d	2.68 ^e
Right GOM	19	26	-77	6	1585	0.29	3.26 ^d	2.74 ^e
Left GTs/GTm	22/39	-47	-57	14	5726	0.65	3.10 ^d	3.59 ^d
Right GTi	37	42	-65	2	658	-0.03	2.25 ^e	2.74 ^e
Retrieval								
Left GOM	18/19	-28	-77	-10	224	2.79 ^d	2.44 ^e	1.64
Left GOM	19	-35	-76	13	135	2.48 ^e	2.06 ^e	2.34 ^e
Right GOM	19	26	-77	6	1102	4.13 ^d	3.01 ^d	1.83
Left GTm	37	-44	-62	5	3716	3.98 ^d	2.64 ^e	2.34 ^e
Right GTi	37	40	-66	1	679	3.19 ^d	3.67 ^d	1.03

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.

^aVisual 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.

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

^cThe *t* values are listed for ROI-based 2-tailed *t* tests comparing group differences for individual WM load conditions.

^d $P < .01$.

^e $P < .05$.

decreased with increasing WM load in controls. We found correlations of P370 amplitudes with performance in controls for the higher WM load conditions during encoding and retrieval. A similar effect was found for the P1 and P570 only for encoding. Thus, both early activity of sensory areas, reflected by the P1, and later cognitive processes, as indexed by the subcomponents of the P300, seem to be crucial for effective memory performance in healthy controls. However, linear regression analysis revealed that a stronger P1 amplitude augmentation with increasing WM load predicted better performance. This finding suggests that P1 is of particular relevance for successful WM encoding.

This WM load-dependent modulation of component amplitudes was absent or greatly attenuated in the patients with the exception of a linear WM load effect on the P3a component. The P3a is elicited by items for which no memory template is available but reorienting is required,⁶⁰ which suggests that patients were still able to refocus on each new stimulus. In contrast, the P370 was significantly smaller in patients, which suggests a deficit in the categorization or evaluation of the stimuli.

During retrieval there was no effect of WM load on P1 in either group. Only patients demonstrated a decrease in P3a and P370 amplitude with increasing WM load. Both groups showed a linear decrease in P570. The amplitude reduction in P370 during retrieval suggests that patients have a deficit in the evaluation of the probe stimulus against the stimulus representations held in memory. The normal amplitude and the prolonged latency of the second peak (P570) suggest that template matching takes longer but that the neuronal substrate for this matching process is probably unimpaired.

One possible confounder is the sensitivity of the P3 components to probability effects. The intermixed sequence of WM load conditions in our experiment may thus have had an influence on the P3 load effects. However, we did not

find any significant WM load \times group interaction effects during encoding. Thus, the P3 deficit in patients cannot be attributed to reduced expectancy.^{46,61}

Notably, a neural deficit in patients was already evident for P1 during encoding and retrieval. In our complementary fMRI analysis of extrastriate visual areas, we observed reduced activation for patients during encoding and retrieval in highly overlapping brain areas. During encoding, group differences were particularly pronounced for the highest WM load conditions, which matched the P1 deficit. During retrieval, group differences were more pronounced for the lowest WM load conditions, again mirroring the P1 data. The considerable overlap of group effects for encoding and retrieval in visual areas in the fMRI data shows that mostly the same brain regions contribute to the P1 deficit irrespective of the precise behavioral relevance of the stimuli. However, this overlap might also point to impaired stimulus encoding during both sample and probe presentation in patients.

Reduced P1 amplitudes in schizophrenia have been reported in several studies,⁴¹⁻⁴⁴ but this is the first study, to our knowledge, to do so for early-onset schizophrenia. The decreased blood oxygenation level-dependent signal in extrastriate visual areas observed in our patients implicates reduced neuronal activity as a reason for the P1 deficit. Recent evidence suggests a reduction in the total number of neurons⁶² in the visual cortex in patients with schizophrenia and disruptions of occipital white matter,⁵⁰ which seem to be related to reduced ERP amplitudes.²¹ However, other factors may also play a role, for instance, increased neuronal response variability^{63,64} in patients. Deficits in magnocellular stream processing have been linked to the P1 attenuation.⁴¹⁻⁴⁴ This occurrence could lead to reduced precision with which temporal transients are signaled and thus to reductions in response timing (synchrony).^{22,65,66} Furthermore, dysfunctions in thalamocortical circuits have been associated with reduced inhibition of irrelevant

information⁶⁷ and could give rise to reduced α phase reset that in part generates the P1.⁶⁸

This is the first report, to our knowledge, of a WM load-dependent increase in P1 during encoding. Such a modulation implies a role of P1-related processes for WM. Indeed, better performance could be predicted by a larger P1 increase with WM load. The use of semantically accessible stimuli (eg, letters or numbers) could explain why earlier studies failed to find an effect of WM load on P1.³² Our complex visual shapes probably required more detailed processing to establish perceptual representations for subsequent WM encoding. This would include the inhibition of irrelevant information, spatial shifts of attention required for object feature processing, and feedback from higher intramodal and supramodal areas.⁶⁹ These operations have been associated with the P1 component^{25,26,70-72} and seem to be necessary for further object processing³¹ and encoding into WM.²⁷ The rapid presentation of up to 3 objects makes these processes particularly demanding, which should increase the likelihood that deficits in patients reflected by reduced P1 amplitude contribute to disturbed WM encoding. However, because the P1 is modulated by spatial selective attention only to a small degree, it is unlikely that impaired 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 investigate if the WM load-dependent P1 increase is due to sensitization of sensory processes.⁷³

In summary, adolescents with early-onset schizophrenia demonstrated an attenuated P1 component, an absence of a P1 WM load modulation, and reduced blood oxygenation 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 memory⁷⁴ and auditory sensory memory.⁷⁵ Although sufficient stimulus presentation time may facilitate encoding and normalize WM performance,¹⁷ impairments in WM maintenance still persist when encoding difficulty is adjusted for by reducing stimulus complexity.¹⁴ The influence of impaired encoding on WM maintenance may be further illuminated by analyzing slow potentials⁷⁶ or time frequency patterns.^{77,78} An integration of the present ERP approach with anatomical connectivity^{50,79,80} and EEG measures of functional connectivity^{22,81} will be paramount to further elucidate the underlying neural deficits.

Both impaired P1 generation⁸² and WM dysfunction^{7,8} have been found in unaffected first-degree relatives 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 integration into a composite endophenotype might provide a more robust marker of genetic vulnerability for schizophrenia.⁸⁴

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