

Impaired Visual Object Recognition and Dorsal/Ventral Stream Interaction in Schizophrenia

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Background: Schizophrenia is associated with well-documented deficits in high-order cognitive processes such as attention and executive functioning. The integrity of sensory-level processing, however, has been evaluated only to a limited degree. Our study evaluated the ability of patients with schizophrenia to recognize complete objects based on fragmentary information, a process termed *perceptual closure*. Perceptual closure processes are indexed by closure negativity (N_{cl}), a recently defined event-related potential (ERP) component that is generated within the visual association cortex. This study assessed the neural integrity of perceptual closure processes in schizophrenia by examining N_{cl} generation. Generation of the preceding positive (P1) and negative (N1) ERP components was also examined.

Methods: We evaluated 16 patients with chronic schizophrenia and 16 healthy comparison subjects. Successively less fragmented images were presented during high-density ERP recording, which permitted the monitoring of brain activity during perceptual closure processes prior to object recognition. Analyses were performed at parieto-occipital and occipitotemporal

sites consistent with dorsal and ventral stream generators of P1, N1, and N_{cl} .

Results: Patients with schizophrenia showed significant impairment in the ability to recognize fragmented objects, along with impaired generation of N_{cl} . The amplitude of visual P1 was significantly reduced, particularly over dorsal stream sites. In contrast, the generation of visual N1 was intact.

Conclusions: Patients with schizophrenia are profoundly impaired in perceptual closure as indicated by both impaired performance and impaired N_{cl} generation. The selective impairment in dorsal stream P1 is consistent with prior reports of impaired magnocellular processing in schizophrenia. By contrast, intact ventral N1 generation suggests that the initial stages of ventral stream processing are relatively preserved and that impaired magnocellular dorsal stream functioning in schizophrenia may lead to secondary dysregulation of ventral stream object recognition processing.

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SCHIZOPHRENIA MANIFESTS itself in symptoms that encompass a wide range of human mental activities.¹ Deficits in high-order processes such as working memory and executive processing have been extensively studied. In contrast, relatively little attention has been paid to disturbances in perceptual processing, as can be demonstrated in the auditory, visual, and somatosensory modalities.² In the visual modality, patients with schizophrenia show deficits in eye tracking and motion perception and require prolonged viewing time to recognize briefly presented stimuli.³⁻⁵ Patients also demonstrate increased sensitivity to visual backward masking, which is associated with impaired functioning of the magnocellular visual pathway.⁶⁻⁸ Severity of visual-processing deficits in schizophrenia correlates with poor outcome on social-functioning measures.⁹ Therefore, mechanisms underlying visual-

processing dysfunction in schizophrenia may be informative regarding the underlying cause of the disease.

One process that may be particularly amenable to neurophysiological dissection is perceptual closure.¹⁰ This term refers to the apparent filling-in of missing information by the visual system during partial viewing conditions.^{11,12} This process, for example, allows one to recognize a complete object (eg, a cat) even when that object is partially hidden from view (eg, located behind a venetian blind).

The process of object recognition/perceptual closure can be studied in a laboratory setting using fragmented images and is indexed by the generation of a specific event-related potential (ERP) component termed *closure negativity* (N_{cl}). The N_{cl} increases gradually in amplitude as stimuli are presented in progressively less fragmented forms using an ascending method of limits (**Figure 1**). At the point of identification, N_{cl} amplitude increases

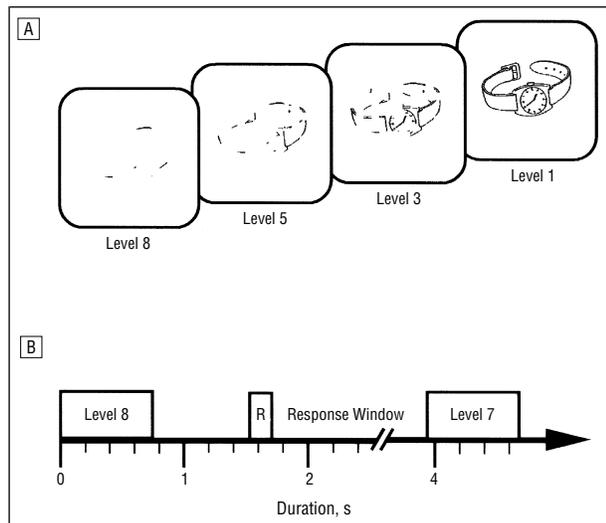


Figure 1. Stimulus configuration. A, Images displayed from least complete to most complete (4 of 8 levels shown). B, Onset of the most fragmented image (level 8) at 0 milliseconds (duration, 750 milliseconds), followed by a yes/no response prompt (R) (duration, 200 milliseconds) at 1550 milliseconds. A no response resulted in presentation of the next-level image 2.2 seconds after the response prompt. A yes response terminated the sequence for the subject's verbal response.

discontinuously, suggesting that N_{cl} generation indexes the perceptual closure process.^{13,14}

A prior study demonstrated that patients with schizophrenia were impaired in their ability to recognize fragmented images even though they benefited equally to controls from manipulations such as object repetition or word priming.¹⁰ This pattern suggests that object recognition deficits in schizophrenia are due to a bottom-up disruption of processing at the level of the visual association cortex rather than top-down dysregulation. The goal of our study was to evaluate the degree to which object recognition deficits in schizophrenia are accompanied by impaired generation of the visual N_{cl} component.

Closure negativity, the N_{cl} , occurs with an approximate peak latency of 290 milliseconds and is localized over lateral occipital scalp regions overlying a system of visual association regions termed the *lateral occipital complex* (LOC). The visual system has 2 main subdivisions.^{15,16} The dorsal stream receives input primarily from the magnocellular division of the lateral geniculate nucleus (LGN) and extends from early visual areas through the occipitoparietal cortex. This system is specialized for processing location information along with properties such as movement, depth, and positional relationships (the "where" system). In contrast, the ventral stream receives input primarily from the parvocellular division of the LGN and extends through the occipitotemporal cortex. This system is specialized for the processing of object form (the "what" system). Featural processing is thus more complex within the ventral stream, and transmission times are slower in ventral than in dorsal visual pathways.¹⁷⁻¹⁹ The LOC occupies the highest tier of the ventral visual stream and plays a critical role in object recognition. The relatively long latency of N_{cl} along with its bilateral occipitotemporal distribution suggests that it indexes activity within the LOC. Impaired N_{cl} generation would reflect impaired activa-

tion of the LOC, which is related to impaired perceptual closure in schizophrenia.

In the paradigm used for our study, N_{cl} is preceded by additional components that reflect prior stages of visual information processing. The surface-positive component (P1) peaks at approximately 100 milliseconds and arises from generators in both dorsal and ventral streams.²⁰⁻²⁵ The dorsal contribution to P1 is best represented at parieto-occipital electrodes (eg, PO5/PO6), whereas the ventral contribution is distributed over the occipitotemporal electrodes (eg, T5/T6). Dorsal activity begins prior to ventral activity. The negative deflection (N1) peaks at around 164 milliseconds and reflects initial stages of form discrimination in the LOC.^{15,26-28} Surface distributions of N1 and N_{cl} are therefore similar. Our study assesses not only N_{cl} generation in schizophrenia but also the generation of earlier ERP components.

In addition to receiving ventral stream input, the LOC receives crossover input from the dorsal visual stream. From behavioral studies alone, it is impossible to determine whether perceptual closure deficits in schizophrenia reflect intrinsic dysfunction of the LOC as compared with impaired afferent information flow. Patients with schizophrenia show consistent deficits on tasks that assess dorsal stream functioning, including velocity discrimination, coherent motion, eye tracking, and spatial localization.^{3,4,29,30} In contrast, early processing within ventral stream visual regions may be intact. By assessing P1 and N1 along with N_{cl} , this study evaluates the degree to which deficits in N_{cl} generation are driven by impaired information flow through dorsal as opposed to ventral visual stream regions.

METHODS

SUBJECTS

Written informed consent was obtained from 16 individuals (3 women) with chronic schizophrenia and 16 healthy control subjects (4 women) following a full description of the study procedures. Demographic information for patients and controls is given in **Table 1**. Patients with schizophrenia and control subjects were of similar age (mean \pm SD, 38.3 ± 8.8 years and 33.7 ± 10.9 years for patients and controls, respectively; $t_{30} = 1.31$; $P = .20$). All subjects reported normal or corrected-to-normal vision. A subset of the control subjects ($n = 9$) had participated in our prior studies.^{13,14} Controls were free of psychiatric illness or symptoms by self-report using criteria from the *Structured Clinical Interview for DSM-III-R—Non-Patient Edition*,³¹ and denied alcohol or substance abuse. Patients with schizophrenia were recruited from inpatient and outpatient facilities associated with the Nathan Kline Institute for Psychiatric Research, Orangeburg, NY. All patients were taking medication at the time of testing. Positive and Negative Syndrome Scale ratings were performed by a single rater. Factors were defined according to White et al.³² Although all patients were receiving antipsychotic medication at the time of testing, there was no significant correlation between dose and ERP amplitude.

STIMULI AND TASK

The stimuli and procedure were identical to those in our previous study.¹³ Subjects were presented with between 350 and 400 sets of line drawings of animate and inanimate objects

obtained from previous studies.^{33,34} Each set consisted of 7 to 8 images with progressively greater fragmentation. Images from each set were presented in accordance with the ascending method of limits, from least complete (levels 7 and 8) to most complete (level 1), as shown in Figure 1A.³⁵ After the presentation of each fragmented image, a yes/no cue appeared, prompting a forced-choice response either orally or by pressing a button. Following yes responses, the picture sequence for that set was terminated, and subjects were required to verbally name the picture. Thereafter, a sequence incorporating a new picture set was presented. The entire experiment consisted of 35 to 40 blocks, each containing 10 picture sequences. Each image appeared for 750 milliseconds, followed by a blank screen for 800 milliseconds, followed by a yes/no response prompt, as shown in Figure 1B. Subjects' response window extended for 2300 milliseconds from the onset of the prompt. Use of the response prompt diminishes the effect of motor responses on sensory ERP.

MEASUREMENTS AND ANALYSES

High-density ERPs were acquired from 64 scalp electrodes (impedance <5 k Ω) referenced to the nose using an electrode cap (Electrocap International, Inc; Eaton, Ohio). Electrical activity was amplified (amplification $\times 20000$, bandpass: 0.05-100 Hz) and digitized at 500 Hz (SynAmp amplifiers; Neuroscan, Herdon, Va). Activity was continuously recorded to a disk along with digital stimulus event markers. Epochs (-100 to 700 milliseconds) were created offline.

Epochs with amplitude exceeding ± 100 μ V at any electrode site during the -100- to 450-millisecond interval were excluded from further averaging. Mean \pm SD rejection rates of trials across conditions were 6.7% \pm 7.5% for controls and 23.7% \pm 16.1% for patients. The mean \pm SD number of accepted sweeps per condition for control subjects was 362 \pm 37 for identification (ID), 354 \pm 41 for 1-prior (1 level of fragmentation prior to ID), 342 \pm 36 for 2-prior (2 levels prior to ID), and 305 \pm 43 for 3-prior (3 levels prior to ID). The mean \pm SD number of accepted sweeps per condition for patients with schizophrenia was 275 \pm 80 for ID, 265 \pm 78 for 1-prior, 250 \pm 74 for 2-prior, and 223 \pm 73 for 3-prior. The ERP averages typically become stable following 20 to 30 sweeps. The number of sweeps collected was sufficient to reduce contributions of the background EEG by 1.5 to 2.5 orders of magnitude.

Baseline was defined as the mean voltage across -100 to 20 milliseconds. A priori analyses^{13,14} examined between-group differences in amplitude of P1, N1, and N_{c1}. For P1 and N1, amplitude measures were derived from a 20-millisecond window centered at the estimated peak latency for each component (P1: 100 milliseconds; N1: 164 milliseconds). For N_{c1}, a broader component, amplitude measures were derived from a 40-millisecond window centered at its estimated peak latency of 290 milliseconds.¹³ Analyses were performed across 3 pairs of scalp electrodes (parietal sites P5 and P6, parieto-occipital sites PO5 and PO6, and occipitotemporal sites T5 and T6). Data from 1 patient with schizophrenia were excluded from all tests that included site T6 because of a broken contact at that electrode site.

The ERP data were also inspected post hoc for further components of interest. Two additional components, an early and late bilateral frontal positivity, were identified. The amplitude of the early frontal positivity was measured within a 20-millisecond window centered at its estimated peak latency of 126 milliseconds at 3 pairs of frontocentral sites (F1/F2, F3/F4, and FC1/FC2). Data from 1 patient were excluded from all tests that included site F2 because of a broken contact at that electrode site. The amplitude of the late frontal positivity (onset, approximately 300 milliseconds) was tested at F3/F4.

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

Diagnosis	
Schizophrenia	14
Schizoaffective disorder	2
Employed	
Yes	9
No	6
Student	1
Use of neuroleptics	
Atypical	13
Typical	1
Both	2
Chlorpromazine daily equivalent, mean \pm SD	1228.63 \pm 292.45
Clinical Global Impressions scale score, mean \pm SD	3.81 \pm 0.83
Education, mean \pm SD, y	12.5 \pm 2.88
Illness duration, mean \pm SD, y	15.94 \pm 8.26
IQ, mean \pm SD	99.41 \pm 9.53
Laterality quotient, mean \pm SD	0.61 \pm 0.51
Positive and Negative Syndrome Scale scores, mean \pm SD	
Positive symptoms	12.38 \pm 4.19
Negative symptoms	15.75 \pm 4.06
Autistic preoccupation	11.69 \pm 2.65
Activation	7.13 \pm 2.55
Dysphoria	12.56 \pm 2.99

*Data are presented as number of patients (n = 16) unless otherwise indicated.

Components were analyzed using repeated-measures multivariate analysis of variance (MANOVA) equivalent to Wilks λ (SPSS statistical software; SPSS Inc, Chicago, Ill), with a between-subject factor of group (patients or controls) and within-subject factors including hemisphere and electrode location, as appropriate. Values in the text represent mean \pm SD.

RESULTS

BEHAVIORAL RESULTS

Stimuli were presented starting with the most fragmented version of each picture (level 7/8) and progressing to lower levels of fragmentation, terminating when subjects were able to identify the object or when the object was presented in its entirety (level 1). Control subjects correctly identified pictures 88% of the time, with a modal ID level of 3, consistent with prior findings.^{13,14} Patients with schizophrenia correctly identified pictures 85% of the time, with a modal ID level of 1. Hence, although patients with schizophrenia were nearly as accurate as controls when they did identify objects, they required significantly more information to do so. **Figure 2** illustrates the between-group performance difference.

ELECTROPHYSIOLOGICAL RESULTS

Closure Negativity: N_{c1}

Figure 3A shows group-averaged visual evoked potentials (VEPs) for the conditions at levels ID, 1-prior, 2-prior, and 3-prior. As in previous studies, waveforms from control subjects revealed a robust increase in activity in the

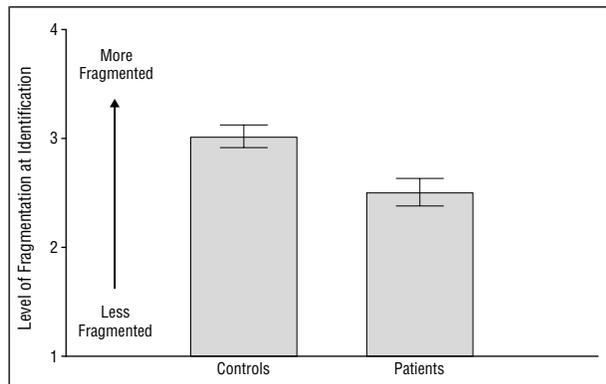


Figure 2. Behavioral performance: mean level of fragmentation at which object recognition was achieved for patients ($n=16$) and controls ($n=16$). For patients, $P<.005$. Error bars indicate SEM.

240- to 340-millisecond-latency range, corresponding to the N_{cl} component.

The N_{cl} amplitude was determined in both patients and controls by the construction of difference waves between the ERP for ID and 1-prior and for ID and 2-prior, followed by the determination of mean amplitude values within specified latency ranges. Mean values for both groups are shown in **Table 2**.

Between-group differences were evaluated by MANOVA across 3 symmetric pairs of electrode locations (P5/P6, T5/T6, and PO5/PO6). A highly significant main effect for group ($P<.008$ for all) was found in both ID/1-prior and ID/2-prior analyses. Scalp topographic distributions for patients and controls are shown in Figure 3B. Group \times electrode location (ID/1-prior: $F_{2,28}=0.41$; $P=.67$; ID/2-prior: $F_{2,28}=1.54$; $P=.23$) and group \times hemisphere (ID/1-prior: $F_{1,29}=2.35$; $P=.14$; ID/2-prior: $F_{1,29}=0.67$; $P=.42$) interactions were not significant between patients and controls, indicating similar topography of the potential in both groups. Mean \pm SD N_{cl} amplitude combined across hemispheres (P5/P6) for patients was -30.1 ± 33.4 μ V/ms (95% confidence interval [CI], -9.1 to -45.5), which was decreased by more than 60% ($t_{30}=3.31$; $P=.002$) relative to control subjects (-76.9 ± 49.1 μ V/ms [95% CI, -50.8 to -103.1]).

The groups differed in the level at which they achieved object recognition, with patients often requiring the complete picture. A control analysis, therefore, evaluated the degree to which this difference might have contributed to between-group differences in N_{cl} amplitude. Patients with schizophrenia showed significantly reduced N_{cl} amplitudes even when data were considered only from pictures identified at a noncomplete level; that is, level 2 or higher (ID/1-prior: $F_{1,29}=5.80$; $P=.03$; ID/2-prior: $F_{1,29}=6.30$; $P=.02$). Thus, the between-group difference in N_{cl} amplitude could not be attributed to the differential level of fragmentation at which ID was achieved in both groups.

The P1 Component

The P1 was defined as mean area within a 90- to 110-millisecond-latency range. **Figure 4A** shows P1 waveforms from electrodes overlying dorsal (PO5) and ven-

tral (T5) visual stream areas. Figure 4B shows scalp distributions for each group. A set of 3 MANOVAs (2 groups \times 2 hemispheres \times 3 electrode locations) tested for between-group differences in P1 amplitude at levels ID, 1-prior, and 2-prior, respectively. Mean amplitudes for P1 are reported in Table 2. All 3 analyses revealed a highly significant main effect for group, reflecting reduced P1 amplitude in patients relative to controls. Mean \pm SD P1 amplitude at the ID level combined across hemispheres (PO5/PO6) in patients was 68.9 ± 46.6 μ V/ms (95% CI, 44.1-93.7), which was decreased by more than 65% ($t_{30}=3.29$; $P=.003$) relative to that of control subjects (23.1 ± 30.4 μ V/ms [95% CI, 6.9-39.3]).

To test for between-group differences in the apparent increase in P1 amplitude from 2-prior to 1-prior to ID, a 4-way MANOVA was performed (2 groups \times 3 levels \times 2 hemispheres \times 3 electrode locations). As in the individual MANOVAs, there was a highly significant main effect for group ($F_{1,29}=18.14$; $P=.001$). There was also a highly significant main effect for level ($F_{2,28}=7.60$; $P=.002$) but no group \times hemisphere ($F_{1,29}=0.27$; $P=.61$) or group \times level ($F_{2,28}=0.07$; $P=.93$) interaction, indicating a similar degree of impairment in P1 generation across levels for patients with schizophrenia.

All MANOVAs revealed a highly significant group \times electrode location interaction ($F>6.11$ for all; $P<.007$ for all). To determine the basis for the interaction, follow-up analyses were conducted on 2 electrode pairs: the most dorsal pair (PO5/PO6) and the most ventral pair (T5/T6). Activity at both pairs of sites peaked at approximately 100 milliseconds for both groups. As shown in Figure 4A, controls demonstrated greater activity at dorsal vs ventral sites, whereas patients had similar amplitudes.

A MANOVA (2 groups \times 2 hemispheres \times dorsal/ventral stream electrode location) tested for differential contribution of putative P1 generators at level ID across groups. A significant main effect for group was found ($F_{1,29}=8.57$; $P=.007$), as was a significant group \times dorsal/ventral stream interaction ($F_{1,29}=12.11$; $P=.002$). This significant interaction may reflect the greater contribution of dorsal as opposed to ventral generators to the reduced P1 in patients with schizophrenia.

To further examine the group \times dorsal/ventral stream interaction, separate MANOVAs (2 groups \times 2 hemispheres) were performed for dorsal and ventral stream electrode locations. Between-group differences were greater at dorsal ($F_{1,30}=10.85$; $P=.004$) than ventral ($F_{1,29}=5.17$; $P=.04$) electrode locations. Because of spatial overlap between dorsal and ventral contributions, multivariate analysis of covariance (MANCOVA) was performed. The main effect for group persisted for dorsal sites following MANCOVA for ventral sites ($F_{1,27}=4.82$; $P=.04$). In contrast, this main effect was no longer significant following MANCOVA for dorsal sites ($F_{1,27}=1.37$; $P=.25$), indicating a primary contribution of the dorsal sites to the between-group deficit.

The N1 Component

The N1 was defined as mean area within a 154- to 174-millisecond-latency range (Figure 3A). A set of 3

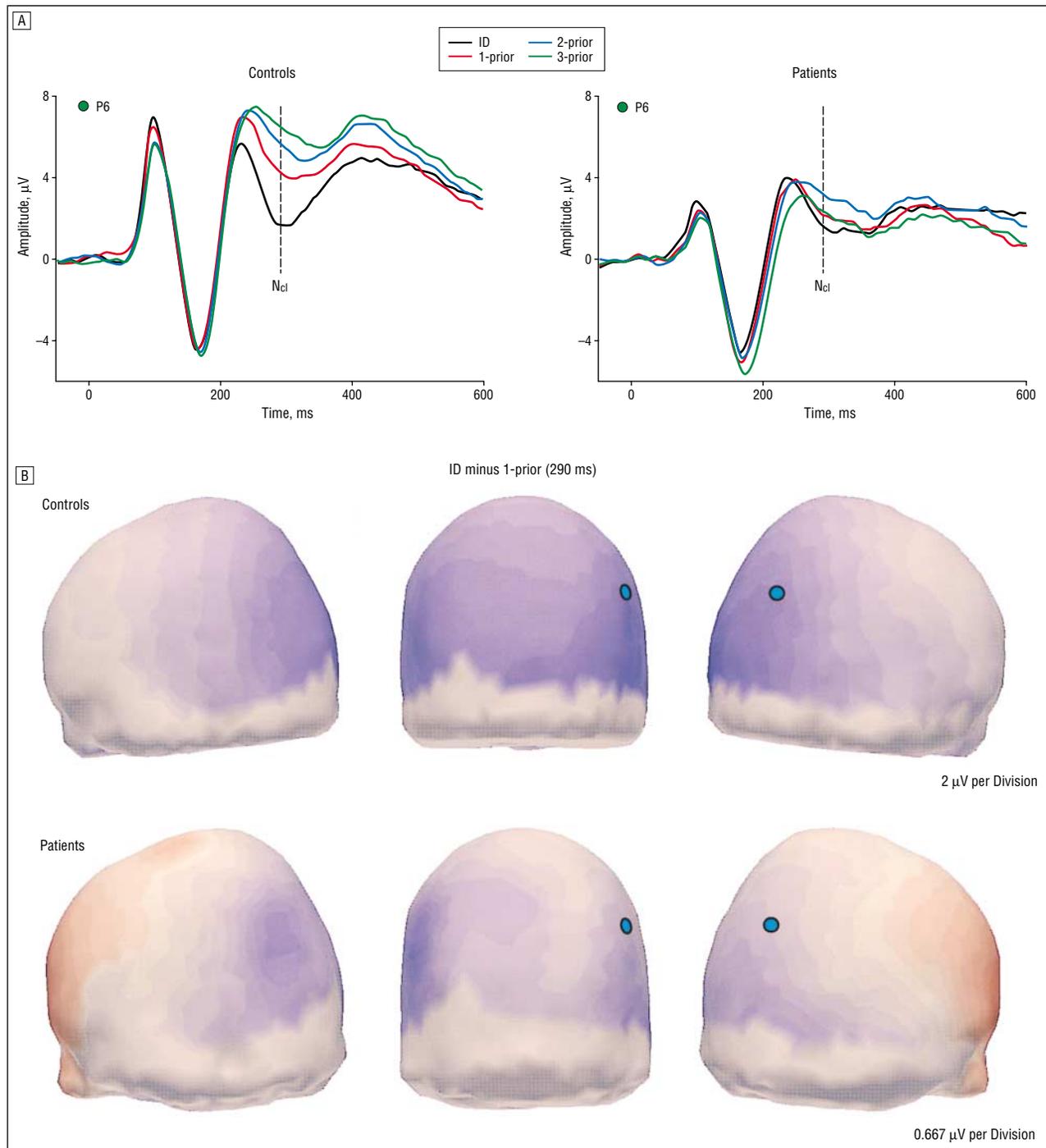


Figure 3. Closure negativity (N_{cl}) effect. A, Group-averaged ($n=16$) voltage waveforms for controls (left plot) and patients with schizophrenia (right plot) at a right-hemisphere parieto-occipital electrode (P6) at the level of object identification (ID) and at 3 prior levels. B, Topographic voltage maps of the difference waveform between levels ID and 1-prior at 290 milliseconds after stimulus onset for controls (top row) and patients with schizophrenia (bottom row). Different scales were used for patients and controls to equate for overall amplitude reduction in patients. Each isocontour line represents a division. Red isocontour lines indicate positive values; purple lines, negative values. A light-blue disk indicates the location of electrode P6 shown in A. Robust bilateral negative foci characteristic of N_{cl} are evident over the occipitotemporal scalp for control subjects but are markedly decreased in patients with schizophrenia, even at a reduced scale.

MANOVAs (2 groups \times 2 hemispheres \times 3 electrode locations) tested for between-group differences in N1 amplitude at levels ID, 1-prior, and 2-prior, respectively. Each of these analyses revealed a nonsignificant main effect for group, reflecting normal N1 generation in the patient group, as shown in Table 2. Furthermore, a 4-way MANOVA (2 groups \times 3 levels \times 2 hemispheres \times 3

electrode locations) resulted in nonsignificant group \times level ($F_{2,28}=0.18$; $P=.80$), group \times hemisphere ($F_{1,29}=0.08$; $P=.80$), and group \times electrode location ($F_{2,28}=1.24$; $P=.30$) interactions. In addition, the 95% CI for N1 averaged across P5 and P6 electrodes was highly similar between patients (95% CI, -21.9 to -64.9) and control subjects (95% CI, -22.9 to -61.7).

Table 2. Event-Related Potential Mean Area Measurements in Control Subjects and Patients With Schizophrenia*

Condition	Controls (n = 16)			Patients With Schizophrenia (n = 15)†			Group Effect		
	P5/P6	T5/T6	P05/P06	P5/P6	T5/T6	P05/P06	F _{1,29}	P Value	
N _{cl}	ID/1-prior	-45.0 (30.0)/	-45.4 (26.1)/	-47.4 (30.2)/	-21.9 (45.6)/	-20.7 (37.1)/	-12.8 (33.7)/	8.57	.007
		-52.6 (39.1)	-54.4 (35.6)	-49.9 (35.3)	-12.9 (34.3)	-14.4 (26.9)	-13.5 (36.2)		
	ID/2-prior	-71.7 (41.6)/	-72.8 (34.4)/	-73.4 (41.8)/	-28.0 (27.9)/	-32.9 (33.1)/	-22.0 (36.0)/	11.70	.002
P1	ID	-82.1 (58.7)	-83.9 (55.1)	-77.4 (48.9)	-32.2 (33.4)	-33.7 (31.0)	-24.2 (33.0)	8.94	.006
		67.9 (37.7)/	54.7 (26.8)/	71.0 (44.7)/	32.8 (25.1)/	30.6 (24.6)/	23.8 (30.0)/		
	1-prior	71.7 (45.5)	57.4 (35.7)	66.9 (49.8)	31.9 (31.7)	34.8 (33.6)	20.3 (35.7)	13.90	.001
N1	ID	63.0 (30.0)/	49.9 (20.6)/	65.8 (36.2)/	25.5 (29.1)/	22.6 (30.3)/	17.7 (31.5)/	16.80	<.001
		67.0 (39.8)	53.0 (29.8)	62.9 (41.5)	22.9 (28.4)	23.3 (24.6)	13.2 (32.9)		
	2-prior	55.6 (28.5)/	45.1 (20.1)/	58.8 (32.4)/	23.4 (19.6)/	20.0 (18.0)/	14.8 (22.0)/	0.007	.90
1-prior	ID	59.3 (34.1)	46.9 (25.1)	55.3 (37.6)	20.8 (20.7)	20.6 (18.4)	10.6 (23.0)	0.53	.50
		-38.8 (38.1)/	-36.4 (31.6)/	-37.0 (42.3)/	-39.8 (43.5)/	-42.3 (37.3)/	-35.5 (44.0)/		
	1-prior	-45.9 (38.0)	-41.8 (34.9)	-42.3 (41.8)	-44.0 (42.8)	-41.7 (37.0)	-45.4 (50.3)	0.08	.80
2-prior	ID	-41.2 (38.7)/	-37.0 (31.6)/	-39.4 (40.0)/	-44.2 (41.6)/	-48.7 (36.1)/	-45.4 (36.9)/	0.08	.80
		-45.1 (31.1)	-51.2 (31.6)	-41.4 (34.7)	-51.9 (37.7)	-51.2 (31.6)	-53.8 (43.2)		
	2-prior	-40.8 (32.1)/	-34.7 (28.9)/	-40.0 (36.8)/	-37.7 (35.8)/	-40.1 (29.3)/	-39.0 (32.7)/		
		-45.5 (26.9)	-38.9 (29.9)	-42.5 (30.8)	-47.2 (35.3)	-45.2 (30.0)	-50.5 (41.3)		

*Data are presented as mean (SD) in microvolts per millisecond. P5/P6 indicate parietal electrodes; T5/T6, occipitotemporal electrodes; P05/P06, parieto-occipital electrodes; N_{cl}, closure negativity; ID, identification; P1, positive component; and N1, negative component.

†Data from 1 patient were excluded because of broken contact at site T6.

Frontal Activity

Both groups showed a frontal positivity starting soon after N_{cl} onset (approximately 230 milliseconds). There was no apparent between-group or between-level difference in this positivity, and no increase in the amplitude of this component was apparent across stimulus levels. Visual inspection of the VEPs revealed an early frontal positivity (peak, approximately 126 milliseconds) in the schizophrenia group that was absent in the control group. Mean amplitude of this positivity across levels ID, 1-prior, 2-prior, and 3-prior was computed for each subject. Significant activity was found in patients ($t_{15} > 2.87$ for all; $P < .01$ for all) but not in controls ($t_{15} < 1.45$ for all; $P > .17$ for all). A between-group MANOVA (2 groups \times 2 hemispheres \times 3 electrode locations) failed to yield a significant main effect for group ($F_{1,29} = 2.79$; $P = .10$), but the group \times electrode location interaction reached significance ($F_{2,28} = 4.47$; $P = .03$). Given that this early frontal positivity became apparent post-hoc and that the group effect failed to reach significance, a full analysis must await future studies targeted at eliciting the positivity.

Finally, a late frontal positivity was observed in both groups starting at approximately 300 milliseconds and continuing until the end of the epoch, as shown in **Figure 5**. This sustained modulation, which occurred exclusively at level ID, probably relates to maintenance of the response decision until onset of the response prompt and was similar in both groups. A MANOVA (2 groups \times 3 levels \times 2 hemispheres) yielded a highly significant main effect of level ($F_{2,29} = 20.10$; $P = .001$) but no main effect of group ($F_{1,30} = 1.57$; $P = .22$) or hemisphere ($F_{1,30} = .004$; $P = .95$) and no group \times level ($F_{2,29} = 0.8$; $P = .46$) or hemisphere \times level ($F_{2,29} = 0.76$; $P = .50$) interaction.

COMMENT

The N_{cl} is a newly defined component of the VEP that indexes perceptual closure processes over ventral stream object recognition areas of the visual system.^{13,14} To our knowledge, this study provides the first demonstration of reduced N_{cl} amplitude in schizophrenia. The deficit is selective in that generation of the preceding N1 component, which is also generated over ventral object recognition areas, is not impaired. Moreover, the deficit in N_{cl} generation is consistent with impaired perceptual closure ability observed previously¹⁰ and in this study.

As we have previously shown, the scalp distribution of N_{cl} is consistent with generators within the LOC. Impaired N_{cl} generation thus suggests brain dysfunction at the level of the LOC. Dysfunction within the LOC may account for other well-documented sensory-processing deficits in schizophrenia, including prolonged duration thresholds for object recognition and increased sensitivity to visual backward masking.^{7,36-38} As with these other deficits, it remains to be determined whether the LOC itself is dysfunctional or whether prior stages of information processing may also be impaired.

Information concerning mechanisms of LOC dysfunction can be obtained by analyzing the integrity of VEPs that precede N_{cl} in response to fragmented stimuli. The N1, a component that indexes perceptual discrimination within the LOC,^{27,39-41} was normal in amplitude across all conditions. In contrast, P1, a component with both dorsal and ventral stream generators, was significantly reduced in amplitude, especially over dorsal stream sites. This pattern of ERP deficits permits specific hypotheses to be developed concerning brain processes underlying impaired visual sensory processing in schizophrenia.

The normal amplitude of the visual N1 observed in our study is consistent with the results of prior VEP studies on schizophrenia⁴² and distinguishes visual N1, which is normal in schizophrenia, from auditory N1, which is reduced.⁴³ Therefore, a consistent finding in the visual system in schizophrenia may be that the initial stages of ventral stream processing are intact, whereas later stages are impaired.

Visual N1 is thought to reflect general feature discrimination mediated by ventral stream object recognition areas such as the LOC. For example, N1 is larger when subjects must discriminate between classes of objects based on intrinsic physical characteristics vs when subjects need only determine whether an object is present or absent.^{28,44} Furthermore, in the fragmented-image task used in our study, N1 is larger for identified repeated images than for the same images at first presentation, suggesting that discrimination between repeated objects vs perceptual closure of novel objects represents discrete stages of processing.¹⁴ Similarly, perceptual discrimination of illusory shapes (Kanizsa figures) also gives rise to N1 enhancement.^{45,46} The finding of normal N1 generation despite impaired N_{cl} generation localizes the information-processing deficit in schizophrenia in both time and space. Further analysis of the perceptual closure deficit may help identify dysfunctional brain processes, as well as dysfunctional brain regions, in schizophrenia.

The finding of intact N1 generation also argues against differential levels of attention or task engagement as an explanation for our findings. The N1 amplitude, in general, is greater for attended stimuli as compared with nonattended stimuli or a neutral condition.^{47,48} The finding that N1 amplitude was similar between patients and controls therefore argues that the 2 groups had similar levels of task engagement.

In contrast to N1, which was unaffected, P1 amplitude was significantly and substantially reduced in the patients with schizophrenia. The P1 arises from generators in both dorsal and ventral stream structures,²⁰⁻²⁵ whereas N1 arises primarily from ventral stream structures. Topographical analyses were conducted to better characterize the basis for the P1 reduction. Although significant reductions were observed over both dorsal and ventral stream structures, the degree of reduction was greater over dorsal than over ventral stream sites. Moreover, the P1 reduction persisted over dorsal structures following MANCOVA for ventral sites but disappeared over ventral structures following MANCOVA for dorsal sites. Thus, the P1 data suggest relatively preserved initial ventral stream processing but substantially impaired processing within the dorsal stream, even at latencies as short as 100 milliseconds following stimulus onset.

The selective impairment of dorsal P1 generation observed in our study is consistent with the results of a recent steady-state VEP study that showed reduced responses to magnocellularly biased (dorsal stream) stimuli but intact responses to parvocellularly biased (ventral stream) stimuli.⁴⁹

The P1 is known to be modulated by spatial attention.^{47,48} However, it is unlikely that differences in spa-

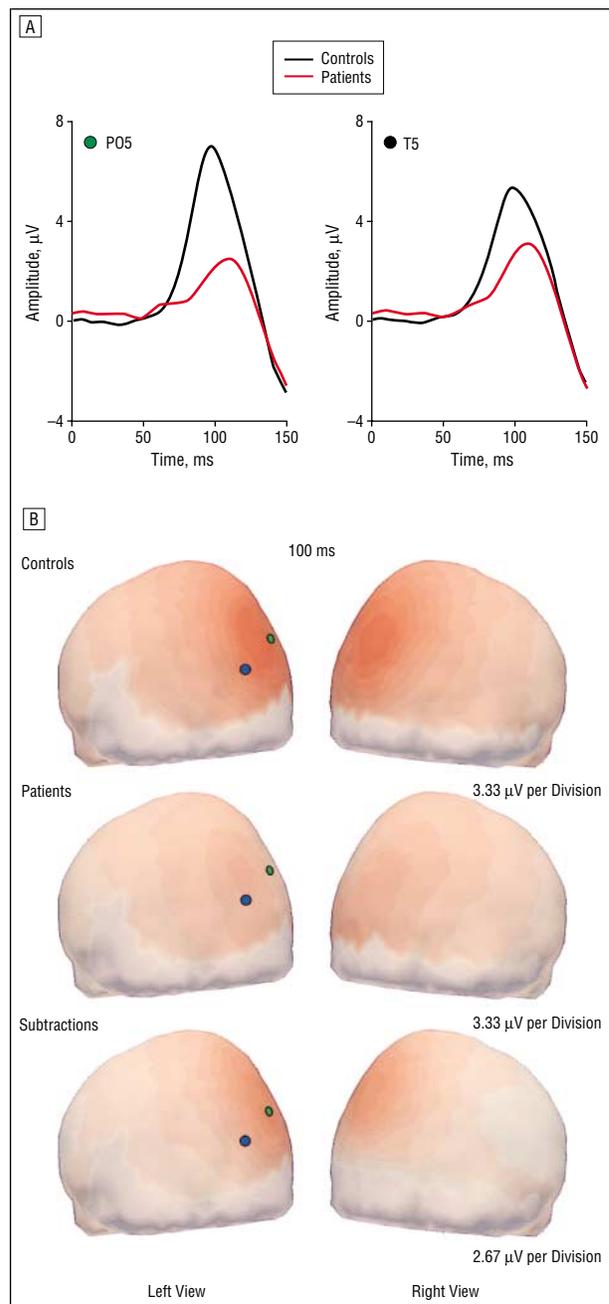


Figure 4. Positive (P1) effect. A, Group-averaged waveforms at dorsal (P05) and ventral (T5) left-hemisphere electrodes for controls ($n=16$) and patients with schizophrenia ($n=16$). Although patients showed comparable P1 amplitude at dorsal and ventral sites, control subjects showed greater amplitude at the dorsal relative to the ventral site. B, Topographic voltage maps at 100 milliseconds for the object identification level (ID) waveform for controls (top row) and patients with schizophrenia (middle row) and for the difference waveform for level ID for controls and patients (bottom row). Red isocontour lines indicate positive values; purple lines, negative values. Patients with schizophrenia show a marked decrease in P1 amplitude relative to controls that can be attributed to dysfunction in dorsal P1 generators.

tial attention account for our findings because there was no spatial attention manipulation. Furthermore, the attentional modulation of P1 has not been observed for stimuli presented centrally, as in this study. Finally, N1 effects typically accompany P1 spatial attention effects.^{50,51} As noted previously, no N1 deficits were observed in our study.

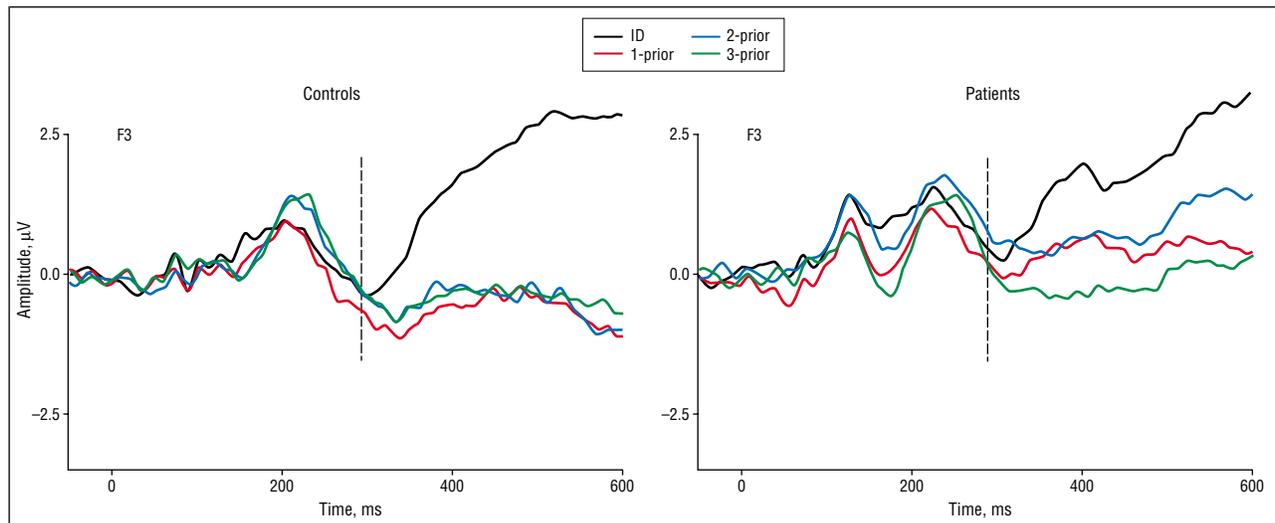


Figure 5. Frontal activity. Group-averaged ($n=16$) voltage waveforms for controls (left plot) and patients with schizophrenia (right plot) at a left-hemisphere frontal electrode (F3) at the level of object identification (ID) and at 3 prior levels.

Because of the highly specific pattern of ERP deficit observed in this study, it is possible to propose a relatively specific, circuit-based model to account for our findings. The ventral visual stream receives not only direct parvocellular projections from the LGN but also indirect crossover projections from the dorsal stream.^{18,52-55} Because transmission is much more rapid in the dorsal stream than the ventral stream, crossover input to higher-tier ventral stream regions such as the LOC may precede direct parvocellular mediated input.¹⁷⁻¹⁹ It has been proposed that the faster transmission and spatial-coding properties of the dorsal stream are ideal for “spotlighting” relevant information for transmission to ventral stream regions, so that crossover input from the dorsal stream may modulate activity within ventral stream structures.^{18,53-55}

These theories raise the possibility that impaired N_{cl} generation reflects impaired modulation of the LOC via crossover input from the dorsal stream, rather than intrinsic LOC dysfunction. Such a model would explain the relatively intact preliminary processing within the LOC, as reflected in the normal N_1 generation. In addition, it would suggest that a single underlying deficit (magnocellular dorsal stream dysfunction) could account for both the P_1 and N_{cl} deficits observed in our study. This model would also explain the behavioral finding that patients with schizophrenia are particularly impaired in the ability to use motion information for object recognition.³⁰

Impaired dorsal stream processing, as reflected by deficient dorsal P_1 generation, may also explain deficits that patients with schizophrenia show in processing local vs global stimulus features. The P_1 amplitude is enhanced when subjects are required to process local vs global features of hierarchical stimuli (eg, large arrows composed of smaller arrows),⁵⁶⁻⁵⁸ reflecting greater activation of the dorsal stream in these conditions. The results of these ERP studies are consistent with those of lesion studies demonstrating that dorsal stream (inferior parietal) lesions impair the ability to alternate between local and global processing, whereas frontal lesions do not.⁵⁹

Patients with schizophrenia have a selective deficit in the ability to process hierarchical stimuli at the local level.^{60,61} Such a deficit is consistent with the reduced P_1 amplitude observed in this study and suggests that the perceptual closure deficit may be due in part to the reduced ability of patients to process local features of the fragmented stimuli.

Although prefrontal dysfunction is known to play an important role in the pathophysiologic characteristics of schizophrenia,⁶²⁻⁶⁵ it is unlikely that such deficits contribute appreciably to such abnormalities in our study. No perceptual closure-related activity was observed over the frontal cortex in either group until after the onset of N_{cl} . Furthermore, post- N_{cl} activity in the frontal cortex was evident exclusively when object recognition had been achieved¹⁴ and did not differ between groups. This late activity is likely related to maintenance of the yes/no decision once closure either had or had not been achieved. These findings are consistent with the results of a recent functional magnetic resonance imaging study showing closure-related activity in the fusiform gyrus and occipitotemporal sulcus but not in frontal regions during object recognition.⁶⁶

Interestingly, the earliest frontal activity was observed in the patients with schizophrenia. This activity (peak, approximately 126 milliseconds) was evident immediately following the reduced posterior P_1 observed in these patients and may reflect attempted frontal compensation for impaired automatic stimulus processing within the visual sensory regions (Figure 5).

A limitation of our study is that all patients with schizophrenia were receiving medication at the time of testing.⁶⁷ However, visual-processing deficits in schizophrenia have been shown irrespective of whether patients were taking medication.⁷ In addition, our study showed no significant correlation between antipsychotic medication dose and behavioral or ERP measures.

In summary, to our knowledge, this is the first study to demonstrate neural dysfunction in perceptual closure processes in schizophrenia. The main finding of our study is profound impairment in N_{cl} (peak, approxi-

mately 290 milliseconds), a novel ERP component generated over the LOC that has been shown to grow incrementally with reduced levels of fragmentation prior to object recognition.^{13,14} In addition, there was a decrease in amplitude of the early P1 component that was greater over dorsal than ventral structures in patients with schizophrenia, indicating selective dysfunction of dorsal stream P1 generators. Decreases in N_{cl} and P1 were in stark contrast to the intervening N1 component, which was of normal amplitude and time course in these patients, suggesting intact ventral stream processing prior to N_{cl} . This study thus supports earlier work showing a dysfunction of magnocellular dorsal stream processing in schizophrenia.^{13,14} Furthermore, it suggests that a primary deficit in magnocellular dorsal stream processing may lead to secondary impairment of object recognition processes within ventral stream object-processing regions such as the LOC. Finally, it indicates a specific time course for interactions between dorsal and ventral processing that may be relevant to the pathophysiologic characteristics of information-processing dysfunction in schizophrenia.

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