Disruption of Neural Systems of Visual Attention in Schizophrenia

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Background: Patients with schizophrenia show attention deficits. The frontal P2a and posterior N2b event-related potential components are early indices of activity in neural systems supporting attention and they are reduced in schizophrenia in auditory tasks. However, the auditory P300 is reduced as well. Thus, the P2a and N2b reductions may simply reflect a general event-related potential amplitude reduction. The visual P300, however, is often spared in schizophrenia. If neural systems supporting attention are specifically disrupted in schizophrenia, the attention-sensitive P2a and N2b should be differentially reduced in patients, compared with the P300, in a visual attention task.

Methods: We analyzed 64-channel event-related potentials from 14 schizophrenic patients and 14 control subjects in a visual object–spatial attention task. We examined the amplitude of the P2a, N2b, and P300 components in the target minus standard difference wave to see if there was a differential reduction of the P2a and N2b compared with the P300.

Results: Both the P2a and N2b waveforms were reduced in the patient group (81% [control mean, 1.99 µV; patient mean, 0.38 µV] and 95% [control mean, 0.55 µV; patient mean, 0.03 µV], respectively) while the P300 was not reduced. Measured at the peak of the frontal P2a, the N2b was larger dorsally in the spatial task and larger ventrally in the object task in the control group.

Conclusions: The spatial distribution of the P2a and N2b was consistent with activity in the prefrontal cortex and modality-specific posterior cortex, respectively. The differential reduction of the P2a and N2b waveforms supports the hypothesis of specific disruption in neural systems of visual attention in schizophrenia.

Arch Gen Psychiatry. 2002;59:418-424

Disruption of attention and working memory are characteristic of patients with schizophrenia.1-4 Attention allocates resources to task-relevant perceptual representations. The ability to attend to and process task-relevant stimuli is critical for generating goal-directed behavior. When attention is disrupted, the ability to generate goal-directed behavior is impaired. Understanding of the neural bases of attention and working memory disruption in schizophrenia might provide insight into the neuropathologic factors of the disorder.

Primate studies suggest that prefrontal cortex and its interactions with perceptual areas in posterior cortex are important for attention and working memory.5,8 For visual stimuli, perceptual processing is divided into 2 streams: the dorsal “where” spatial location stream, projecting to the posterior parietal cortex, and the ventral “what” object feature stream, projecting to the inferior temporal cortex.9,10 Interaction between the posterior parietal cortex and the prefrontal cortex is necessary for visuospatial working memory9 and similar interaction between the inferior temporal cortex and the prefrontal cortex is needed in visual object working memory.11 If the prefrontal cortex and its connections with the posterior brain support attention and working memory, then disruptions in these neural networks may underlie those cognitive disturbances in schizophrenia.12

Event-related potentials (ERPs) have been used to study the neural systems supporting attention. Early studies focused on the P300 component, a large, centroparietal positive component, occurring approximately 400 milliseconds after the presentation of a stimulus.13-15 However, since, in some cases, the P300 can peak after the execution of the behavioral response,16 it cannot be a direct index of the allocation of processing resources to relevant stimuli.

There are more specific, earlier posterior negative ERP indices of attention, including the N2b.17,18 An N2b has been identified to task-relevant stimuli in auditory,
SUBJECTS AND METHODS

SUBJECTS

The patients (n=21) were recruited from outpatient treatment and inpatient wards at the Brockton Veterans Affairs Medical Center, Brockton, Mass. Diagnoses were made from the Structured Clinical Interview for DSM-IV (SCID) under the supervision of a licensed clinical psychologist trained in SCID administration (k intrarater reliability in our laboratory has been 0.99 for schizophrenic vs other diagnoses over the last 5 years). Subjects were between the ages of 19 and 58 years, had no history of electroconvulsive treatment or neurological illness, no alcohol or other drug abuse in the last 5 years or a lifetime history of addiction, no alcohol use 24 hours prior to testing, and the desire to participate as evidenced by giving written informed consent. Control subjects (n=22) were recruited by newspaper advertisement using the same exclusion criteria with the addition of no lifetime history of mental illness.

Subjects who performed at less than 90% accuracy in any task or who had fewer than 20 artifact-free electroencephalographic (EEG) trials in any condition were excluded, leaving 14 patients and 18 control subjects. An additional 4 controls were excluded to make equal-subpopulation (n) groups, selected such that the groups were not significantly different for age. The groups did differ on verbal IQ, parental socioeconomic status, and years of education (Table). One control and 2 patients were left-handed; all were male. The diagnostic conditions of the patients were as follows: 6 were paranoid, 4 undifferentiated, 2 residual, and 2 schizoaffective. All patients were medicated at the time of testing, 7 with typical antipsychotic medications, 6 with atypical antipsychotic medications, and 1 with a combination therapy. Seven of the patients were also taking anticholinergic medication.

STIMULI AND TASKS

Stimuli were presented using a personal computer (Macintosh Centris 650; Apple Computer, Cupertino, Calif) running PsyScope software communicating with the EEG amplifiers via a Button Box (New Micros, Dallas, Tex). During the experiment, there was a fixation dot at the center of the screen and 4 boxes at the 4 corners of an invisible square. Each box subtended approximately 2° of visual angle and was approximately 6° from fixation. On each trial, 1 of 4 objects would appear in 1 of the boxes and remain onscreen for 150 milliseconds with a 1250-millisecond intertrial interval. The 4 objects were an “X,” a “T,” a “check mark,” and a “triangle” (96 pixels per object). The object and location on any given trial were equiprobable and selected randomly without replacement from a pool of trial types (Figure 1).

Subjects performed 2 blocked target detection tasks: selection by location and selection by object. In the location task, 1 of the 4 boxes was designated the target location. Subjects were instructed to press a key whenever any object appeared at the target location. In the object task, 1 of the 4 objects was designated the target. Subjects were instructed to press a key any time the target object appeared at any location. The target objects and target locations were randomly selected for each subject. Halfway through each run, a new location and object were selected as targets, constrained such that each subject had a target location in each visual field. Each subject participated in 4 task blocks of 200 trials each, 2 location and 2 object blocks, with a break every 100 trials. Task order and response hand were counterbalanced across subjects.

EEG RECORDING AND PROCESSING

The EEG was referenced to the vertex and sampled at 250 Hz using 2 linked 32-channel EEG amplifiers (SynAmps; Neuroscan Labs, Herndon, Va) and 64-channel electrode nets (Geodesic Sensor Nets; Electrical Geodesics Inc, Eugene, Ore). Epochs were 1000 milliseconds, including a 200-millisecond prestimulus baseline. The epochs were scanned by an artifact detection algorithm and trials with eye blinks or out-of-range data (0±75 µV) excluded from further analysis. The EEG was digitally low-pass filtered at 30 Hz to eliminate high-frequency noise. The EEG epochs were averaged by stimulus type (nontarget, target), visual field (left, right), and task block (spatial, object) to create the ERP waveforms, then transformed into an average reference representation to attenuate spatial distortions due to choice of reference sensor.7 Grand average waveforms were created by averaging together the individual subject averages for each group (schizophrenic, control) in each condition. Since the psychological operation of interest was the detection of the task-relevant targets, the ERP components in common to both the targets and nontargets were removed by creating target minus nontarget difference waves. Target and nontarget waveforms comparing the spatial and object tasks for the control and patient groups at the frontal, dorsal, and ventral regions of interest (ROIs) are shown in Figure 2. Target minus nontarget waveforms are shown in Figure 3.

DATA ANALYSES

Temporal windows were selected around the P2a, N2b, and P300 peaks in the difference wave by inspection of the waveforms and a peak latency analysis was performed. Where significant effects on latency were found between groups or conditions, latency adjustments were made to the windows and the mean amplitude was extracted (latencies below). To reduce the dimensionality of an electrode factor, ROIs were identified containing subsets of the electrodes.2,3 These ROIs were frontal (bilateral electrode pairs 2-59, 6-62, and 5-58) for the P2a; dorsal (8-34, 13-46, and 61-49) and ventral (20-38, 26-37, and 27-32) for the N2b; and centroparietal (8-34, 20-38, 24-33) and temporal (13-47, 16-45, 18-43, and 23-42) for the P300. The frontal, dorsal, and ventral ROIs are shown on a map of the electrode locations in Figure 4. Six independent repeated-measures analysis of variances (ANOVA)s were performed, a peak latency and a mean amplitude analysis for each component window, with the within factors task (spatial, object), visual field (left, right), and hemisphere (left, right), plus an ROI factor (dorsal, ventral) in the N2b analysis, and a between factor group (control, schizophrenic). A seventh ANOVA was performed on the amplitude only at the temporal lobe ROI to test for laterality differences as seen in the auditory P300 with the same electrode array.8 An ANOVA was also performed on the reaction time data. Correlations were computed between the frontal P2a and the N2b at the 2 posterior ROIs and probabilities computed with the Fisher r-to-z test. Tests for differences between groups on demographic variables were performed using 2-tailed t tests. An α-level of .05 was used for all comparisons.
somatosensory and visual modalities. The N2b usually overlies and has been associated with activity in the cortical areas responsible for perceptual processing.

Some studies report a positivity over frontal sites at about the same latency as the N2b. The frontal positivity, referred to here as the P2a, is due to different neural generators than the N2b, demonstrated by differences in latency, laterality, and psychological responsiveness. While the N2b is modulated by stimulus properties and task demands, the P2a is sensitive only to the task relevance of the stimulus. Thus, the P2a and N2b may provide an index of interaction between posterior stimulus representation areas and the frontal executive in the processing of task-relevant stimuli.

The most commonly reported ERP finding in schizophrenia is an amplitude reduction of the auditory P300. Some studies have shown a left-sided lateralization of this reduction and this has been linked to structural abnormalities in the left temporal lobe. The visual P300 seems to be less affected in schizophrenia, with most studies showing either no reduction or less reduction of the visual than the auditory P300. There have been a few reports of auditory N2 reduction in schizophrenia. To our knowledge, there are only 2 reports of visual N2 reduction in schizophrenia, both of which found the reduction despite a P300 of normal amplitude. The single report, by our group, of the auditory frontal P2a in schizophrenia, found it reduced. We know of no studies of the visual P2a or related components in schizophrenia. Thus, it is unclear if there is a specific disruption of the neural networks supporting visual attention in schizophrenia, or whether the disruption is confined to the auditory modality.

This study used a visual selective attention task, where targets were defined either by their spatial location or their visual object features. This task has been shown to elicit a P2a and N2b with a spatiotemporal distribution consistent with interaction between prefrontal cortex and the dorsal where pathway in location selection and the ventral what pathway in object selection. We compared the ERPs from a 64-channel recording array, which provided the spatial resolution needed to assess activity in specific processing pathways. Reduction of the frontal P2a and posterior N2b in the patients, despite sparing of the P300, would provide evidence of specific disruption of the neural systems supporting visual attention in schizophrenia.

**RESULTS**

**BEHAVIORAL MEASURES**

The groups differed on reaction time, with the patient group (mean [SD], 593.99 [92.32]
were the Task and an effect for hemisphere, $F=31.97, P<.001$, with the reaction time in the spatial task (mean, 488.43 [84.05] milliseconds) about 93 milliseconds faster than in the object task (mean, 580.91 [108.79] milliseconds). Mean accuracy was 99% (792/800) for controls in the spatial task and 97% (776/800) in the object task; the patients were 97% (775/800) in the spatial task and 94% (750/800) in the object task.

**ELECTROPHYSIOLOGICAL MEASURES**

**Latency**

Effects for task and group were used for latency correction. The latency window for the P2a and N2b was from 160 to 400 milliseconds For the P2a there was a main effect for task, $F=46.93, P<.001$, with the spatial task peak (mean, 263.26 [73.12] milliseconds) about 51 milliseconds earlier than the object task peak (mean, 313.96 [60.19] milliseconds). There was an effect for task on the N2b, $F=81.37, P<.001$, showing a shorter peak latency in the spatial task (mean, 248.82 [56.360] milliseconds) than in the object task (mean, 296.67 [68.16] milliseconds). The latency window for the P300 was from 320 to 600 milliseconds. There was an effect for task, $F=78.43, P<.001$, showing shorter peak latency in the spatial task (mean, 455.81 [69.64] milliseconds) than in the object task (mean, 520.12 [63.13] milliseconds). There was also an effect for group, $F=4.10, P=.03$, showing a faster latency in the control group (mean, 469.92 [67.69] milliseconds) than in the patient group (mean, 506.67 [66.95] milliseconds).

**Amplitude**

**Figure 5** shows ERP from a midline electrode between Cz and Pz (electrode 21) comparing the patient and control groups with the amplitude windows for the P2a/N2b and P300. The latency corrected amplitude windows for the P2a and N2b were 160 to 300 milliseconds for the spatial task and 228 to 368 milliseconds for the object task. There was an effect on the P2a for group, $F=14.22, P<.001$, showing reduced amplitude in the patient group. For the N2b, there was a main effect for group, $F_{1,26}=10.13, P=.004$, showing a smaller amplitude in the patient group and an effect for hemisphere, $F=31.97, P<.001$, which was modified by group, $F=26.89, P<.001$, showing a larger amplitude over the left hemisphere in the controls only. Task $\times$ ROI $\times$ Group was significant, $F=14.22, P<.001$, showing a larger N2b in the ventral path in the spatial task and a larger N2b in the dorsal path in the spatial task in the control group (**Figure 6**). Task $\times$ ROI $\times$ Field was significant, $F=7.67, P=.01$, as were the Task $\times$ ROI $\times$ Field $\times$ Group, $F=6.63, P=.016$, and Task $\times$ ROI $\times$ Hemisphere $\times$ Group, $F=4.77, P=.04$ interactions, indicating that the larger dorsal N2b in the spatial task and ventral N2b in the object task in the control group was mostly for stimuli in the left visual field and over the left hemisphere.

The P300 amplitude window was latency corrected for differences in group and task. For the spatial task the window was from 360 to 520 milliseconds for the controls and 392 to 552 milliseconds for the patients; for the object task the window was from 416 to 576 milliseconds for the controls and 464 to 624 milli-
interaction was significant, $F=7.29, P=.02$, showing a larger P300 in the spatial task. The Field was an effect for task, $F=6.10, P=.03$, showing the P300 window for the patients is in the dark dots. In the centroparietal ROI there was an effect for task, $F=6.10, P=.03$, showing a larger P300 in the spatial task. The Field $\times$ Hemisphere $\times$ Group interaction was significant, $F=7.29, P=.01$, suggesting a larger P300 contralateral to the visual field of the stimulus for the control subjects. In the temporal lobe ROI, there was a Field $\times$ Hemisphere interaction, $F=5.00, P=.03$, showing the P300 larger contralateral to the visual field of the stimulus. Task $\times$ Hemisphere $\times$ Group interaction was significant, $F=6.30, P=.02$, indicating that, for the controls, the P300 in the spatial task was larger over the left hemisphere and in the object task was larger over the right hemisphere.

**CORRELATIONS**

For the controls, the strongest correlations were between the frontal and ventral ROIs in both tasks (object task: $r=-0.34, P<.001$; spatial task: $r=-0.39, P<.001$). However, the P2a was significantly correlated with the dorsal N2b in the object task only, $r=-0.23, P=.003$; in the object task the correlation only approached significance, $r=-0.15, P=.06$. In the patients, the correlation was actually stronger between the frontal P2a and ventral N2b in the object task that for the controls, $r=-0.48, P<.001$. However, for the patients, the correlation between the P2a and ventral N2b in the spatial task was reduced compared with the controls, $r=-0.22, P=.005$, and the correlation between the P2a and dorsal N2b was not significant in the spatial task, $r=-0.12, P=.11$.

In this visual attention study, the patients with schizophrenia showed a reduced P2a and a reduced N2b, despite a P300 of normal amplitude and spatial distribution. This suggests that the neural systems and cognitive operations indexed by the P2a and the N2b were differentially affected in the patient group.

Attention requires the direction of processing resources to task-relevant perceptual representations. Prior research indicates that the N2b indexes the formation of a perceptual representation in modality specific areas of posterior cortex. The P2a, with its inferior prefrontal distribution and enhancement to target stimuli, may index activity in orbitofrontal cortical areas of task-related operations.

**Figure 5.** Difference waves at a posterior midline site, near parietal electrode 21 showing the N2b reduction despite amplitude sparing of the P300 in the patient group compared with the control subjects. The amplitude windows are shown here, the object windows on the object, left visual field plot, and the spatial windows on the spatial left visual field plot. The N2b windows are in long dashes, the P300 windows for the controls are in the light dots, and the P300 window for the patients is in the dark dots.
relevance computation or salience evaluation.\textsuperscript{26} One of the functions of orbitofrontal cortex appears to be to evaluate the motivational value of a stimulus, independent of its physical features.\textsuperscript{49} The topographic distribution and psychological responsiveness of the P2a and N2b are consistent with simultaneous activity in posterior cortical areas of perceptual representation and prefrontal cortical areas of salience evaluation.\textsuperscript{26,29} For the controls, at the peak of the P2a, the N2b was larger at the ventral ROI when target detection was based upon object feature and larger at the dorsal ROI when target detection was based upon stimulus location (Figures 3 and 6). This relationship was not true for the patients, indicating a disruption in the visual attention network between prefrontal cortex and stimulus-specific posterior cortex. The patients were able to perform the task, thus, there had to be some level of activity in the network. However, if the activity was sufficiently degraded, it might be unable to generate a scalp detectable P2a and N2b. In a more difficult task, the performance of the patients might start to decline more precipitously than that of the controls as the network became more challenged.

From the data presented here it is impossible to determine if the location of the physiological dysfunction is in one of the contributing cortical areas (prefrontal cortex or multiple posterior areas) or in the connections between the areas. There is substantial evidence that structural and functional abnormality in the frontal brain contributes to cognitive disruption in schizophrenia.\textsuperscript{46-52} There are also hypotheses that posit functional disconnections in the brain in schizophrenia,\textsuperscript{53-55} one of which proposes a disruption in communication between prefrontal and posterior cortex.\textsuperscript{56,57} There is less evidence of distributed posterior dysfunction. The correlation analysis here is ambiguous, suggesting disrupted communication in the spatial task but not in the object task, consistent with behavioral data suggesting differential disruption in the dorsal pathway in schizophrenia.\textsuperscript{28}

This study used a heterogeneous group of long-term, medicated patients, and there were significant differences between the control and patient groups. The ERP effects might be medication induced, although a prior study found visual N2 reduction in unmedicated patients.\textsuperscript{50,59} Despite these limitations, the large and differential degradation of the P2a and N2b in the patient group provides evidence of specific disruption of the neural system supporting detection of task relevant visual stimuli in schizophrenia.

Submitted for publication October 4, 2000; final revision received September 7, 2001; accepted October 1, 2001.

This study was supported by a young investigator’s award from the National Alliance for Research on Schizophrenia and Depression, Great Neck, NY (Dr Potts). Additional support was provided by grant MH0799-09 from the National Institutes of Health, Bethesda, Md (Dr McCarley) and by the Veterans Administration through the Research Center for Basic and Clinical Neuroscience Studies of Schizophrenia, Washington, DC (Dr McCarley).

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