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Attentional Modulation of Early-Stage Visual Processing in Schizophrenia

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Abstract

This study shows that paying attention to the color of a visual stimulus is manifested by an early endogenous scalp-positive event-related brain potential (ERP) component, referred to as “selection positivity”, that occurs within the first 100 ms after stimulus onset in healthy observers. In contrast, recently ill and chronically ill schizophrenia patients as well as patients at high risk for schizophrenia all failed to show this early ERP component while attending to color. These results suggest that a relatively early stage of visual-selective processing in posterior extrastriate cortex is disrupted in schizophrenia.

Keywords

Schizophrenia; high-risk; brain function; selective attention; vision; event-related brain potential (ERP)

It has been long recognized that the brain mechanisms of attention and information processing are disrupted in patients with schizophrenia (Braff and Light, 2004; Cornblatt and Malhotra, 2001; Kraepelin, 1919; Nuechterlein and Dawson, 1984). Although attention deficits are believed to underlie a variety of higher-order cognitive and social impairments seen in schizophrenia patients, it remains to be clarified whether these deficits also compromise their sensory-perceptual processing (Green et al., 2003; Li, 2002), such as the detection or discrimination of elementary stimulus properties. To address this issue, we examined the modulatory effect of selective attention on color processing in schizophrenia by means of scalp recordings of event-related potentials (ERPs).

In the present study, we examined an early endogenous scalp-positive ERP component, variously labeled P2a, early positive difference, or frontal “selection positivity” (SP), that is elicited when a human observer selects visual stimuli on the basis of a salient object feature, such as color or spatial frequency (Anllo-Vento et al., 1998; Kenemans et al., 1993; Mangun and Hillyard, 1995; Michie et al., 1999; van der Stelt et al., 1998; Wijers et al., 1996). The SP typically occurs between about 100 and 250 ms after stimulus onset and is thought to reflect attention-related modulations of visual processing in the occipito-temporal cortical pathway, at a relatively early level where only basic visual surface features are encoded and prior to

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anterior temporal lobe areas where full object identification occurs (Anllo-Vento et al., 1998; Baas et al., 2002; Lange et al., 1998). The neural mechanisms of the SP are poorly understood, but could involve a tonic, preset sensory “bias” of neuronal activity that is invoked specifically to select or re-direct relevant visual inputs into specialized cortical processing circuits for further analysis (Hillyard et al., 1998; Näätänen, 1992; Schroeder et al., 2001). Here, we assessed the color attention-related SP in patients in the recent-onset and chronic stages of schizophrenia, as well as in patients at high risk for developing schizophrenia, to determine whether attentional modulation of early-stage visual processing is disrupted in schizophrenia.

Study participants consisted of 14 patients with recent-onset schizophrenia (mean age = 22.4 years, S.D. = 3.4; mean illness duration = 0.7 years, S.D. = 0.5; 11 males), 14 patients with chronic schizophrenia (mean age = 37.3 years, S.D. = 8.2; mean illness duration = 14.7 years, S.D. = 7.5; 11 males), 12 patients at risk of being prodromally symptomatic for schizophrenia (mean age = 22.0 years, S.D. = 4.5; 6 males), and 14 healthy comparison subjects (mean age = 24.0 years, S.D. = 4.1; 9 males), who were age-matched to the recent-onset and high-risk patients. In contrast to the patients with DSM-IV schizophrenia, putatively prodromal patients did not meet formal diagnostic criteria for schizophrenia at study entry, but were clinically considered at high imminent risk for developing schizophrenia, that is, between 36% and 54% of them were anticipated to develop frank psychotic symptoms within one year (McGlashan et al., 2003). In this high-risk group, 6 subjects were taking antidepressant medication, 1 subject was taking antidepressant and antipsychotic medications, and the remaining 5 subjects were on no medication. Thirteen recently ill and all chronically ill patients were taking antipsychotic medications. Clinical symptom severity was generally mild and did not differ significantly between the 3 patient groups. Healthy comparison subjects were free from any diagnosed psychiatric or neurological problems. All subjects gave written informed consent.

Electroencephalograms (EEGs) were recorded from 30 scalp electrodes against a right mastoid reference, while participants performed a visual (color) selective attention task (van der Stelt et al., 1998, 2001). We also recorded horizontal and vertical electro-oculograms to measure eye movements and blinks. The EEGs and electro-oculograms were bandpass filtered between 0.15 and 70 Hz, digitized at 500 Hz, and stored on computer disk for off-line processing. Task stimuli involved red and blue circles ($N = 400$), each with a diameter of 2 cm. One half of the circles had a small gap, the gap being randomly distributed over 4 possible locations (0, 90, 180 and 270 degrees); the other half of the circles had no gap. Circles with a gap served as nontargets; circles without a gap as targets. Subjects were pre-instructed to focus attention on stimuli with a task-relevant (e.g., red) color, while ignoring the other, irrelevant (e.g., blue) stimuli. The task was to make a right index finger button-press response each time a target stimulus occurred among the relevant stimuli, emphasizing both speed and accuracy. The color-selection cue (red or blue) was counterbalanced across subjects. Targets were presented among both relevant (attended) and irrelevant (unattended) stimuli. Thus, each subject received 4 types of stimuli (viz., 100 relevant nontarget stimuli, 100 relevant target stimuli, 100 irrelevant nontarget stimuli, and 100 irrelevant target stimuli), with only the relevant target stimuli requiring a button-press response. The stimuli were presented in a pseudo-random order with equal probabilities (25%), for the duration of 107 ms, and with interstimulus intervals varying randomly between 1300 and 1700 ms. The rationale for choosing the particular numbers of stimuli was to obtain the ERP responses of interest with adequate signal-to-noise ratios in a relatively short period of time, as well as maximizing the co-operation and alertness of subjects during the task performance and minimizing sensory adaptation effects and changes in participants' state that may occur across a recording session of longer duration.

Performance measures consisted of the target hit rate, false-alarm rate, and reaction time to relevant target stimuli. We excluded EEG recordings associated with incorrect behavioral responses or containing voltages in excess of $\pm 100 \mu V$. An eye movement correction algorithm

was used to control for ocular artifacts. For each subject, ERPs were obtained for each stimulus type and electrode, using a 200-ms prestimulus baseline period and a 1000-ms poststimulus period. The color attention effect, as manifested by SP, was then isolated in the “difference wave” formed by subtracting the ERPs to irrelevant nontarget stimuli from the ERPs to relevant nontarget stimuli, separately for each subject. We focused on the data from the frontal (Fz), central (Cz) and parietal (Pz) electrode locations where the SP was maximal. One-way (4 group) analysis of variance (ANOVA) tests, followed by independent-samples *t*-tests, were used to assess group differences in performance and the SP at each electrode. Pearson correlation coefficients and analysis of covariance (ANCOVA) were used to assess, and eventually to control for, effects of age, clinical symptom severity, and current medication status on performance and the SP.

Significant overall group differences were observed in the mean hit rates and reaction times, reflecting that chronically ill patients performed significantly worse than high-risk subjects and healthy subjects (Table 1). However, age showed significant correlations with the hit rate ($r = -0.45$, $P = 0.001$, $N = 54$) and reaction time ($r = 0.47$, $P < 0.001$, $N = 54$). When age was included as a covariate, overall group differences in performance no longer reached significance (Table 1). Thus, chronically ill patients, who were on average older than the other subject groups, did not differ significantly in performance after age effects were statistically controlled. Mean false-alarm rates were generally low ($< 1.1\%$) and did not differ between individual groups.

In healthy subjects, the earliest ERP sign of selective attention to stimulus color was indexed in the time region of N1 and P2 by an early broadly distributed SP that occurred between about 80 and 190 ms after stimulus onset (Fig. 1). In contrast, high-risk, recent-onset, and chronic schizophrenia patients all failed to generate a significant color attention-related SP (Fig. 1). A three-way (4 group $\times$ 2 attention $\times$ 3 electrode) repeated-measures multivariate analysis of variance on the raw, unsubtracted mean voltage data across the 120- to 160-ms poststimulus latency range substantiated that the color attention effect, as indexed by the SP, differed as a function of group [attention $\times$ group: Wilks' lambda = 0.79, $F(3,50) = 4.56$, $P = 0.007$, $\eta^2 = 0.22$] and was significant only for healthy subjects [attention: $F(1,13) = 23.49$, $P < 0.001$]. The SP showed no significant correlations with performance, age, clinical symptom ratings, or current medication status.

These study results show that selective attention to stimulus color is manifested in the ERPs of healthy observers by a characteristic early endogenous SP between about 80 and 190 ms poststimulus, but that this early color attention effect is absent or substantially reduced in patients in the recent-onset and chronic stages of schizophrenia as well as in patients at high imminent risk for developing schizophrenia. These electrophysiological data suggest that a relatively early stage of color-selective processing in extrastriate visual cortex is deficient in schizophrenia. We speculate that this deficit is mediated by cortical feedback mechanisms that fail to project attentional influences onto visual processing areas (Schroeder et al., 2001), but we are unable to infer whether this involves a relative inability to facilitate processing of relevant stimuli, a failure to inhibit processing of irrelevant stimuli, or a mixture of poor attentional enhancement and suppression. The present results substantiate prior clinical and behavioral findings (Braff and Light, 2004; Cornblatt and Malhotra, 2001; Kraepelin, 1919; Nuechterlein and Dawson, 1984) indicating that impaired visual attention and brain function reflect an enduring and core feature of schizophrenia.

In this study, no statistically significant group differences were observed in task performance, although marked group differences were present in the SP. In particular, the minor though non-significant performance differences between the schizophrenia patients and the healthy subjects are noteworthy, because previous studies have shown that schizophrenia patients are

often significantly impaired on many attention tasks (Braff and Light, 2004; Mathalon et al., 2004; Nuechterlein and Dawson, 1984). Possible reasons why we did not detect significant performance deficits in our patient samples are: (a) the level of task difficulty experienced by the patients, which can reduce the magnitude of patient-control differences (Callicott et al., 2000); (b) the possibility that the performance measures are less sensitive to schizophrenia pathology than the SP; and (c) the small sizes of the subject samples examined, which result in poor statistical power to detect between-group differences. Whilst the patient groups did not display a significant SP, it seems that they were able to accomplish the performance of the task by using only later stimulus selection processes, as indexed by N2 and P3, instead of also implementing an early sensory filter as the healthy subjects did. In conjunction with the observation that the SP did not show a significant correlation to performance here (but see van der Stelt et al., 1998, 2001), these findings suggest that the SP reflects not only “tactical” or immediate processing of the actual visual stimulus, but also “strategic” or future-oriented information processing that is not directly related to the quality of encoding and responding to the presented stimuli.

This study has certain limitations, including the examination of small and medicated patient samples. However, the SP was found to be consistently reduced across patient groups and did not correlate with current medication status or age, indicating that the finding is reliable and valid as opposed to random or confounded by medication or age effects. Another study limitation is that, on the basis of the electrophysiological data alone, no inferences can be made about the anatomical bases of impaired SP generation in schizophrenia. Accordingly, in terms of the conceptual distinction between performing and controlling mechanisms of attention (Näätänen, 1992; Parasuraman, 1998), it is uncertain whether the SP abnormality seen here in schizophrenia reflects disruption of data-processing mechanisms in extrastriate visual cortex (Butler and Javitt, 2005), of controlling mechanisms in prefrontal cortical circuits (Callicott et al., 2000), or of both mechanisms. Nevertheless, assuming that the neuropathology of schizophrenia is widespread or multi-focal (Goldman-Rakic and Selemon, 1997), and in light of evidence that the integrity of selective attention is compromised in the illness, not only in the visual modality but also in the other sensory modalities (e.g., Braff and Light, 2004; Mathalon et al., 2004; Nuechterlein and Dawson, 1984), we favor the interpretation that both modality-specific performing mechanisms and modality-nonspecific or supramodal control mechanisms are disrupted in schizophrenia.

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Fig 1.

Event-related potentials elicited by relevant nontarget stimuli, relevant target stimuli, irrelevant nontarget stimuli, and irrelevant target stimuli at the Cz electrode [A] and color attention-related difference waveforms at the Fz, Cz and Pz electrodes [B] for healthy comparison subjects ($n = 14$), patients at high risk for schizophrenia ($n = 12$), patients with recent-onset schizophrenia ($n = 14$) and patients with chronic schizophrenia ($n = 14$)^a

^a In each group, the event-related potentials (ERPs) consisted of a sequence of negative and positive peaks or components, labeled N1, P2, N2 and P3. In healthy subjects, the earliest ERP sign of selective attention to stimulus color, as isolated in the difference waveforms formed by subtracting the ERPs to irrelevant nontarget stimuli from the ERPs to relevant nontarget stimuli, consisted of an early selection positivity (SP) that occurred between about 80 and 190 ms after stimulus onset (running t -tests showed a significant SP at Pz, Cz and Fz during the 80-190-ms, 100-180-ms, and 130-180-ms poststimulus latency ranges, respectively, $t = 2.3$ -5.0, $df = 13$, all $p < 0.05$). In contrast, the difference waveforms obtained from the high-risk, recent-onset, and chronic schizophrenia groups did not deviate significantly from zero during the 50- to 230-ms poststimulus latency range (t -tests at Pz, all $p > 0.29$; Cz, all $p > 0.13$; Fz, all $p > 0.05$). That is, the patient groups all failed to show a significant color attention-related SP. For the healthy comparison group, mean values of the SP amplitude, quantified as the mean voltage data across the 120- to 160-ms poststimulus latency window, were 1.4 μV , S.D. = 1.0 at Pz; 1.4 μV , S.D. = 1.2 at Cz; and 0.9 μV , S.D. = 0.9 at Fz. Correlational effect size estimates (η^2) of the magnitude of the differences between the healthy comparison group and each patient group in the SP amplitude ranged from 0.22 to 0.37 at Pz, from 0.19 to 0.35 at Cz and from 0.10 to 0.17 at Fz. In patients, the earliest ERP sign of color attention was indexed by enlarged late anterior negative (N2) and/or posterior positive (P3) components. Recently ill and

chronically ill schizophrenia patients, but not high-risk patients, also displayed a significantly smaller color attention effect on the P3 amplitude than healthy comparison subjects.

Table 1
Age-Unadjusted and Age-Adjusted Task Performance Data as a Function of Study Group

Performance	Healthy subjects (n = 14)	High-risk subjects (n = 12)	Recent-onset schizophrenia subjects (n = 14)	Chronic schizophrenia subjects (n = 14)	One-way ANOVA F(3,50) or One-way ANCOVA F(3,49)
Age-Unadjusted					
Hit rate (%)	94.6 _a (4.1)	94.8 _a (3.2)	88.9 _{ab} (8.8)	81.7 _b (14.2)	6.54 ^{***}
Reaction time (ms)	450 _a (42)	476 _a (60)	505 _a (78)	554 _a (136)	3.60 [*]
Age-Adjusted					
Hit rate (%)	93.9 (2.4)	93.6 (2.8)	87.8 (2.6)	84.6 (3.4)	2.37
Reaction time (ms)	465 (23)	502 (26)	528 (24)	494 (32)	1.38

Note. Data values represent mean ± S.D. After rejecting the omnibus null hypothesis of equal group means, pairwise comparisons were tested using independent-samples t tests for equal or unequal variances. Means in the same row that share a letter in their subscripts do not differ significantly from each other, using Holm's sequential Bonferroni procedure to control for Type I error across all pairwise comparisons at the 0.05 level of statistical significance.

^{*} $\bar{p} < 0.05$

^{***} $\bar{p} < 0.01$