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The Contingent Negative Variation Laterality and Dynamics in Antisaccade Task in Normal and Unmedicated Schizophrenic Subjects

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Contingent negative variation (CNV) topography, hemispheric asymmetry and time-course were investigated in healthy subjects and non-medicated paranoid schizophrenic patients in two antisaccade paradigms with the short (800-1000 ms) and long (1200-1400 ms) durations of the fixation period. EEG and electrooculogram (EOG) were recorded. Saccade characteristics and mean amplitudes of slow cortical potentials time-locked to peripheral target were analyzed in 23 healthy volunteers and 19 schizophrenic patients. Compared to healthy control subjects, schizophrenic patients had significantly slower antisaccades and committed significantly more erroneous saccades in the both antisaccade tasks. The prolongation of the fixation period resulted in noticeable decrease of error percent in patients group. The analysis of CNV time-course has revealed two distinct stages in both groups. The early CNV stage was represented by a negative wave with the maximal amplitude over midline fronto-central area, and the late stage was characterized by increased CNV amplitude at the midline and left parietal electrode sites. In healthy subjects the simultaneous activation of frontal and parietal areas was observed in the paradigm with the shorter fixation interval; the increase of the fixation period produced consecutive activation of these areas. Schizophrenic patients' CNV amplitude was generally smaller than that of healthy subjects. The most pronounced between-group differences of the negative shift amplitude were revealed at frontal electrode sites during the early CNV stage in both modifications of the antisaccade task. The deficit of frontal activation revealed in patients at the early stage of antisaccade preparatory set in both antisaccadic paradigms may be related to pathogenesis of paranoid schizophrenia.
Keywords: antisaccades, slow cortical potentials, Contingent Negative Variation, schizophrenic patients.

Se ha investigado la topografía de la variación contingente negativa (CNV), su curso temporal, y asimetría hemisférica en sujetos normales y en pacientes esquizofrénicos paranoides no medicados durante dos paradigmas de movimientos antisacádicos con duración corta (800-1000 ms) y larga (1200-1400 ms) del periodo de fijación. Se registraron el EEG y electro-oculograma. Las características de los movimientos sacádicos y las amplitudes medias de los potenciales corticales lentos relacionados a objetivos periféricos se analizaron en 23 voluntarios sanos y 19 pacientes esquizofrénicos. Comparados con el grupo sano control, los pacientes esquizofrénicos tuvieron movimientos antisacádicos significativamente más lentos y cometieron significativamente más movimientos sacádicos erróneos en ambas tareas antisacádicas. La prolongación del periodo de fijación resultó en un decremento notable del porcentaje de errores en el grupo de pacientes. El análisis del curso temporal de la CNV ha revelado dos etapas distintas en ambos grupos. La etapa temprana de la CNV estuvo representada por una onda negativa con amplitudes máximas en regiones fronto-centrales de la línea media y la etapa tardía estuvo caracterizada por un incremento de la amplitud de la CNV en electrodos parietales izquierdos y de la línea media. En sujetos sanos se observó activación simultánea de áreas parietales y frontales durante el paradigma de intervalo de fijación corto; el incremento del periodo de fijación produjo activación consecutiva de estas áreas. La amplitud de la CNV de pacientes esquizofrénicos fue generalmente menor que la de los sujetos sanos. Las diferencias más pronunciadas entre-grupos en la amplitud de la deflección negativa fueron evidentes en electrodos frontales durante la etapa temprana de la CNV en ambas modificaciones de la tarea antisacádica. El déficit de la activación frontal demostrado en pacientes durante el estado temprano de la preparación antisacádica en ambos paradigmas puede estar relacionado con la patogénesis de la esquizofrenia paranoide.
Palabras clave: movimientos antisacádicos, potenciales corticales lentos, Variación Contingente Negativa, pacientes esquizofrénicos.

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Eye movements provide a behavioral measure of sensorimotor processing and higher cognitive functions of the brain. Application of saccadic paradigms allows for assessing neuronal circuitry abnormalities in psychiatric disorders.

The antisaccade paradigm has been widely used to explore the programming of voluntary saccades. In the antisaccade task, subjects are instructed to inhibit saccades toward the target and to initiate ones in the opposite direction. This paradigm puts an increased demand on higher order cognitive functions thought to be mediated by the prefrontal cortex which integrity is necessary for correct performance of antisaccades (Broerse, Crawford, & den Boer, 2001; Everling & Fischer, 1998; Klein, Heinks, Andresen, Berg, & Moritz, 2000).

Prior results have demonstrated poor antisaccadic task performance in patients with schizophrenia as well as the efficacy of antisaccades clinical application (Broerse et al., 2001; Holzman, 1996; Sereno & Holzman, 1995). However, only the saccade characteristics have been typically analyzed in the majority of clinical investigations. Brain activity associated with performance of the saccadic tasks has been mainly investigated with functional tomography (FT) methods in healthy subjects (Anderson et al., 1994; Curtis & D'Esposito, 2003; Doricchi et al., 1997; Ford, Goltz, Brown, & Everling, 2005; O'Driscoll et al., 1995; Sweeney et al., 1996; Sweeney, Luna, Keedy, McDowell, & Clementz, 2007). A few FT studies have been performed in schizophrenic patients and frontal cortex dysfunction has been found (Camchong, Dyckman, Austin, Clementz, & McDowell, 2008; McDowell & Clementz, 2001; McDowell et al., 2002; O'Driscoll et al., 1998). While providing good spatial resolution, neuroimaging techniques (even such as functional magnetic resonance imaging - fMRI) has a relatively poor temporal resolution, limiting analysis of different neural processes involved in a preparatory set.

Scalp-recorded event-related potentials (ERPs) are used to study cortical preparatory processes that precede the saccade onset with a high temporal resolution. There is an increase in the surface negative potential referred to as the contingent negative variation (CNV) between the warning (WS) and imperative (IS) stimuli in the two-stimulus paradigm (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). This slow negative wave is considered to be a reflection of the endogenous attentional effort, expectation of forthcoming imperative stimulus and motor preparation (Brunia, 1999; Gomez, Marco, & Grau, 2003). The fixation and target stimuli in saccadic tasks correspond to WS and IS, respectively. Amplitude and spatial/temporal parameters of saccadic CNV are dependent on a saccadic paradigm and brain functioning (Evdokimidis, Mergner, & Lucking, 1992; Evdokimidis, Smyrnis, Constantinidis, Gourtzelidis, & Papageorgiou, 2001; Everling, Krappmann, & Flohr, 1997; Klein et al., 2000; Mattews, Flohr, & Everling, 2002). Although pre-saccadic ERPs have been intensively studied in healthy subjects, only isolated ERP studies have been performed with participation of schizophrenic patients (Klein et al., 2000; Reuter, Herzog, Endrass, & Kathmann, 2006). Noteworthily, some important questions remain largely unexplored. Particularly, the time-course and hemispheric asymmetry of cortical activation during the saccadic preparatory set are poorly understood.

The different stages of negative shift evolution in time are interpreted as reflecting the progressive activation of cortical regions related to cognitive operations and generation of corticofugal activity (Gomez et al., 2003; Lee, Chang, & Roh, 1999; Shibasaki, Barret, Halliday, & Halliday, 1980). The several stages of slow potential shifts that precede voluntary finger movements (Barret, Shibasaki, & Neshige, 1986) and remembered saccades (Evdokimidis et al., 2001) have been found to be related to different issues of preparatory set in healthy subjects. In antisaccade task, a set of processes, including rule-holding, motor response programming, inhibition of prosaccades to peripheral cue are carried out during the fixation interval. Depending on the task temporal parameters, these processes can take place both simultaneously and in series (Posner, 2005). Most ERP and fMRI saccadic studies have used relatively long intervals between WS and IS (i.e. fixation intervals), typically more than 3-4 sec. The long fixation intervals allow subjects to delay the shifting of attention to the imperative stimulus and use the "waiting strategy" (Talsma, Slagter, Nieuwenhuis, Hage, & Kok, 2005). At that, some additionally processes are involved. Therefore, to get a better understanding of the time course of main central processes responsible for control of antisaccades, two short fixation intervals were experimentally selected for the present research. The comparison of two durations of fixation intervals was thought to clarify the temporal pattern of activation of cortical areas involved in antisaccade performance.

The structural, functional and neurochemical hemispheric specificity is well known (Geschwind & Galaburda, 1987). Altered cerebral dominance in schizophrenia has been long recognized (Doty, 1989; Green, Sergi, & Kern, 2003), and relationships between handedness and eyedness as well as gender of patients and clinical syndrome have been shown (Doty, 1989; Kalinin, 2001). However, the asymmetry of activation of cortical areas involved in executive function has not been evaluated in the saccadic ERP studies.

To investigate the CNV asymmetry, the careful selection of the male subjects with left hemisphere preference for hand and eye was done in the present research. Eye preference is thought to influence the structural and functional organization of the brain networks, controlling perception, visual spatial awareness and oculomotor functions. Recently, the effects of eydness on the lateral organization of presaccadic EEG changes have been described (Kirenskaya et al., 2008; Lazarev & Kirenskaya, 2008). Recruitment of the subjects for the present study brought about the specific selection of schizophrenic patients with paranoid syndrome. It has been noted (Dvirsky, 1983; Gruzelier, 2003) that patients with left hemisphere functional advantage often demonstrate paranoid, acute, reactive, positive symptoms, while subjects

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with the right hemispheric functional advantage usually have non-paranoid, chronic negative symptoms. Thus, the present research sought to evaluate CNV topography, hemispheric asymmetry and time-course in antisaccade task in healthy subjects and paranoid schizophrenics. A particular attention was paid to the results of healthy subjects because those results could be important for both basic research and clinical applications.

Method

Participants

The data from 42 out of total 48 male subjects (aged 21 - 40 years) who participated in the study were analyzed. Data for five schizophrenics and one control participant were excluded because of artifacts. During the study, subjects participated in one of two experiments. In the experiment I, the sample comprised 13 healthy volunteers (mean age 26,8 ± 1,4 years) and 10 patients (mean age 31,0 ± 2,0 years), and in the experiment II, the data for 10 healthy volunteers (mean age 30,5 ± 2,6 years) and 9 patients (mean age 29,1 ± 1,6 years) were analyzed.

In order to study lateral organization of preparatory processes that precede the stimulus onset in saccadic tasks, we selected right-handed males with the right eye preference. Handedness was assessed by the Annett questionnaire (Annett, 1970), and eye dominance was determined by the near-far alignment test (Berman, 1971) and a card with a hole (Annett & Kilshaw, 1982).

The patients were admitted to Serbsky National Centre of Social and Forensic Psychiatry to undergo examination. Twelve patients were antipsychotic-naive, and seven patients were withdrawn from medication for the period exceeding one year. All of the patients received an ICD-10 diagnosis of a schizophrenic disorder (F20). Patients' current symptomatology was assessed with Positive and Negative Symptom Scale (PANSS). Most of patients (17 subjects) were classified as paranoid (F20.06), and 2 patients had simple schizophrenia (F20.6). We believe that prevalence of paranoid schizophrenia among the patients was related to left hemisphere motor and visual dominance (Gruzelier, 2003; Kalinin, 2001). Formal thought disorders were observed in all cases. Written informed consent for the investigation was obtained from all subjects.

Procedure

Experiments were carried out in a darkened room. The subjects were seated 100 cm in front of a board with 3 red light-emitting diodes (LED's) – the central LED and two peripheral LED's located 10 ° left and right of the central one. The central LED was used as the fixation point (FP). Two other LED's were used as peripheral targets (PT). Participants performed antisaccades and were instructed to look as quickly as possible at the horizontal mirror position of the cue. During the experiment, FP was extinguished simultaneously with PT onset. The duration of PT was 100 ms. Left or right target locations were randomly chosen for each trial. The correction visual stimulus (CS) at the mirror position was presented 1.5-2 s after the PT onset (fig. 1A). To initiate each trial, the subject pressed and held down a mouse button with the right index finger. The mouse was located on the elbow-rest. The button press was introduced in the experimental paradigm to increase attention and motivation levels that are generally reduced in schizophrenic patients. FP was switched on 100-1500 ms after the press. The LED's were controlled by a custom designed computer program.

Two modifications of the antisaccadic task with different fixation times were used. In the A1 task (experiment I), the duration of the interval between the FP and PT onset varied between 800 and 1000 ms, in the A2 task (experiment II), the duration was varied between 1200 and 1400 ms (fig. 1). All intervals varied randomly. 4-5 blocks of 45 trials each were provided during either experiment. Rest interval between the blocks lasted about 3 min.

Recording

The EEG was recorded with 19 electrodes according to the international 10-20 system using an EEG-24 AC amplifier (MBN, Russia). Horizontal electrooculogram (EOG) was recorded with Ag-AgCl skin electrodes placed at the outer corners of both eyes. All active electrodes including EOG ones were referred to the left earlobe, signal from the right earlobe was recorded as the 20^{th} active channel. Electrode impedance was kept below 5-10 kΩ. Prior to further analysis, all channels were recalibrated (off-line) with respect to linked (averaged) earlobes. During the recording, the high cut-off 70 Hz, the time constant 0.3 s and the notch filter 50 Hz were used. Data were sampled at 200 Hz and stored for off-line analysis.

Data analysis

An off-line analysis was performed separately for the A1 and A2 antisaccade tasks. Eye artifact rejection was accomplished by the multiple-source eye correction method (Klein et al., 2000; Novototsky-Vlasov, Garakh, & Kovalev, 2007). Additionally, all of the trials were visually inspected for remaining artifacts and saccade onset correction.

Prior to averaging EEG records were transformed to time constant of 5 s to obtain slow potentials. The transformation procedure makes use of the fact that cut-off frequency of analog filters denotes only –3 dB rejection, and so part of slow activity passes through the filter. Therefore, the remaining activity in the filter stop band may be restored with the exception of DC component (see Ruchkin, Sutton, Mahaffey, & Glaser, 1986, for details).

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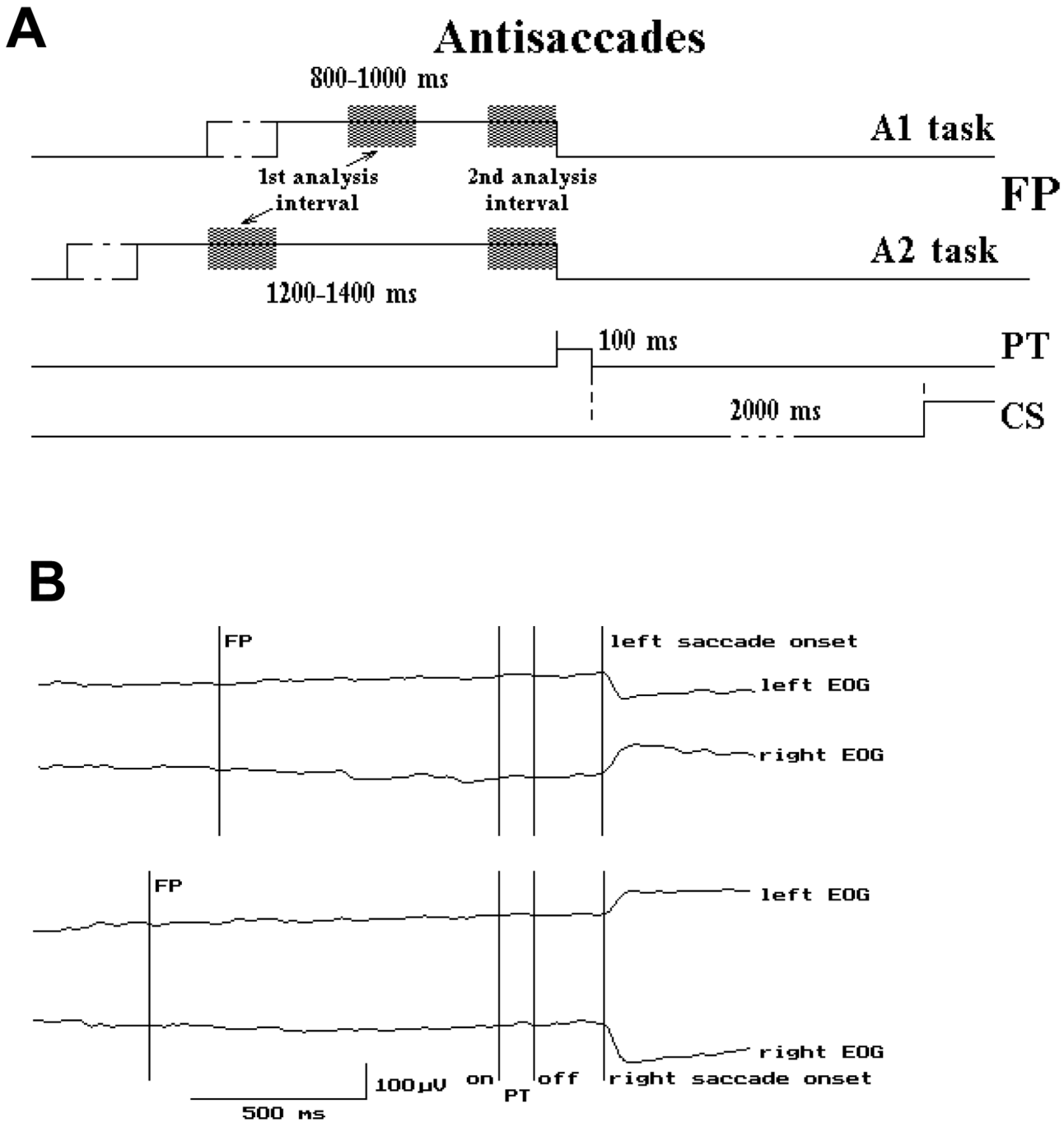

Figure 1. Experimental paradigm and examples of EOG recording.

A. Time-course of the visual stimulus presentation. The square waves denote onset and offset of each stimulus. The first box shape on each line represents the jitter in stimulus onset. The shaded areas depict the analysis intervals.

B. Examples of EOG recording.

FP – fixation point

PT – peripheral target

CS – correction stimulus

EOG - electrooculogram

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The EOG channel was used for automatic saccade onset detection and for measuring saccade latency and direction. Saccade onset was defined as a starting point of EOG deflection exceeding predetermined threshold by slope, and which amplitude exceeded EOG standard variation value. The sign of deflection determined saccade direction (fig. 1B). Each trial was classified according to the latency and direction (correct or wrong with respect to the task instruction) of the saccade. The percentage of correct and wrong saccades was determined. Slow EEG potentials were averaged for correct regular (latency > 120 ms) saccades only, if their number was sufficient for averaging (> 40).

The averages were triggered on peripheral target stimulus onset, and responses to right and left PTs were pulled together for analysis. EEG records 1500 ms before and 500 ms after the trigger onset were averaged. 600 ms analysis epoch before the PT was used for quantitative evaluation of negative potentials amplitude in the A1 task, and 1000 ms epoch before the PT was used in A2 task. Thus, the beginning of the analysis epoch was equally delayed from the FP onset in both tasks. Baseline was determined as mean value of potentials during 100 ms immediately preceding the analysis epoch. Baseline area overlapped intervals from 100 to 400 ms after FP onset due to stimulus onset asynchrony (SOA) between FP and PT. As slow ERP components such as P300 were absent in response to FP onset SOA between FP and PT cancelled out EP influence on CNV parameters.

Two intervals were selected for analysis in accord with dynamics of slow potentials – the first and last 200 ms of the analysis epoch in each task, the 1st interval, corresponding to early preparatory period, and the 2nd interval, corresponding to late preparatory period (fig. 1). Mean amplitudes of the potentials in these two intervals were subjected to further statistical analysis. Sample averaged potentials for two groups are represented in fig. 2.

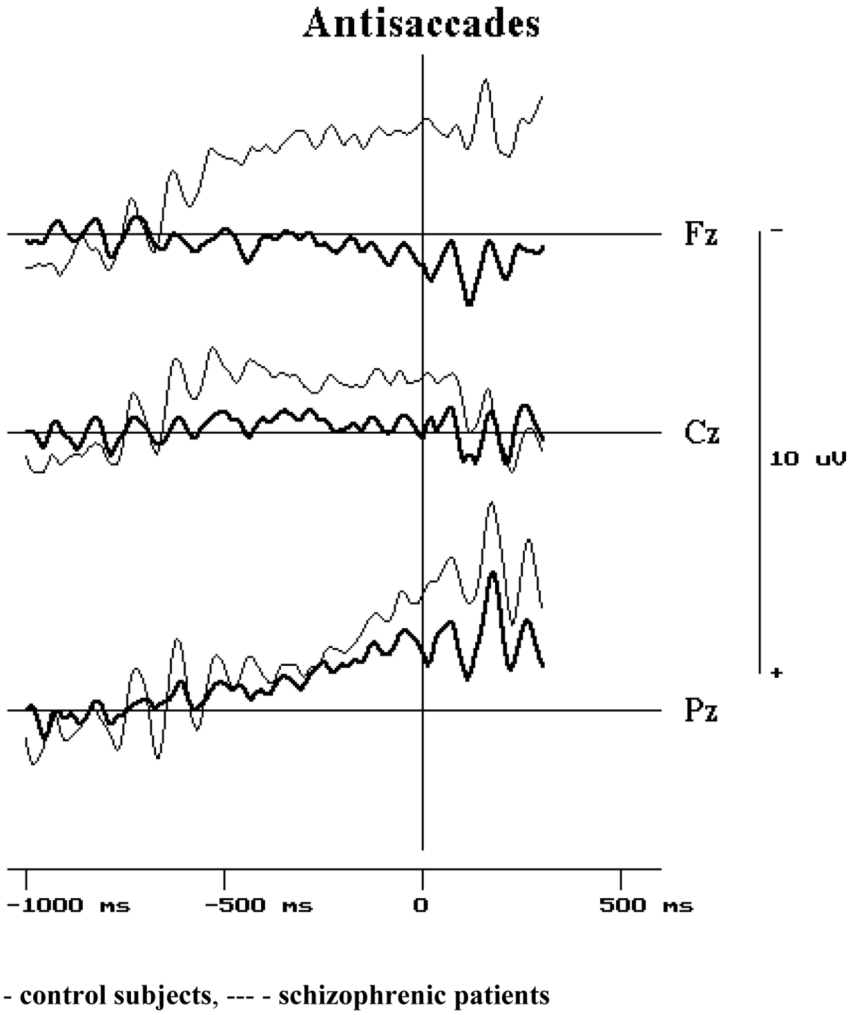

Figure 2. Grand average curves at the midline sites in the groups of control subjects (thin lines) and schizophrenic patients (thick lines) in A1 task.
Zero depicts peripheral stimulus onset.

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Statistical analysis

Statistical analysis of the obtained results was performed using SPSS 11.0 software.

Antisaccade latencies and percent of errors were analyzed by non-parametric Mann-Whitney and Wilcoxon tests.

Mean amplitudes of the slow cortical potentials were analyzed by two different methods using analysis of variance (ANOVA). For the first method (8x2), 16 channels were selected (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6), and ANOVA included between-subjects factors, GROUP (n = 2: patients vs. control subjects) and TASK (A1 vs. A2), and within-subjects factors, INTERVAL (n = 2), ELECTRODE (n = 8) and HEMISPHERE (n = 2: left vs. right sites). The second method included 9 channels (3x3) of analysis (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4), and ANOVA comprised between-subjects factors, GROUP and TASK, and within-subjects factors, INTERVAL (n = 2), ELECTRODE (n = 3: frontal vs. central vs. parietal sites) and LATERALITY (n = 3: left vs. sagittal, vs. right sites). For all main and interaction effects including within-subject factors with more than two levels, violations of the sphericity assumption were controlled for by *df* adjustment. Hence, Greenhouse–Geisser epsilons and corrected p values are reported. For post-hoc analysis of contrasts of group means, we used the Student's t-test for independent samples.

Additionally, Pearson's correlations between PANSS scales and slow potentials amplitudes at frontal, central and parietal electrodes related to localization of negativity zones were analyzed in schizophrenic patients. Only significant ($p < .05$) correlations were examined.

Results

Experiment I - *A1 antisaccade task*

Compared to control subject, the antisaccade latencies were significantly longer in schizophrenic patients. Furthermore, schizophrenic patients made six times more direction errors during the A1 task than control subjects (table 1). Groups of normal and schizophrenic subjects also differed significantly in the characteristics of the slow cortical potentials.

In healthy subjects, during the 1st analysis interval saccadic CNV was widespread over the frontal, central and parietal cortical regions and in the frontal sites it tended to be symmetric. CNV maximums localized at Fz and Cz sites (fig. 3). Further, the CNV amplitudes elevated over the left and midline frontal and parietal areas. During the last 200 ms before PT two distinct zones of the negative shift over frontal and parietal areas (with the maximums at Fz, F3 and Pz, P3 sites respectively) were recorded (fig. 3, ANOVA, 3x3 way – INTERVAL x LATERALITY: $F(2, 24) = 9.17$, $\varepsilon = 0.87$, $p < .005$). Compared to the 1st analysis interval, a significant increase in the CNV amplitude of the 2nd analysis interval was found in parietal sites Pz and P3 ($p < .001$ by pair-wise t-test).

Schizophrenic patients exhibited generally smaller CNV amplitudes than healthy subjects. The most pronounced reduction of the CNV amplitude was revealed at frontal electrode sites and at the vertex electrode (fig. 3A and 3B). At that, the asymmetrical CNV topography with the left hemisphere preponderance was observed during the both intervals of analysis, and negative potentials weren't registered at the right electrode sites in the group of patients. In the 1st analysis interval maximal CNV amplitude was found at

Table 1
Saccade characteristics in antisaccade tasks A1 and A2

		Controls		Patients		Significance of between-group differences Mann-Whitney test
Antisaccade latencies, ms	A1	n = 13	306.6 ± 19.5	n = 10	446.3 ± 37.1	$Z = 2.73$, $p < .01$
	A2	n = 10	303.9 ± 24.0	n = 9	490.7 ± 51.5	$Z = 2.69$, $p < .01$
Significance of between-task differences Wilcoxon test		—		—		
Errors, %	A1	n = 13	4.1 ± 0.8	n = 10	26.3 ± 5.5	$Z = 3.78$, $p < .001$
	A2	n = 10	4.1 ± 1.0	n = 9	13.6 ± 4.4	$Z = 2.21$, $p < .05$
Significance of between-task differences Wilcoxon test		—		$Z = 1.80$, $p = .07$		

The data are presented as Mean ± SEM

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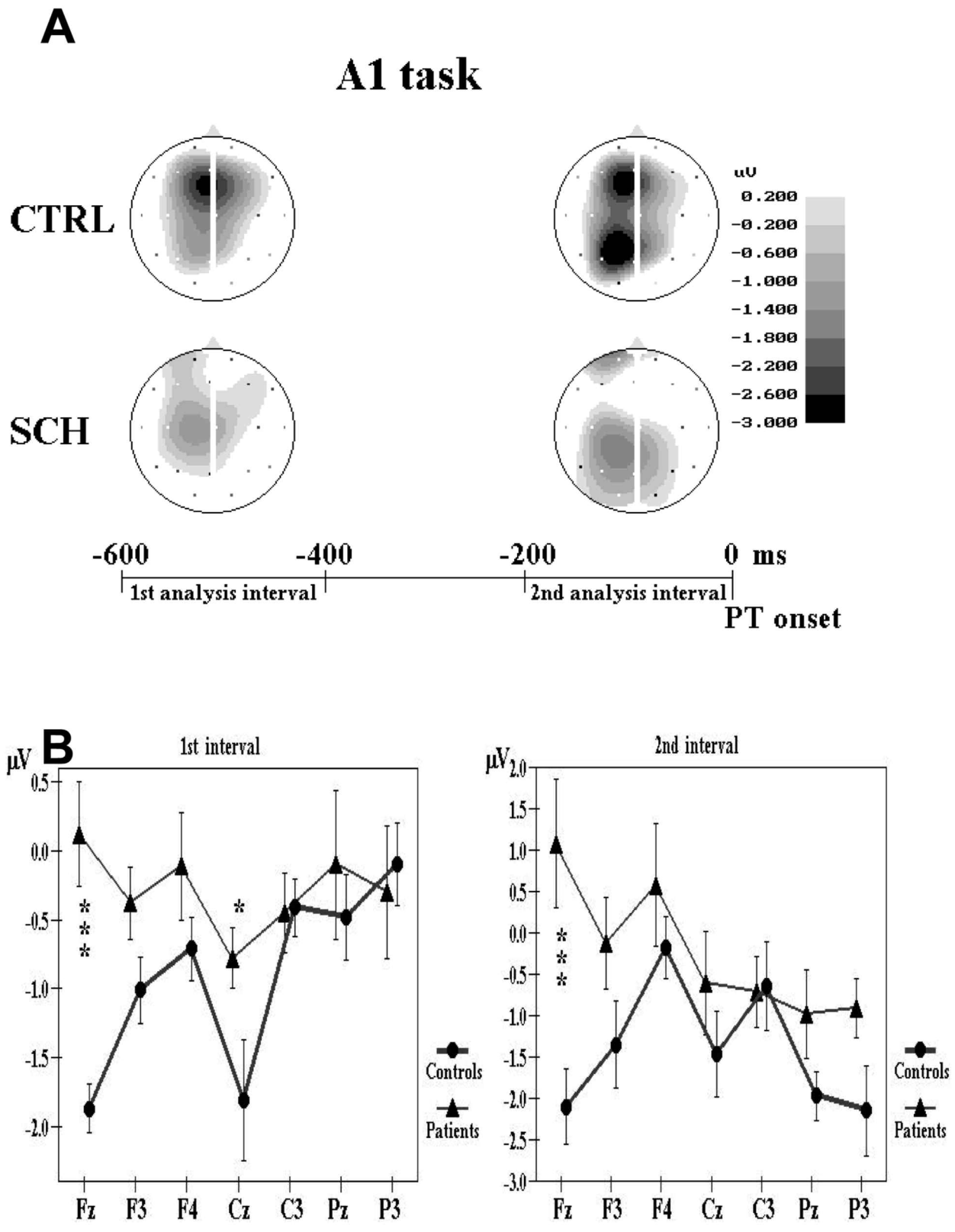

Figure 3. The characteristics of the saccadic CNV in A1 task in healthy subjects and schizophrenic patients.
A. Scalp potential maps of negative shift. Negative potentials are depicted in gray, positive potentials in white.
B. Average CNV amplitudes.
Level of significance: * - $p < .05$, ** - $p < .01$, *** - $p < .001$.

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vertex, and in the 2nd interval maximal values of negativity were recorded at Pz, P3 and at Fp1 (-1,10 ± 0,60 μV) sites (fig. 3). Compared to the 1st analysis interval, a significant ($p < .05$) increase in the CNV amplitude of the 2nd analysis interval was found at left parietal and occipital sites (P3 and O1) (ANOVA, 8x2 way - INTERVAL x ELECTRODE: $F(7, 63) = 4.22$, $\varepsilon = 0.34$, $p < .05$; 3x3 way - INTERVAL x LATERALITY: $F(2, 18) = 7.25$, $\varepsilon = 0.6$, $p < .05$).

The comparison of patients and healthy subjects showed a significant effect for the interaction GROUP x INTERVAL (3x3 way - $F(1, 21) = 8.93$, $p < .01$). There were also significant effects of GROUP (3x3 way - $F(1, 21) = 8.93$, $p < .01$) and GROUP x LATERALITY (3x3 way - $F(2, 42) = 5.82$, $\varepsilon = 0.95$, $p < .01$) in the 1st analysis interval. Significant effects of GROUP (8x2 way - $F(1, 21) = 6.71$, $p < .05$; 3x3 way - $F(1, 21) = 8.30$, $p < .01$), GROUP x ELECTRODE (8x2 way - $F(7, 147) = 2.47$, $\varepsilon = 0.54$, $p = .054$; 3x3 way - $F(2, 42) = 3.71$, $\varepsilon = 0.98$, $p < .05$) and GROUP x LATERALITY (3x3 way – $F(2, 42) = 3.76$, $\varepsilon = 0.89$, $p < .05$) were observed in the 2nd interval. The post-hoc analysis showed that mean CNV amplitudes for the control subjects were significantly larger as compared to patients at Fz during both intervals of analysis (1st interval: $p < .001$; 2nd interval: $p < .001$).), and at Cz during the 1st interval ($p = .054$) (fig. 3).

Experiment II - *A2 antisaccade task*

The saccade characteristics showed no significant differences in the A1 and A2 tasks in healthy subjects (table 1). Mean percent of errors in patients decreased from 26.3 ± 5,5% in A1 to 13.6 ± 4,4% in A2 task ($p = .09$), but remained significantly higher than in the control group ($p < .05$). The saccade latencies of patients were also significantly longer than in the control group (table 1).

The characteristics of the slow potentials differed clearly in dependence of duration of the fixation period *in healthy subjects*. During the 1st analysis interval, the CNV zone situated at the frontal-central area (fig. 4), and had the maximal amplitude at the midline cites (Fz: -1,28 ± 0,44 μV and Cz: -1,17 ± 0,38 μV).

During the 2nd interval, a decrease in the CNV amplitude was observed in the frontal-central area, and an increase – in the sagittal and left parietal-occipital area (fig. 4). The maximal values of CNV amplitude were recorded at the midline parietal (Pz), and left occipital (O1) sites (fig. 4B). Besides, two stable zones of negativity were recorded in the left anterior frontal (Fp1: -1,07 ± 0,32 μV) and in the right anterior temporal (F8: -0,68 ± 0,29 μV) areas. The INTERVAL x ELECTRODE (ANOVA, 8x2 way - $F(7, 63) = 4.03$, $\varepsilon = 0.46$, $p < .05$; 3x3 way - $F(2, 18) = 12.38$, $\varepsilon = 0.96$, $p < .005$) and INTERVAL x LATERALITY (8x2 way - $F(1, 9) = 20.61$, $p < .005$; 3x3 way - $F(2, 18) = 4.80$, $p < .05$) interactions were significant. Pair-wise comparison of the mean potential amplitudes revealed a significant increase in the CNV amplitude for the 2nd analysis interval compared to the 1st one at Pz, P3, Fp1 ($p < ,05$), O1 ($p < ,01$) and T5 ($p = .055$) sites, and its decrease at Fz, Cz ($p < ,05$) and F4 ($p < ,01$) sites.

Significant differences between the A1 and A2 tasks in healthy subjects were obtained only for the 2nd analysis interval. ANOVA revealed significant effects of TASK (8x2 way: $F(1, 21) = 4.67$, $p < .05$; 3x3 way – $F(1, 21) = 7.62$, $p < .05$) and TASK x ELECTRODE interaction (8x2 way: $F(7, 147) = 2.66$, $\varepsilon = 0.61$, $p < .05$; 3x3 way: $F(2, 42) = 3.05$, $\varepsilon = 0.76$, $p = .074$). These differences were related to the lack of negative shift in the frontal cortical regions in A2 task (fig. 4). A comparison of the mean potential amplitudes revealed that during the 2nd analysis interval the CNV amplitude was significantly higher in the A1 task compared to one in the A2 task at Fz ($p < .01$) and Cz ($p = .09$) sites; in the A2 task, CNV amplitude was higher at Fp1, O1 ($p < .05$), F8 ($p = .057$), and T5 ($p = .053$) sites because of the expansion of negativity zone to these cortical regions.

In schizophrenic patients, negative shift of low amplitude localized mainly in the left hemisphere in the 1st analysis interval in the A2 task as well in the A1 one. CNV amplitudes were clearly decreased in patients compared to controls especially at frontal area (fig. 4). Maximal CNV amplitude was noted at the vertex in this group (Cz: -0,58 ± 0,25 μV). The amplitude of negative potentials gradually increased during the fixation period in the left hemisphere except temporal zones (fig. 4). The between-interval contrasts calculated for the group of 5 left electrodes (Fp1, F3, C3, P3, O1) revealed significantly higher left hemisphere activity in the 2nd interval ($F(1, 8) = 132.5$, $p < .001$). Pair-wise comparison of slow potentials' amplitudes between the 1st and 2nd intervals also revealed its significant increase at Pz ($p < .05$). During the 2nd interval, the maximal amplitudes of negative shift were recorded in the left parietal (P3) and left occipital (O1) areas (fig. 4). ANOVA comparison of CNV amplitudes in A1 and A2 tasks in schizophrenic patients didn't reveal any significant differences.

Healthy and schizophrenic subject groups significantly differed in the 1st interval only in the A2 task (GROUP, 3x3 way - $F(1, 17) = 5.32$, $p < .05$). The post-hoc analysis showed that mean CNV amplitudes for the control subjects were significantly larger as compared to patients at Fz ($t = 2.33$, $df = 17$, $p < .05$) and at F8 ($t = 2.1$, $df = 17$, $p = .051$) in the 1st interval of analysis, and at F8 in the 2nd interval ($t = 2.0$, $df = 17$, $p = .061$) (fig. 4).

The analysis of correlations of PANSS scales with absolute values of slow potentials' amplitudes revealed that high PANSS values corresponded to lower amplitudes of negative shifts. The significant correlations were mainly obtained for frontal sites during the 1st analysis interval and for the PANSS scales predominantly related to productive symptomatology typical of paranoid patients (see table 1-A in the Appendix). Maximal number of correlations was found for Fz ($n = 15$) and F3 ($n = 9$) sites (fig. 5).

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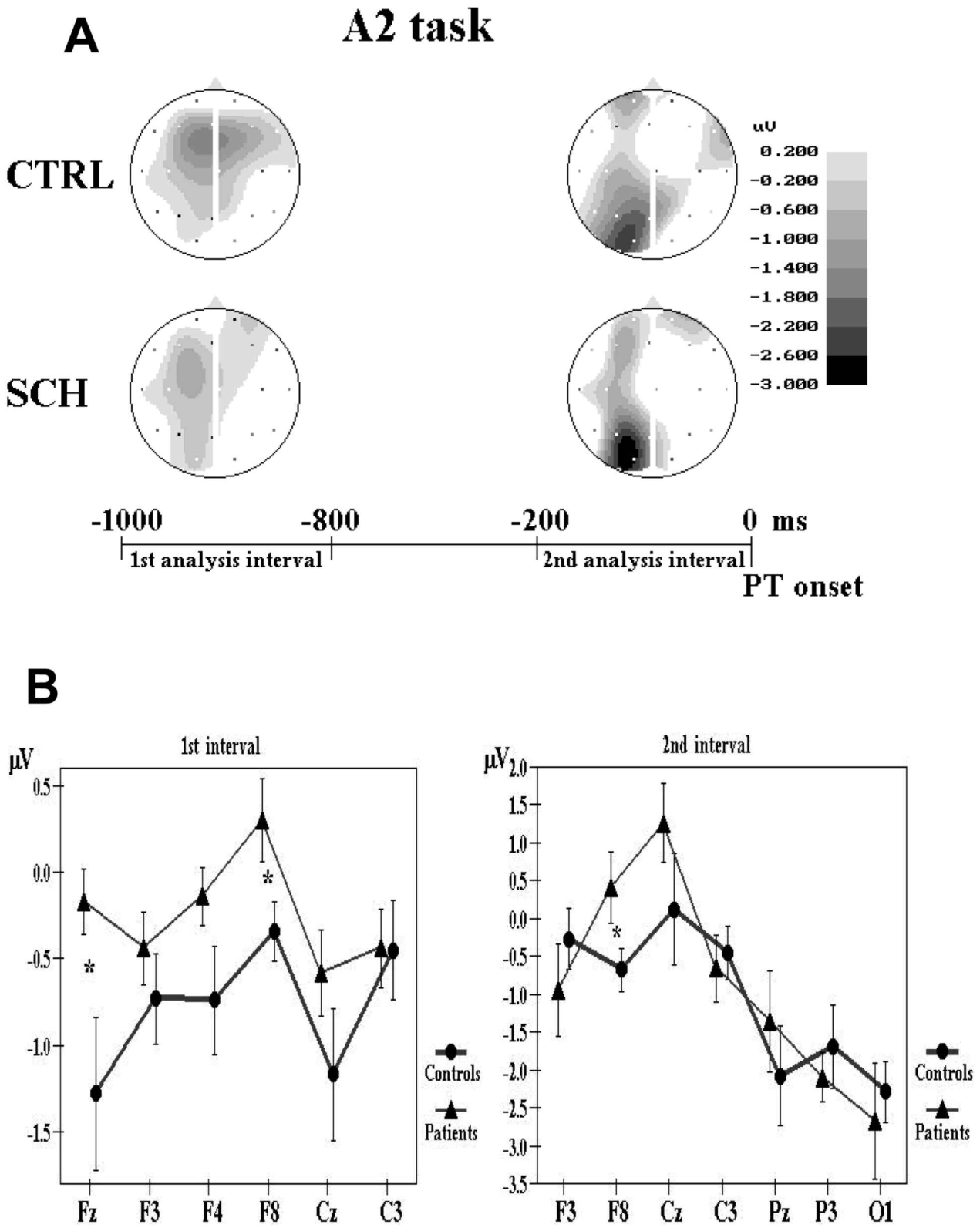

Figure 4. The characteristics of the saccadic CNV in A2 task in healthy subjects and schizophrenic patients.
A. Scalp potential maps of negative shift. Negative potentials are depicted in gray, positive potentials in white.
B. Average CNV amplitudes.
Level of significance: * - $p < .05$, ** - $p < .01$, *** - $p < .001$.

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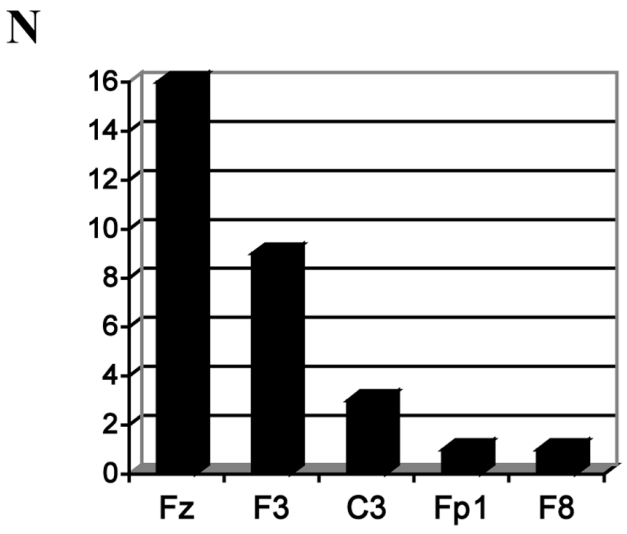

Figure 5. Significant ($p < .05$) correlations between PANSS scales and SCP mean amplitude at frontal sites in A1 and A2 tasks. N – number of correlations.

Discussion

Our findings demonstrate that compared to healthy control subjects, schizophrenic patients had significantly slower antisaccades and committed significantly more direction errors, that is, reflexive prosaccades, in both antisaccade tasks. An analysis of CNV time-course has revealed two distinct stages in both groups. In healthy subjects, the early CNV stage was represented by a negative wave with the maximal amplitude over midline fronto-central area, and the late stage was characterized by increased CNV amplitude at the midline and left parietal areas. Schizophrenic patients' CNV amplitude was generally smaller than that of healthy subjects. The most pronounced CNV reduction was observed at frontal electrode sites during the early stage in both modifications of the antisaccade task.

The characteristics of the saccades and pre-saccadic negative EEG-potentials in healthy subjects found in the present study are mainly in line with previous reports (Everling et al., 1997; Richards, 2003). However, a careful selection for the study of male subjects with the right hand and eye preference and use of two durations of the fixation period allowed us to determine CNV time-course and lateral organization during antisaccade preparatory set more precisely. A novel finding of our experiments is that CNV time-course during the fixation period consists of two distinct stages, compatible with a rostro-caudal gradient of cortical activation during the motor preparatory period (Evdokimidis et al., 2001; Fuster, 1989; Rushworth, Passingham, & Nobre, 2002). In A1 paradigm, the early negative wave in healthy subjects localized over frontal-central-parietal electrode sites and reached the maximum at the medial frontal site (Fz). The late negative wave (200 ms before the PT) consisted of two foci of negativity over the frontal and parietal areas and showed left and midline prevalence, suggesting a simultaneous activation of frontal and parietal areas of the cortex. In A2 paradigm, a symmetrical frontal activation was observed at the early stage of the preparatory period, and at the late stage, the negativity amplitude attenuated over fronto-central area and increased over left and midline parietal and occipital areas. Thus, the data suggest a successive activation of frontal and parietal areas in A2 paradigm. Interestingly, in A2 but not in A1 paradigm, the negative potentials of the moderate amplitudes were recorded in healthy subjects at Fp1 and F8 sites that correspond to left orbitofrontal and right frontal dorsolateral cortices. The activation of these cortical areas may be related to additional processes initiated during a longer preparatory period in A2 task.

The early CNV frontal maximum observed in healthy subjects in both modifications of antisaccade task is in agreement with the results of other saccadic ERP studies (Everling et al., 1997; Klein et al., 2000; Richards, 2003). At that, the frontal activation was found in relation to inhibitory motor control in the 'no-go" task (van Boxtel, van der Molen, Jennings, & Brunia., 2001). Increased frontal activity before antisaccades has been also found in several human fMRI studies in the frontal eye field (FEF), supplementary eye field (SEF), supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC) and in the anterior cingulate cortex (ACC) (Brown, Vilis, & Everling, 2007; Curtis & D'Esposito, 2003; Doricchi et al., 1997; Ford et al., 2005; McDowell & Clementz, 2001; McDowell et al., 2002; O'Driscoll et al., 1995; Paus, Petrides, Evans, & Meyer, 1993; Sweeney et al., 1996). In similar vein, the increased neural firing in the prefrontal cortex (SEF, DLPFC, and ACC) before antisaccades has been demonstrated in monkeys (Amador, Schlag-Rey, & Schlag, 2004; Johnston & Everling, 2008; Schlag-Rey, Amador, Sanchez, & Schlag, 1997). The frontal cortex activity during the preparatory period in antisaccade task is thought to be related to various cognitive processes involved in preparing the system for appropriate task performance, such as sustained attention, preparation to the inhibition of the reflexive prosaccades, maintenance of information in working memory.

The maximal amplitudes of the early CNV were recorded at the medial frontal central area in our study. The results of magnetoencephalography, stereoelectroencephalography, fMRI studies, and EEG LORETA analysis demonstrated the importance of the frontal medial brain walls to initiate and sustain the CNV component (Bares, Nestrasil, & Rektor, 2007; Cui et al., 2000; Gomez et al., 2004; Gomez, Flores, & Ledesma, 2007; Nagai et al., 2004;). The data also support a role for the dorsomedial frontal cortex in tasks with competing responses (Carter, Botvinick, & Cohen, 1999; Casey B., et al., 2000; Pardo, Pardo, Janer, & Raichle, 1990; Rushworth, Walton, Kennerley, & Bannerman, 2004), and

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are consistent with ACC activation during response conflict processing (Brown, Vilis, & Everling, 2007; Fan et al., 2007; Paus et al., 1993).

The late stage of CNV was characterized by the expansion of activation to post-central cortical regions. Maximal CNV amplitudes were recorded at the medial and left parietal sites. Several saccadic ERP studies have already shown a parietal activation that was related to the initiation of the saccadic eye movement (Evdokimidis et al., 2001; Everling et al., 1997; Richards, 2003). It has been demonstrated that the posterior parietal cortex is involved in attentional processes as well as in the motor planning and preparation of saccades (Andersen, Brotchie, & Mazzoni, 1992; Barash & Zhang, 2006; Goldberg & Segraves, 1989; Rushworth, Johansen-Berg, Gobel, & Devlin, 2003). Thus, the parietal negativity observed in our study may reflect an activation of visual-motor centers in the posterior parietal cortex.

Several current models have demonstrated the importance of interplay between frontal and parietal cortex for performance of different variants of the delay tasks. It is supposed that activation of fronto-parietal networks during the CNV reflects the endogenous attention effort during the preparatory period, the imperative stimulus expectation and preliminary motor activation (Brunia, 1999; Corbetta & Shulman, 2002; Cui et al., 2000; Fan et al., 2007; Gomez et al., 2003). The fronto-parietal networks contribution in the CNV generation was shown by LORETA techniques, PET and fMRI methods (Brown et al., 2007; Cabeza & Nyberg, 2000; Fan et al., 2007; Gomez et al., 2003; Gomez et al., 2007). It has been suggested that the certainty of decision to move is reflected in the activity of both DLPFC and posterior parietal (PPC) cortices that is supported by anatomical connections between the two areas (Selemon & Goldman-Rakic, 1988). Prefrontal-parietal interaction has been observed in spatial working memory and antisaccade tasks (Brown et al., 2007; Chafee & Goldman-Rakic, 2000; Evdokimidis et al., 2001; McDowell & Clementz, 2001; Selemon & Goldman-Rakic, 1988). Performance of antisaccades may require computation and maintenance of the target coordinates in working memory during the pre-saccade period. Our data concerning time-course of frontal and parietal activation during the fixation period are in line with this notion. We think that a shorter time interval between onsets of FP and PT in A1 task (800-1000 ms) determined a simultaneous activation of frontal and parietal networks during the last 200 ms before PT. The increase of the fixation interval in A2 paradigm produced a consecutive rather than synchronized activation of frontal and parietal areas in antisaccade preparation.

Another interesting result of the work is demonstration of the asymmetrical topography of the late presaccadic negativity. Midline and left hemisphere locations of pre-saccadic negativity during the last 200 ms before PT were found in both groups and may be attributed to our selection of male subjects with left hemisphere advantage. Our results are in agreement with the concept of the left hemisphere dominance in motor attention and preparation of motor response (Astafiev et al., 2003; Khonsari et al., 2007; Rushworth et al., 2003; Tucker & Williamson, 1984).

The increased errors' percent in schizophrenic patients obtained in the study confirmed results of other studies (Broerse et al., 2001; Everling, & Fischer 1998; Holzman 1996; Klein et al., 2000) suggesting an impaired inhibition of a "stimulus-driven" response. Error proportions vary greatly between different laboratories (reviewed in Broerse et al., 2001; Everling & Fischer 1998). We found that the prolongation of fixation period led to noticeable decrease of errors committed by patients, but not healthy subjects. Thus, patients' antisaccade task performance was particularly influenced by different stimulation conditions, and it have to be kept in mind while comparing results of different studies.

We found that compared to healthy subjects, schizophrenic patients generally exhibited a reduced amplitude of CNV and failed to show the frontal focus of negativity. These alterations were observed during the early stage of CNV in both antisaccadic paradigms. The present findings are corroborated by the results that have described the reduced CNV before pre-warned manual motor responses (reviewed in Klein, 1997) and frontal and prefrontal hypo-metabolism in schizophrenic patients (Broerse et al., 2001; Camchong et al., 2008; McDowell & Clementz, 2001; McDowell et al., 2002).

The significant decline of the negativity amplitude at the frontal sites found in schizophrenic patients suggests functional abnormalities in medial and dorsolateral frontal cortical areas (SEF, SMA, DLPFC and ACC) that may be responsible for the observed antisaccade deficit. These prefrontal cortical areas and the medial dorsal nucleus (MD) comprise a part of the anterior attention system, mediating executive function and attention. Deficits in these areas in schizophrenia have been reported in structural and functional brain imaging studies (Berman, 2002; Hazlett et al., 2004; Lehrer et al., 2005; Salgado-Pineda et al., 2004; Yücel et al., 2002). Besides, the pattern of simultaneous activation of frontal and parietal cortices before antisaccades in A1 task was not found in schizophrenic patients. The frontal-parietal interaction impairments in schizophrenia may also be related to frontal dysfunction.

The increase of the fixation period in the A2 paradigm apparently simplifies antisaccade task performance in schizophrenic patients, which demonstrated significant decrease of errors percent in A2 task compared to A1 task. In addition, the CNV topography and amplitude during the last 200 ms before target cue were similar in healthy subjects and patients in A2 task. In contrast, in A1 task with the short fixation interval, the differences between groups were observed throughout the entire analysis period. One can assume some slowing in neuronal processes in patients, consistent with

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significantly increased saccade latency. Thus, it was enough time for realization of the processes related to the late CNV in the A2 task with the extended fixation interval. However, in the A2 task as well as in the A1 one the early stage of CNV characterized reduced amplitude in medial frontal area in schizophrenics compared to healthy subjects.

As the early stage of CNV is associated with cognitive aspects of preparatory set, reduced CNV in schizophrenic patients might reflect its deficit such as attentional disorders and disability to voluntarily suppress prepotent behavioral responses. The revealed in the study positive correlations between the decreased negativity amplitude at Fz and F3 sites (mainly during the 1st analysis interval) and PANSS scales also suggest close relations between deficit of medial and dorsolateral frontal cortical areas activation during the early CNV period and psychopathological abnormalities in schizophrenic patients.

Thus, it may be supposed that deficit of frontal activation at the early stage of antisaccade preparatory set concerns the pathogenesis of schizophrenia. The obtained results complement the reports about saccadic CNV reductions in schizophrenic patients (Klein et al., 2000) with respect to the gender, hemisphere functional asymmetry and clinical syndrome.

Conclusions

The present findings demonstrate two CNV stages in antisaccade task in healthy subjects. Early bilateral CNV in frontal cortical regions is considered to be a reflection of various cognitive aspects of preparatory set. Late CNV in left and medial parietal areas apparently relates to preparation of saccadic motor output and sensory attention enhancement. Compared to healthy controls, paranoid schizophrenic patients showed a deficit of frontal negativity at the early stage of CNV in both antisaccadic paradigms. One can suggest that this deficit of frontal activation at the early stage of antisaccade preparatory set concerns the pathogenesis of schizophrenia. The quantitative CNV analysis in antisaccade task may be useful for clinical research of frontal deficit in schizophrenic disorders.

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