Eur Arch Psychiatry Clin Neurosci (2005) 255 : 299–307 DOI 10.1007/s00406-005-0562-1

ORIGINAL PAPER

Ann-Christine Ehlis · Jürgen Zielasek · Martin J. Herrmann · Thomas Ringel · Christian Jacob · Andreas J. Fallgatter

Beneficial effect of atypical antipsychotics on prefrontal brain function in acute psychotic disorders

Received: 10 May 2004 / Accepted: 18 November 2004 / Published online: 7 January 2005

Abstract Disturbance of prefrontal brain functions is assumed to be responsible for prominent psychopathological symptoms in psychotic disorders. Treatment with atypical, in contrast to typical antipsychotics is considered as a possible strategy for an improvement of prefrontal brain function. In the present study, response control as a specific prefrontal brain function was assessed by means of the Nogo-anteriorization (NGA) derived from the event-related potentials elicited during a Go-NoGo task in a consecutive sample of 39 patients suffering from acute psychotic disorders (brief psychotic disorders, 298.8, n = 34 and schizoaffective disorders, 295.70, n = 5; cycloid psychoses according to the Leonhard classification). A highly significant positive correlation between the amount of antipsychotic medication in terms of chlorpromazine equivalents per day and the NGA as a measure of prefrontal response control was only found in the subgroup of patients treated exclusively or predominantly with atypical antipsychotics but not for those treated with typical antipsychotics. These results are in line with the notion that atypical antipsychotics may exert a beneficial effect on prefrontal brain function.

Key words cycloid psychosis · atypical antipsychotics · anterior cingulate cortex (ACC) · nogo-anteriorization (NGA) · schizophrenia

A.-Ch. Ehlis, MA · J. Zielasek, MD · M. J. Herrmann, PhD · Th. Ringel, MD · Ch. Jacob, MD · A. J. Fallgatter, MD (✉)
Laboratory for Psychophysiology and Functional Imaging
Department of Psychiatry and Psychotherapy
University Hospital of Wuerzburg
Fuechsleinstrasse 15
97080 Wuerzburg, Germany
Tel.: +49-931/201-77650
Fax: +49-931/201-77550
E-Mail: Fallgatter_A@Klinik.uni-wuerzburg.de

Introduction

There is extensive evidence from neuropsychological (Abbruzzese et al. 1997; Riley et al. 2000) and neuroimaging (Andreasen et al. 1992; Carter et al. 1997; Hazlett et al. 2000; Higashima et al. 2000; Volz et al. 1999; Yücel et al. 2002) studies indicating a functional hypofrontality in patients suffering from schizophrenia (hypofrontality concept; Ingvar and Franzen 1974). Recent findings from studies on both animals and humans suggest that atypical antipsychotics preferentially exert their effects within frontal and prefrontal brain areas (Braus et al. 2001, 2002; Ende et al. 2000; Honey et al. 1999; Ichikawa et al. 2002; Pehek et al. 1994), whereas conventional antipsychotics were found to have little or no impact on frontal structures (Ichikawa et al. 2002; Li et al. 1998) or even seem to interfere with frontal functioning/metabolism (Bartlett et al. 1994; Braus et al. 2001; Madsen et al. 1998; Miller et al. 2001). Since impairments in frontal and prefrontal brain areas have been suggested to at least contribute to the cognitive dysfunctions observed in schizophrenic patients (Lidow et al. 1998), findings fit well that indicate a more favorable effect of atypical as compared to typical antipsychotics on neurocognition in schizophrenia (Braus et al. 2002; Bilder et al. 2002; Canadian Cognition and Outcome Study Group 1998; Cuesta et al. 2001; Gallhofer et al. 1996; Green et al. 1997; Lee et al. 1994; Purdon et al. 2001; Stip and Lussier 1996; Velligan et al. 2002).

The Continuous Performance Test (CPT; Rosvold et al. 1956) is a Go-Nogo task that demands the execution of appropriate responses to pre-defined target-stimuli (Go) as well as the inhibition of prepared motor responses following other stimuli (Nogo). Consequently, performance of the CPT involves prefrontal structures that are activated during such processes of cognitive response control. Performance of the CPT leads to a specific electrophysiological pattern that involves a shift of the positive brain electrical field from posterior to anterior during the Nogo as compared to the Go condition

(Nogo-anteriorization, NGA; Fallgatter et al. 1997, 2000; Fallgatter and Strik 1999). Electrophysiological source localization (LORETA; Pascual-Marqui et al. 1994) revealed a close relationship between the NGA and a Nogo-hyperactivity in certain prefrontal brain areas, particularly the anterior cingulate cortex (ACC), in healthy subjects (Fallgatter et al. 2002; Strik et al. 1998). Thus, the NGA has been suggested to be an electrophysiological correlate of prefrontal response control (Fallgatter and Strik 1999). In accordance with the hypofrontality concept mentioned above, schizophrenic patients were found to have a significantly reduced mean NGA (Fallgatter and Müller 2001) and do not show a significant activation of the ACC during the Nogo condition of the CPT (Fallgatter et al. 2003).

The present study aimed at comparing the effects of typical and atypical antipsychotic medication on prefrontal brain function in a group of patients suffering from acute psychotic disorders. If atypical neuroleptic drugs are superior to typical antipsychotics in facilitating prefrontal functioning, treatment with atypical medication might improve/ameliorate mechanisms of prefrontal response control resulting in higher values of the Nogo-anteriorization in atypically medicated patients. To examine this issue, we investigated a group of patients with acute psychotic disorders (brief psychotic disorders and schizoaffective disorders according to DSM-IV) who were either receiving typical neuroleptic medication or were being treated with atypical compounds alone or in combination with small amounts of typical antipsychotics. According to Leonhard's nosology (Leonhard 1999) the patients were all classified as suffering from different types of cycloid psychoses.

Clinically, cycloid psychoses are mainly characterized by a phasic course with full remission after the psychotic episodes and a favorable long-term outcome. They usually exhibit a polymorphous and bipolar symptomatology, often rapidly changing from one pole to the other (e. g. from a hyperkinetic to an akinetic state). On the other hand, they usually lack severe negative symptoms and other features typically related to this symptom cluster (e. g. severe and chronic social impairment; Jäger et al. 2003). In the international classification systems (ICD-10 and DSM-IV), the diagnosis of a cycloid psychosis often corresponds to an acute polymorphic psychotic disorder or the acute schizophrenia-like psychotic disorder (ICD-10: F23.0; F23.1; F23.2), to a schizophreniform disorder (DSM-IV: 295.40), or to a schizoaffective disorder (ICD-10: F25.x; DSM-IV: 295.70).

On a neurophysiological level, patients suffering from cycloid psychoses were found to exhibit some characteristic features, comprising e. g. normal P300 topographies and latencies in a standard auditory oddball paradigm, but significantly increased P300 amplitudes as compared to a healthy control sample (Strik et al. 1996). During performance of the CPT, our own group reported intact Go potentials, but significantly reduced Global Field Power (GFP) values and latencies during Nogo trials in cycloid psychoses as compared to matched control subjects, indicating mild deficits in prefrontal response control in these patients (Ehlis et al., in press). Preliminary functional imaging studies indicate an "acute hyperfrontality" in some cases of cycloid psychoses, which later returns to normal in the course of the treatment (cf. Jabs et al. 2002).

Since one of the major characteristics of a cycloid psychosis is the phasic course of the illness with transient psychotic episodes and full remission of the symptomatology after each episode, it seems to be a reasonable assumption that the underlying cerebral abnormalities are also particularly influenceable and non-static. Accordingly, transient psychotic disorders might be an optimal clinical group to assess the physiological effects of different types of antipsychotic medication on prefrontal brain functioning.

Therefore, we investigated a group of patients with acute psychotic disorders/cycloid psychoses electrophysiologically employing the Continuous Performance Test, to compare patients receiving typical antipsychotic medication to patients treated with atypical drugs. Based on the findings cited above it was hypothesized that atypically medicated patients would display higher values of the NGA than patients treated with typical antipsychotics, reflecting stronger prefrontal activation in the atypically medicated group.

Material and methods

Subjects

A total of 69 patients suffering from acute psychotic disorders were investigated electrophysiologically after written informed consent was obtained. Due to an insufficient number of artifact-free EEG-epochs ($n < 20$), 30 of them were excluded from further analyses. The remaining 39 patients (17 male, 22 female) were all either psychiatric in- ($n = 36$) or outpatients ($n = 3$) at the Psychiatric University Hospital in Wuerzburg. Of the 39 patients, 37 were right-handed according to Oldfield (1971); mean age was 33 ± 8 years (mean ± standard deviation (SD)).

According to DSM-IV criteria, patients were diagnosed as brief psychotic disorders (298.8; $n = 34$) and schizoaffective disorders (295.70; $n = 5$). According to Leonhard's nosology (Leonhard 1999) patients were all classified as suffering from different types of cycloid psychoses (13 anxiety-happiness, 18 excited-inhibited confusion, and 8 hyperkinetic-akinetic motility psychoses).

Diagnoses were made by at least two experienced psychiatrists, and only patients were included in the study who could be diagnosed unequivocally. In more detail, the course of action during the diagnostic procedure was as follows: The psychiatrist on duty during admission of the patient made a first diagnosis following a detailed diagnostic interview. The ward's senior physician then examined the patient in a separate session, coming to an independent diagnostic evaluation. Finally, the researcher assigned to the data analysis of the present study only included the data of such patients whose diagnoses were agreed on by both psychiatrists and were in agreement with the patients' past medical records.

Mean duration of illness was 69 ± 60 months with an average of 3.3 ± 2.8 psychiatric hospitalizations and a total duration of inpatient treatments of 6 ± 5 months. Mean duration of the current hospitalization was 47 ± 38 days (outpatients were excluded from this latter statistic).

Patients underwent electroencephalographic and neuroradiolog-

ical investigations carried out routinely, revealing a mild or moderate slowing of the basic EEG rhythm in nine patients, as well as a discrete extension of the interior ventricles in three cases and mild to moderate brain atrophy in six other cases. Four patients had positive family histories for schizophrenia with an affected first-degree relative. Patients were all treated with neuroleptic medication and received 604 ± 463 mg (mean ± SD) chlorpromazine equivalents per day, daily doses ranging from 30 mg to 2392 mg. 26 patients received typical (haloperidol, perazine, flupentixol) and 9 patients atypical antipsychotics (clozapine, quetiapine, olanzapine, risperidone) only, whereas 4 patients were medicated with both groups of substances simultaneously. Patients' charts were examined carefully to ensure that none of the typically medicated patients had received atypical neuroleptic medication in the past.

The present article deals with the influence of the type of neuroleptic medication on prefrontal response control in acutely psychotic patients and mainly focuses on comparing typically and atypically medicated patients. A detailed comparison of the electrophysiological data of the present sample of patients as a whole and a matched control group has been reported elsewhere (Ehlis et al., in press). The control group consisted of 39 healthy volunteers matched for age and sex (19 male, 20 female; mean age: 33 ± 8 years). They were free of medication and had no history of neurological or psychiatric illness. Of the 39 healthy controls, 38 were right-handed according to Oldfield (1971). The study was approved both by the Ethics Committee of the University of Wuerzburg and by the research conference of the Department of Psychiatry and Psychotherapy.

Electrophysiological paradigm

For the electrophysiological investigation, subjects were seated on a comfortable chair in front of a computer screen in an electrically shielded, dimly lit room to perform the Continuous Performance Test (CPT). Letters were presented sequentially in a pseudo-randomized order and participants were instructed to press a response button whenever the letter "O" was directly followed by the letter "X". Speed and accuracy were emphasized equally during explanation of the test. The whole stimulus set consisted of 400 letters, with 80 primer conditions (O), 40 Go (O-X) and Nogo (O-any other letter) conditions and 240 distractors (other letters, or letter X without a preceding O). With an interstimulus interval of 1650 ms, each letter was presented for 200 ms. After a short training session, subjects performed this version of the CPT for about 13 minutes while the ongoing EEG was recorded.

EEG recording

The EEG was recorded from 21 electrodes according to the International 10–20 system (Jasper 1958; Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, T5, T6, P3, P4, O1, O2, Fpz, Fz, Cz, Pz, and Oz). Three additional electrodes were placed at the outer canthi of both eyes and below the right eye to register horizontal and vertical eye movements. Linked mastoids were used as the recording reference and electrode impedances were constantly kept below 5 kΩ. The recording system consisted of a 32-channel DC amplifier (Brain Star System) and the Neuroscan data acquisition software that was calibrated with an external 100 μV/10 Hz signal. The hardware filter was set to a bandpass of 0.1–70 Hz; A/D rate was 256 Hz.

Data analysis

A computerized artifact rejection excluded all segments with amplitudes exceeding 98 μV in any of the EEG or EOG channels within the first 500 ms after stimulus onset. The remaining artifact-free EEG segments were then averaged to one Go and one Nogo event-related potential (ERP) for each participant, whereby only trials with correct responses were included. Subjects with less than 20 artifact-free EEG epochs in either the Go or the Nogo condition were excluded from further analyses. In the individual Go and Nogo ERPs the global field power (GFP; Lehmann and Skrandies 1980) peaks were determined within a P300 microstate. The GFP represents the mean of all possible potential differences in a given scalp potential field and is used as an estimator of the electrical field strength in multi-channel recordings. At the individual GFP peaks, the amplitude, latency and anterior-posterior location of the positive centroid (the amplitude-weighted center of gravity of the positive brain-electrical field; Lehmann 1987) were calculated. A two-dimensional delineation of the electrode array was used as a coordinate system with the integers 1 to 5 indicating the electrode positions in the anterior-posterior and left-right direction to quantify the centroid locations. Finally, the Nogo-anteriorization (NGA), defined as the distance between the individual Go and Nogo centroid within this coordinate system, was calculated separately for each subject.

LORETA method

LORETA (Low Resolution Electromagnetic Tomography; Pascual-Marqui et al. 1999) is a three-dimensional source localization method that aims at identifying in three-dimensional space the electrical sources contributing to the electrical scalp field. To this end, LORETA calculates the current density at each of 2394 voxels in the gray matter and the hippocampus of a reference brain (Brain Imaging Centre, Montreal Neurologic Institute; MNI305) as the linear, weighted sum of the scalp electric potentials, whereby the smoothest of all possible current density configurations throughout the brain volume is chosen by minimizing the total squared Laplacian of source strengths. LORETA does not make any assumptions about the number of sources contributing to the scalp potentials; the only pre-assumption that is made is that neighboring voxels have a maximally similar electrical activity. The LORETA method has been described in more detail elsewhere (Pascual-Marqui et al. 1994, 1999; Strik et al. 1998).

The version of LORETA employed in the present study uses a three-shell spherical head model registered to the Talairach space (Pascual-Marqui et al. 1994, 1999). In a simulation experiment, LORETA has been shown to localize sources more reliably than four other source localization techniques (Pascual-Marqui 1999). Further studies that aimed at validating the source localization properties of LORETA have shown that LORETA detects activation in the same brain areas as other brain imaging techniques during simple acoustic and visual processes (Pascual-Marqui et al. 1994) as well as during performance of more complex cognitive tasks (Lehmann et al. 2001; Mulert et al. 2001; Strik et al. 1998; Winterer et al. 2001). In a combined ERP-fMRI study that aimed at evaluating the statistical correspondence of cerebral activation measured by LORETA and fMR imaging, LORETA has been shown to localize activation in similar structures as fMRI during a language-processing task (Vitacco et al. 2002). The same was true for a simultaneous EEG-fMRI study employing an auditory oddball paradigm; here the LORETA source localization again corresponded closely to the activated areas detected by fMRI (Mulert et al. 2004).

For the present study, LORETA calculations are based on the mean of the individual GFP peaks. For the CPT Nogo condition, this GFP latency approximated 379 ± 27 ms in controls, 358 ± 46 ms in typically medicated patients, and 347 ± 30 ms in atypically medicated patients.

Statistical analysis

To investigate the effects of typical and atypical antipsychotics on electrophysiological parameters, the sample of patients was subdivided into two groups according to the participants' medication status. The "typical" group consisted of 26 patients receiving typical neuroleptic medication only (648 mg mean chlorpromazine equivalents per day), whereas the "atypical" group included 13 patients receiving either atypical antipsychotics only (n = 9; 470 mg mean chlorpromazine equivalents per day) or atypical along with typical medication (n = 4; mean 431 mg atypical and 184 mg typical chlorpromazine equivalents per day). The latter two subgroups were combined to the "atypical" group for two reasons: First, referring to the studies cited above only atypical antipsychotics were expected to affect prefrontal structures and second, atypical drugs constituted the major compo-

nent of medication in the four patients treated with both types of substances. Chlorpromazine equivalents were calculated according to the specifications of Laux et al. (2000) on clinical-empirical equivalent-doses of neuroleptic drugs.

For statistical purpose, 2 x 2 analyses of variance (ANOVAs) for repeated measurements with the factors "group" (typical vs. atypical antipsychotics) and "condition" (Go vs. Nogo) were calculated for the patients' electrophysiological variables (GFP value and latency, positive centroid in the anterior/posterior direction). Posthoc analyses were conducted using two-tailed t-tests for matched samples. Reaction times and the mean Nogo-anteriorization (NGA) of both groups of patients were compared by means of Student's t-test for independent samples. Equality of variances was tested by means of Levene's test and corrections for inequality were performed whenever necessary.

Since the numbers of omission and commission errors were not normally distributed, Mann-Whitney U tests were applied to analyze these variables.

Furthermore, correlation analyses by means of Pearson's product-moment correlations were conducted separately for both groups of patients to further investigate the influence of the amount of neuroleptic medication on behavioral and electrophysiological parameters.

The statistical LORETA analysis for the comparison of different groups or conditions is based upon a bootstrap method with 5000 randomized samples (LORETA-Key-01 FreeBrainWare, Pascual-Marqui 1999). This procedure gives the exact significance thresholds for significant differences between groups or conditions, regardless of non-normality and corrected for multiple comparisons. The differences in localization between the two groups of patients and the control group were computed by means of voxel-by-voxel t-tests for independent measures of the LORETA images, based on the log-transformed power of the estimated electric current density.

Table 1 Patients' characteristics

	Typical antipsychotics	Atypical antipsychotics	t-values (df = 37)
n	26	13	
Age	34.9 ± 8.4	30.9 ± 6.8	t = 1.13
Duration of illness	70.3 ± 62.5	64.9 ± 56.4	t = 0.26
Number of admissions	3.4 ± 3.0	3.3 ± 2.8	t = 0.04
Tot. duration inpatient	5.6 ± 4.0	7.1 ± 6.7	t = –0.87
Duration current	42.4 ± 35.3	58.6 ± 44.1	t = –1.18
Mean chlor. equ.	647.9 ± 536.2	514.6 ± 260.6	t = 0.84

Mean age, duration of illness since first episode (months), number of admissions to a psychiatric hospital, total duration of inpatient treatments (months), duration of current hospitalization (days), and mean chlorpromazine equivalents per day for the typically and the atypically medicated group of patients (mean ± SD). No significant differences occurred

Table 2 Behavioral data (CPT performance)

	Typical antipsychotics	Atypical antipsychotics	t-values/ Mann-Wh.U
n	26	13	
RT	539.7 ± 117.6	486.8 ± 78.8	$t_{37} = 1.46$
Errors omission	2.2 ± 2.4	2.7 ± 3.9	U = 162.0
Errors commission	2.9 ± 7.4	2.2 ± 6.1	U = 154.5

Mean reaction time (RT; ms), number of commission and number of omission errors for the typically and the atypically medicated group of patients (mean ± SD). No significant differences occurred

Results

Typically and atypically medicated patients did not differ significantly regarding their mean age, duration of illness, number of admissions to a psychiatric hospital, total duration of inpatient treatments or mean duration of the current hospitalization (Table 1). They also did not differ significantly concerning the overall daily dose of neuroleptic treatment (mean chlorpromazine equivalents per day). On a behavioral level, both groups did not differ significantly regarding reaction times, number of omission or number of commission errors (Table 2).

To analyze the electrophysiological variables, ANOVAs for repeated measurements were calculated with "medication status" (typical vs. atypical drugs) as the between subjects factor and "condition" (Go vs. Nogo) as the repeated measures factor. For the Global Field Power (GFP) this analysis revealed a significant main effect of the factor "condition" ($F_{1, 37} = 16.81$, $p < 0.001$) with significantly higher GFP values in the Go as compared to the Nogo condition ($GFP_{Go} = 5.33 \pm 1.26$ µV versus $GFP_{Nogo} = 4.32 \pm 1.24$ µV; $t_{38} = 4.75$, $p < 0.001$). No significant main effect of the factor "medication status" and no significant interaction occurred. For the GFP latency, no significant main effects or interactions were observed.

For the positive centroid of the brain electrical field, the analysis again only revealed a significant main effect of the factor "condition" ($F_{1, 37} = 20.73$; $p < 0.001$) with significantly smaller values in the Nogo as compared to the Go condition ($Centroid_{Go} = 3.87 \pm 0.36$ versus $Centroid_{Nogo} = 3.35 \pm 0.65$; $t_{38} = 4.65$, $p < 0.001$), indicating positive centroids located significantly more anterior during the CPT Nogo condition.

In the group of patients as a whole, none of the electrophysiological parameters significantly correlated with the amount of neuroleptic medication. However, conducting the same correlation analysis separately for the group of patients receiving typical medication only and the group receiving atypical antipsychotics, striking differences emerged: Whereas in the typically medicated group no significant correlations were observed, in the "atypical group" the amount of atypical medication significantly correlated with the Nogo latency ($r = 0.656$, $p < 0.05$), the location of the Nogo centroid ($r = –0.656$, $p < 0.05$) and the NGA ($r = 0.694$, $p < 0.01$) (Figs. 1 and 2).

Comparing the mean NGA of both groups of patients directly by means of Student's t-test, no significant difference was observed, although the typically medicated group displayed a mean NGA that was lower than in the "atypical group" ($NGA_{typ.} = 0.47 \pm 0.69$ versus $NGA_{atyp.} = 0.62 \pm 0.72$; $t_{37} = –0.61$, n. s.). However, comparing the mean Nogo-anteriorizations of both groups of patients to the mean NGA of the matched control group mentioned above, only the typically medicated group of patients tended to have a reduced NGA as com-

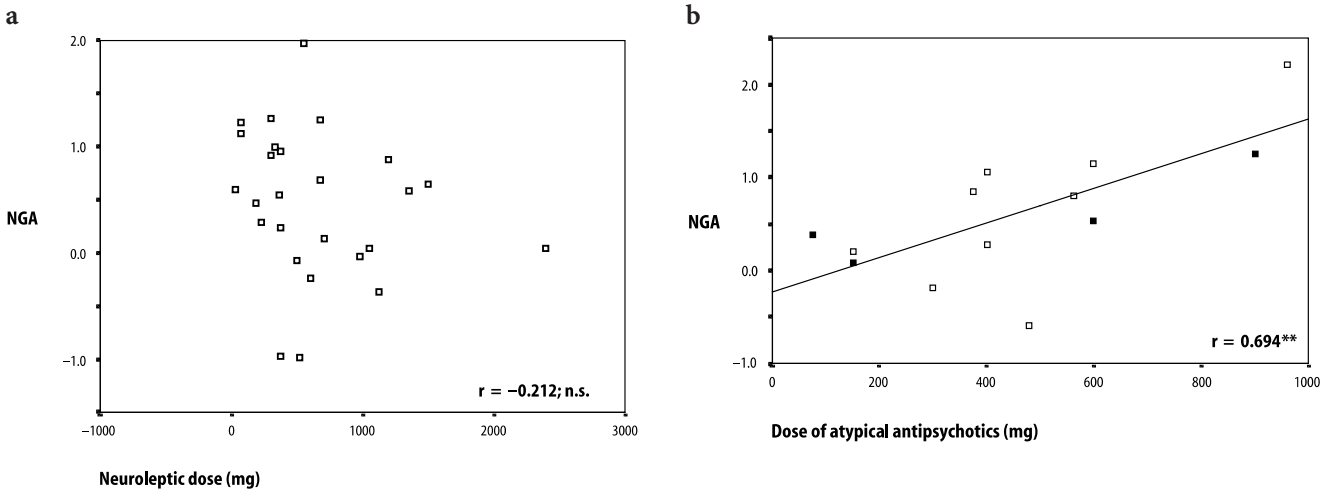

Fig. 1 Correlation between NGA (difference of the positive Go minus Nogo centroid) and daily amount of (**a**) neuroleptic medication (mg) in typically medicated patients (n = 26) or (**b**) atypical medication (mg) in patients receiving atypical antipsychotics alone (n = 9) or along with typical medication (n = 4; filled squares). *n. s.* indicates a correlation that did not reach significance, ** indicates a significant correlation with $p < 0.01$

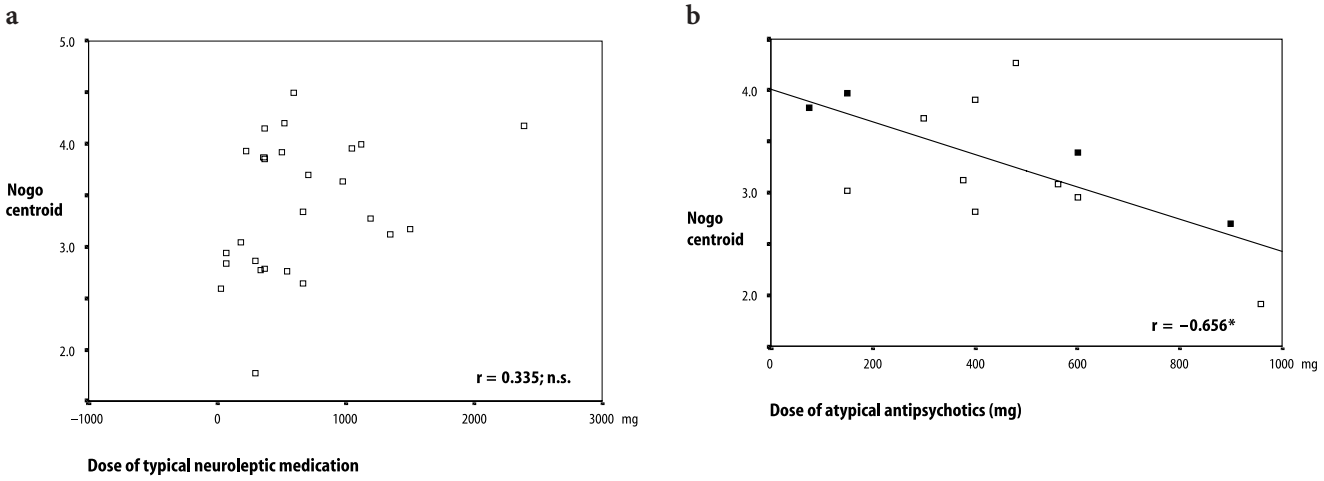

Fig. 2 Correlation between positive Nogo centroid (in unit 'electrode positions') and amount of (**a**) neuroleptic medication (mg) in patients receiving typical antipsychotics or (**b**) atypical medication (mg) in patients receiving atypical antipsychotics alone (n = 9) or along with typical medication (n = 4; filled squares). *n. s.* indicates a correlation that did not reach significance, * indicates a significant correlation with $p < 0.05$

pared to the healthy controls ($NGA_{typ.} = 0.47 \pm 0.69$ versus $NGA_{controls} = 0.73 \pm 0.41$, $t_{37} = -1.73$, $p < 0.1$), whereas the atypically medicated patients displayed a mean NGA very similar to the control group ($NGA_{atyp.} = 0.62 \pm 0.72$ versus $NGA_{controls} = 0.73 \pm 0.41$, $t_{15} = -0.55$, n. s.).

With regard to the LORETA source localization, similar results were obtained. Based on a previous investigation that found indications for reduced activity of the anterior cingulate in a group of schizophrenic patients as compared to a healthy control group (Braus et al. 2001), we used LORETA to compare the Nogo activity of the two groups of patients and the matched control group. Comparing the typically and the atypically medicated patients directly by means of the LORETA voxel-by-voxel t-test analysis, no significant differences occurred. However, comparing both groups of patients separately to the control group, the atypically medicated patients did not differ significantly from the controls, whereas the typically medicated patients showed a significantly diminished activation of the anterior cingulate (BA 24) as compared to the controls ($t = 5.03$, $p < 0.001$) (Fig. 3). No other region of the brain was significantly altered in these patients. Furthermore, the three groups did not differ significantly regarding the activation pattern evoked by the Go condition of the CPT.

To ensure that our grouping of atypically medicated patients and patients receiving atypical antipsychotics plus a small amount of typical compounds into 'the atypical group' did not bias the present results, we compared the two subgroups of atypically medicated patients regarding their electrophysiological data. First of all, the two groups (atypically medicated patients, n = 9 versus patients receiving both typical and atypical an-

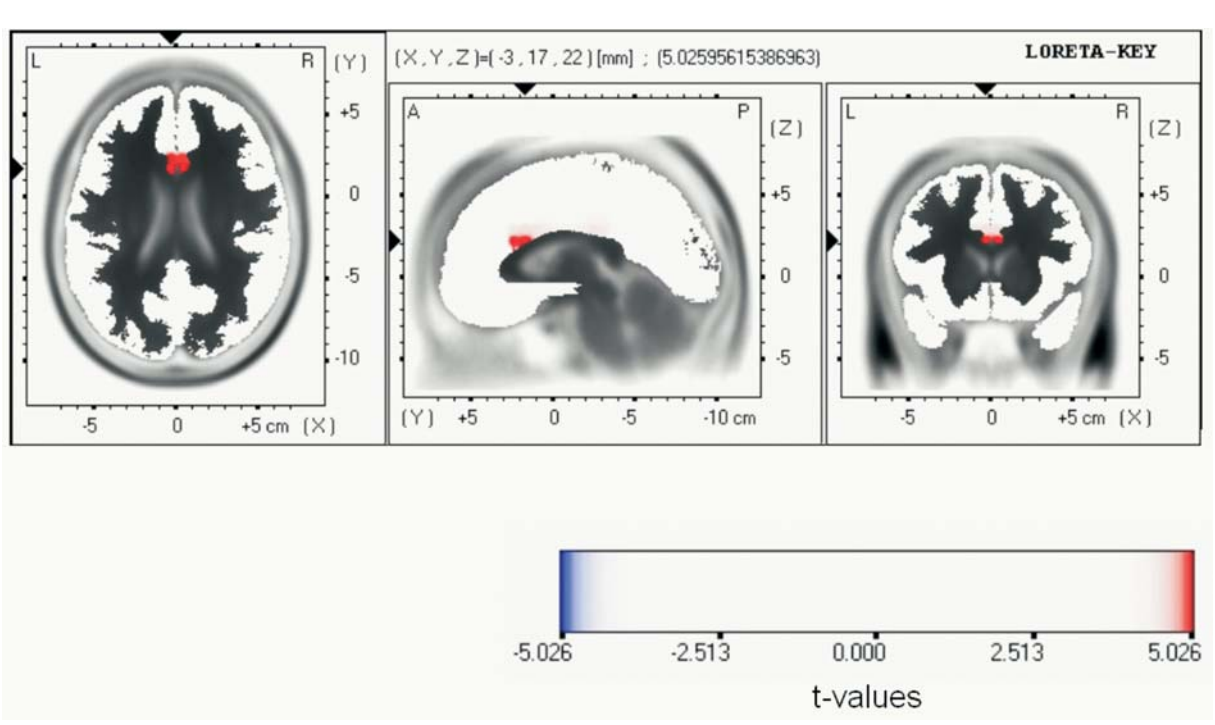

Fig. 3 Graphical presentation of the LORETA t-statistics comparing the Nogo-ERPs of healthy controls and typically medicated patients (**a**) or controls and atypically medicated patients (**b**). The red area indicates the location (ACC, Brodman area 24) of a significantly reduced activity in the typically medicated patients' brain in an axial, a saggital, and a coronar slice through the reference brain. Black arrows mark the centers of differences in activation

tipsychotics, n = 4) did not differ significantly regarding any of the neurophysiological parameters ($t < 1.3$, $p > 0.2$). This result was confirmed employing a non-parametric statistical test (Mann-Whitney U) that also did not find a significant difference between the two groups of atypically medicated patients ($U \geq 9.0, p \geq 0.2$). In particular their mean NGAs were quite similar (0.64 ± 0.83 in the atypically medicated group versus 0.56 ± 0.50 in patients receiving combined medication; $t = 0.18$ or $U = 18.0$, n. s.). Furthermore, excluding the four patients with combined medication from the correlation analysis revealed that the remaining group of purely atypically medicated patients still exhibited a significant positive correlation between the amount of atypical medication they were receiving and their NGA ($r = 0.73$, $p < 0.05$).

Discussion

The major finding of the present study is a highly significant positive correlation between the amount of atypical medication and the individual NGA in a group of patients suffering from acute psychotic disorders (cycloid psychoses). In contrast, patients treated with conventional antipsychotics displayed a weak (non-significant) negative correlation between the amount of neuroleptic medication and the NGA. The significant correlation in the

atypically medicated group can be attributed to a highly significant negative correlation of the amount of atypical medication and the positive Nogo centroid (i. e. the center of gravity of the positive brain electrical field during the CPT Nogo condition): The higher the dose of atypical medication was, the more anteriorly the positive Nogo centroid was located. The anteriorization of the positive brain electrical field during the Nogo condition of the CPT has been shown to be associated with an increased activation within certain prefrontal structures – particularly the anterior cingulate cortex (ACC) – during the Nogo as compared to the Go condition (Fallgatter et al. 2002; Strik et al. 1998). Therefore, the increased anteriorization of the Nogo centroid with growing amounts of atypical medication might reflect the beneficial effect of atypical antipsychotics on prefrontal structures such as the ACC. This interpretation is supported by findings of Braus et al. (2001), who observed a positive correlation between the neuronal viability of the ACC and the time on atypical medication. Such an enhanced prefrontal neuronal functioning due to atypical drugs might be the reason for the highly significant correlation between the NGA/positive Nogo centroid and the amount of atypical medication observed here. Furthermore, Lahti et al. (2004) found that the atypical substance Clozapine was able to normalize an abnormal regional Cerebral Blood Flow (rCBF) pattern in the ACC during performance of an auditory discrimination task and a control condition, whereas the typical compound haloperidol was not. This finding again supports the notion of improved frontal functioning under the influence of atypical antipsychotic treatment.

The assumption that the prefrontal cortex is the locus of the ability of atypical antipsychotics to improve negative symptoms and cognitive dysfunction in schizophrenia (Ichikawa and Meltzer 1999; Ichikawa et al. 2002) might be supported by the present findings. Typical antipsychotics on the other hand have been shown to exhibit weaker or even negative effects on prefrontal brain areas (Bartlett et al. 1994; Braus et al. 2001; Ichikawa et al. 2002; Li et al. 1998; Madsen et al. 1998; Miller et al. 2001), and therefore would not be expected to influence the NGA – as a measure of prefrontal response control – in a positive way. The weak negative correlation between the amount of typical medication and the NGA/positive Nogo centroid that has been observed in the present study goes well with these findings.

In the atypically medicated group of patients another significant finding was a positive correlation between the Nogo latency of the GFP peak and the amount of atypical medication patients were receiving. Given the fact that the present sample of patients exhibited significantly decreased Nogo latencies as compared to a healthy control group (Ehlis et al., in press), this positive correlation again indicates values that are closer to "normal" with growing amounts of atypical medication.

The fact that both groups of patients did not show significantly different mean NGAs or Nogo centroids might be attributed to the circumstance that patients with cycloid psychoses do not seem to be as impaired in mechanisms of prefrontal response control as schizophrenic patients. During performance of the CPT, the present patient sample as a whole exhibited a slightly – though not significantly – reduced NGA when compared to a matched control group (Ehlis et al., in press), whereas a group of schizophrenic patients investigated by Fallgatter and Müller (2001) displayed a significantly reduced mean NGA probably reflecting highly impaired mechanisms of prefrontal response control. These findings fit well with the results of other studies demonstrating particularly marked frontal impairments in patients suffering from *chronic* (schizophrenic) illness (e. g. Desco et al. 2003) or marked *negative* symptomatology (e. g. Andreasen et al. 1992; Berman et al. 1997; Vaiva et al. 2002), factors that are usually not present in cycloid psychoses, which are characterized by acute "positive" symptoms and a non-chronic course of the disease. An impaired interhemispheric transfer was also particularly present in patients with residual schizophrenia and chronic symptoms, and not in patients suffering from acute, transient psychotic disorders (Gorynia et al. 2003). The less severe neurophysiological impairment associated with acute psychotic disorders (cycloid psychoses) might then leave less room for a significant difference between both subgroups of patients investigated here. However, comparing the typically and the atypically medicated group of patients separately to the healthy control group, the typically medicated group of patients showed a statistical trend for a reduced NGA, whereas the atypically medicated patients did not.

The LORETA analyses resulted in the same pattern of results: Comparing the nogo-related activation in typically and atypically medicated patients directly by means of the LORETA voxel-by-voxel t-test analysis, both groups did not differ significantly. However, comparing both groups of patients separately to the healthy controls, the atypically medicated group did not differ significantly from the controls (which was also true for the NGA), whereas the typically medicated patients showed a significantly diminished ACC activity as compared to the control group. This goes well with the notion that the NGA reflects activation of the anterior cingulate cortex and that atypical antipsychotics exert a more positive effect on prefrontal structures than typical neuroleptic drugs.

In summary, the major finding of the present study is a highly significant positive correlation between the amount of atypical neuroleptic medication and the Nogo-anteriorization (NGA) during performance of the CPT in a group of patients suffering from acute psychotic disorders (cycloid psychoses). Since the NGA is assumed to be a neurophysiological correlate of prefrontal response control, this finding supports the notion of a beneficial influence of atypical neuroleptic drugs on prefrontal brain function.

Acknowledgements The authors would like to thank B. Neuhauser and I. Gröbner for skillful and dedicated technical support.

References

1. Abbruzzese M, Ferri S, Scarone S (1997) The selective breakdown of frontal functions in patients with obsessive-compulsive disorder and in patients with schizophrenia: A double dissociation experimental finding. Neuropsychologia 35:907–912
2. Andreasen NC, Rezai K, Alliger R, Swayze VW 2nd, Flaum M, Kirchner P, Cohen G, O'Leary DS (1992) Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. Arch Gen Psychiatry 49:943–958
3. Bartlett EJ, Brodie JD, Simkowitz P, Dewey SL, Rusinek H, Wolf AP, Fowler JS, Volkow ND, Smith G, Wolkin A (1994) Effects of haloperidol challenge on regional cerebral glucose utilization in normal human subjects. Am J Psychiatry 151:681–686
4. Berman I, Viegner B, Merson A, Allan E, Pappas D, Green AI (1997) Differential relationships between positive and negative symptoms and neuropsychological deficits in schizophrenia. Schizophr Res 25:1–10
5. Bilder RM, Goldman RS, Volavka J, Czobor P, Hoptman M, Sheitman B, Lindenmayer JP, Citrome L, McEvoy J, Kunz M, Chakos M, Cooper TB, Horowitz TL, Lieberman JA (2002) Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 159:1018–1028
6. Braus DF, Ende G, Weber-Fahr W, Demirakca T, Henn FA (2001) Favorable effect on neuronal viability in the anterior cingulate gyrus due to long-term treatment with atypical antipsychotics: an MRSI study. Pharmacopsychiatry 34:251–253
7. Braus DF, Ende G, Weber-Fahr W, Demirakca T, Tost H, Henn FA (2002) Functioning and neuronal viability of the anterior cingulate neurons following antipsychotic treatment: MR-spectroscopic imaging in chronic schizophrenia. Eur Neuropsychopharmacol 12:145–152
8. Canadian Cognition and Outcome Study Group (1998) Neuropsychological changes in early phase schizophrenia over twelve months of treatment with olanzapine, risperidone, or haloperidol. Schizophr Res 29:152–153
9. Carter CS, Mintun M, Nichols T, Cohen JD (1997) Anterior cingulate gyrus dysfunction and selective attention deficits in schizophrenia: [15O]H2O PET study during single-trial Stroop task performance. Am J Psychiatry 154:1670–1675
10. Cuesta MJ, Peralta V, Zarzuela A (2001) Effects of olanzapine and other antipsychotics on cognitive function in chronic schizophrenia: a longitudinal study. Schizophr Res 48:17–28
11. Desco M, Gispert JD, Reig S, Sanz J, Pascau J, Sarramea F, Benito C, Santos A, Palomo T, Molina V (2003) Cerebral metabolic patterns in chronic and recent-onset schizophrenia. Psychiatry Res 122:125–135
12. Ehlis AC, Zielasek J, Herrmann MJ, Ringel T, Jacob C, Wagener A, Fallgatter AJ (2004) Evidence for unaltered brain electrical topography during prefrontal response control in cycloid psychoses. Int J Psychophysiol (in press)
13. Ende G, Braus DF, Walter S, Weber-Fahr W, Soher B, Maudsley AA, Henn FA (2000) Effects of age, medication, and illness duration on the N-acetyl aspartate signal of the anterior cingulate region in schizophrenia. Schizophr Res 41:389–395
14. Fallgatter AJ, Bartsch AJ, Herrmann MJ (2002) Electrophysiological measurements of anterior cingulate function. J Neural Transm 109:977–988
15. Fallgatter AJ, Bartsch AJ, Zielasek J, Herrmann MJ (2003) Brain-electrical dysfunction of the anterior cingulate in schizophrenic patients. Psychiatry Research: Neuroimaging 124:37–48
16. Fallgatter AJ, Brandeis D, Strik WK (1997) A robust assessment of the NoGo-Anteriorisation of P300 microstates in a cued Continuous Performance Test. Brain Topogr 9:295–302
17. Fallgatter AJ, Eisenack SS, Neuhauser B, Aranda D, Scheuerpflug P, Herrmann MJ (2000) Stability of late event-related potentials: topographical descriptors of motor control compared with the P300 amplitude. Brain Topogr 12:255–261
18. Fallgatter AJ, Müller TJ (2001) Electrophysiological signs of reduced prefrontal response control in schizophrenic patients. Psychiatry Res: Neuroimaging 107:19–28
19. Fallgatter AJ, Strik WK (1999) The NoGo-anteriorisation as a neurophysiological standard-index for cognitive response control. Int J Psychophysiol 32:115–120
20. Gallhofer B, Bauer U, Lis S, Krieger S, Gruppe H (1996) Cognitive dysfunction in schizophrenia: comparison of treatment with atypical antipsychotic agents and conventional neuroleptic drugs. Eur Neuropsychopharmacol 6(Suppl 2):S13–S20
21. Gorynia I, Campman V, Uebelhack R (2003) Intermanual coordination in relation to different clinical subgroups in right-handed patients with schizophrenic and other psychotic disorders. Eur Arch Psychiatry Clin Neurosci 253:53–59
22. Green MF, Marshall BD Jr, Wirshing WC, Ames D, Marder SR, McGurk S, Kern RS, Mintz J (1997) Does Risperidone improve verbal working memory in treatment-resistant schizophrenia? Am J Psychiatry 154:799–804
23. Hazlett EA, Buchsbaum MS, Jeu LA, Nenadic I, Fleischman MB, Shihabuddin L, Haznedar MM, Harvey PD (2000) Hypofrontality in unmedicated schizophrenia patients studied with PET during performance of a serial verbal learning task. Schizophr Res 43:33–46
24. Higashima M, Kawasaki Y, Urata K, Sakai N, Nagasawa T, Koshino Y, Sumiya H, Tonami N, Tsuji S, Matsuda H (2000) Regional cerebral blood flow in male schizophrenic patients performing an auditory discrimination task. Schizophr Res 42:29–39
25. Honey GD, Bullmore ET, Soni W, Varatheesan M, Williams SC, Sharma T (1999) Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. Proc Natl Acad Sci USA 96:13432–13437
26. Ichikawa J, Dai J, O'Laughlin IA, Fowler WL, Meltzer HY (2002) Atypical, but not typical, antipsychotic drugs increase cortical acetylcholine release without an effect in the nucleus accumbens or striatum. Neuropsychopharmacology 26:325–339
27. Ichikawa J, Meltzer HY (1999) Relationship between dopaminergic and serotonergic neuronal activity in the frontal cortex and the action of typical and atypical antipsychotic drugs. Eur Arch Psychiatry Clin Neurosci 249(Suppl 4):90–98
28. Ingvar DH, Franzen G (1974) Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiatr Scand 50:425–462
29. Jabs BE, Pfuhlmann B, Bartsch AJ, Cetkovich-Bakmas MG, Stöber G (2002) Cycloid psychoses – from clinical concepts to biological foundations. J Neural Transm 109:907–919
30. Jaeger M, Hintermayr M, Bottlender R, Strauss A, Möller, H-J (2003) Course and outcome of first-admitted patients with acute and transient psychotic disorders (ICD-10:F23). Eur Arch Psychiatry Clin Neurosci 253:209–215
31. Jasper H (1958) Report of committee on methods of clinical exam in EEG. Electroencephalogr Clin Neurophysiol 10:370–375
32. Lahti AC, Holcomb HH, Weiler MA, Medoff DR, Frey KN, Hardin M, Tamminga CA (2004) Clozapine but not Haloperidol re-establishes normal task-activated rCBF patterns in schizophrenia within the anterior cingulate cortex. Neuropsychoparmacology 29:171–178
33. Laux G, Dietmaier O, König W (2000) Pharmakopsychiatrie. Urban and Fischer, 3rd ed, Munich, p 237
34. Lee MA, Thompson PA, Meltzer HY (1994) Effects of clozapine on cognitive function in schizophrenia. J Clin Psychiatry 55 (Suppl B):82–87
35. Lehmann D (1987) Principles of spatial analysis. In: Gevins A, Remond A (eds) Methods of Analysis of Brain Electrical and Magnetic Signals. Handbook of Electroencephalography and Clinical Neurophysiology. Elsevier; 2nd ed, Amsterdam, pp 309–354
36. Lehmann D, Faber PL, Achermann P, Jeanmonod D, Gianotti LR, Pizzagalli D (2001) Brain sources of EEG gamma frequency during volitionally medication-induced, altered states of consciousness, and experience of the self. Psychiatry Res 108:111–121

37. Lehmann D, Skrandies W (1980) Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalogr Clin Neurophysiol 48:609–621
38. Leonhard K (1999) The cycloid psychosis. In: Beckmann H (ed) Classification of endogenous psychoses and their differentiated etiology. Springer, 2nd ed, Vienna, New York, pp 61–75
39. Li XM, Perry KW, Wong DT, Bymaster FP (1998) Olanzapine increases in vivo dopamine and norepinephrine release in rat prefrontal cortex, nucleus accumbens and striatum. Psychopharmacology (Berl) 136:153–161
40. Lidow MS, Williams GV, Goldman-Rakic PS (1998) The cerebral cortex: a case for a common site of action of antipsychotics. Trends Pharmacol Sci 19:136–140
41. Madsen AL, Keiding N, Karle A, Esbjerg S, Hemmingsen R (1998) Neuroleptics in progressive structural brain abnormalities in psychiatric illness. Lancet 352:784–785
42. Miller DD, Andreasen NC, O'Leary DS, Watkins GL, Boles Ponto LL, Hichwa RD (2001) Comparison of the Effects of Risperidone and Haloperidol on Regional Cerebral Blood Flow in Schizophrenia. Biol Psychiatry 49:704–715
43. Mulert C, Gallinat J, Pascual-Marqui R, Dorn H, Frick K, Schlattmann P, Mientus S, Herrmann WM, Winterer G (2001) Reduced event-related current density in the anterior cingulate cortex in schizophrenia. Neuroimage 13:589–600
44. Mulert C, Jäger L, Schmitt R, Bussfeld P, Pogarell O, Möller H-J, Juckel G, Hegerl U (2004) Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. NeuroImage 22:83–94
45. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113
46. Pascual-Marqui R (1999) Review of methods for solving the EEG inverse problem. Int J Bioelectromagnetism 1:75–86
47. Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MC, Hell D, Koukkou M (1999) Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatry Res 90:169–179
48. Pascual-Marqui RD, Michel CM, Lehmann D (1994) Low resolution electromagnetic tomography, a new method for localizing electrical activity in the brain. Int J Psychophysiol 18:49–65
49. Pehek EA, Yamamoto BK (1994) Differential effects of locally administered clozapine and haloperidol on dopamine efflux in the rat prefrontal cortex and caudate-putamen. J Neurochem 63: 2118–2124
50. Purdon SE, Malla A, Labelle A, Lit W (2001) Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. J Psychiatry Neurosci 26:137–149
51. Riley EM, McGovern D, Mockler D, Doku VCK, OCeallaigh S, Fannon DG, Tennakoon L, Santamaria M, Soni W, Morris RG, Sharma T (2000) Neuropsychological functioning in first-episode psychosis – evidence of specific deficits. Schizophr Res 43:47–55
52. Rosvold HE, Mirsky A, Sarason I, Bransome ED Jr, Beck LH (1956) A continuous performance test of brain damage. J Consult Psychol 20:343–350
53. Stip E, Lussier I (1996) Effect of risperidone on cognition in patients with schizophrenia. Can J Psychiatry 41(Suppl 8):35–40
54. Strik WK, Fallgatter AJ, Stoeber G, Franzek E, Beckmann H (1996) Specific P300 features in patients with cycloid psychosis. Acta Psychiatr Scand 94:471–476
55. Strik WK, Fallgatter AJ, Brandeis D, Pascual-Marqui R (1998) Three dimensional tomography of event-related potentials during response inhibition: evidence for phasic frontal lobe activation. Electroencephalogr Clin Neurophysiol 108:406–413
56. Vaiva G, Cottencin O, Llorca PM, Devos P, Dupont S, Mazas O, Rascle C, Thomas P, Steinling M, Goudemand M (2002) Regional cerebral blood flow in deficit/nondeficit types of schizophrenia according to SDS criteria. Prog Neuropsychopharmacol Biol Psychiatry 26:481–485
57. Velligan DI, Newcomer J, Pultz J, Csernansky J, Hoff AL, Mahurin R, Miller AL (2002) Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophr Res 53:239–248
58. Vitacco D, Brandeis D, Pascual-Marqui R, Martin E (2002) Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. Human Brain Mapping 17:4–12
59. Volz HP, Gaser C, Häger F, Rzanny R, Pönisch J, Mentzel HJ, Kaiser WA, Sauer H (1999) Decreased frontal activation in schizophrenics during stimulation with the Continuous Performance Test – a functional magnetic resonance imaging study. Eur Psychiatry 14:17–24
60. Winterer G, Mulert C, Mientus S, Gallinat J, Schlattmann P, Dorn H, Herrmann WM (2001) P300 and LORETA: comparison of normal subjects and schizophrenic patients. Brain Topogr 13: 299–313
61. Yücel M, Pantelis C, Stuart GW, Wood SJ, Maruff P, Velakoulis D, Pipingas A, Crowe SF, Tochon-Danguy HJ, Egan GF (2002) Anterior Cingulate Activation During Stroop Task Performance: A PET to MRI Coregistration Study of Individual Patients With Schizophrenia. Am J Psychiatry 159:251–254