Electrophysiological measurement of anterior cingulate cortex (ACC) function in schizophrenic patients treated with Seroquel® or Fluanxol®

ISS, Study Code D1443L00016

Clinical Study Report

supported by an unrestricted grant from AstraZeneca Germany

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List of Abbrevations

ACC	Anterior cingulate cortex
ERN	Error related negativity
PFC	Prefrontal cortex
fMRI	Functional magnetic resonance imaging
PET	Positron emission tomography
EEG	Electroencephalography
NIRS	Near-infrared spectroscopy
Pe	Error related positivity
DLPFC	Dorsolateral prefrontal cortex
SCID	Structured clinical interview for the *DSM–IV*
PANSS	Positive and negative symptom scale
GAF	Global assessment of functioning
BPRS	Brief psychiatric rating scale
HDRS	Hamilton Depression Rating Scale
BLQP	Berliner Lebensqualitätsprofil
TMT	Trail making test
VFT	Verbal fluency test
QoL	Quality of life
EOG	electrooculography
ANOVA	Analysis of variance
M	Mean
SD	Standard derivation
ERP	Event related potential

Abstract

Atypical antipsychotic agents are a frequently and effectively used treatment in schizophrenia and psychotic disorders. Other than conventional/typical antipsychotics which mainly exert their pharmacologic effect in subcortical dopaminergic systems, atypical/second generation antipsychotics additionally affect partly serotonergically innervated structures within the prefrontal areas, such as the Anterior Cingulate Cortex (ACC). However, only few controlled, randomized studies investigating direct and indirect effects of atypical antipsychotics on the ACC exist and so far there is no clinical investigation exclusively addressing the specific effect of Seroquel® (pharmacologic agent: Quetiapine) on ACC function.

In a first step, the present study assessed ACC function in 22 Quetiapine medicated patients suffering from acute psychosis by means of the error related negativity (ERN), a neurophysiologic marker of ACC function.

Our results indicate a positive effect of Quetiapine treatment on ACC function as well as neurocognitive performance, symptom severity and quality of life. An additional comparison with a group of 13 Fluanxol® pharmacologic agent: Flupentixol) treated patients revealed a superior effect of Quetiapine on prefrontal cortex (PFC) function despite similar improvement in psychopathology, cognitive performance and quality of life. Moreover, treatment effects depended on baseline PFC function in both groups.

We conclude that both, Flupentixol and Quetiapine improve prefrontal function especially in patients with weak initial ACC function which might be due to their common affinity for 5HT receptors in frontal brain regions. However, possibly because this affinity is more strongly pronounced for Quetiapine, patients treated with Quetiapine seemed to profit more than Flupentixol medicated patients concerning PFC function, but not regarding psychopathology.

Introduction

Schizophrenia is one of the most severe of all psychiatric disorders and it is often associated with a complex combination of different serious psychopathological symptoms, such as delusions, hallucinations and mood disturbances. On the neurobiological side, a decrease in frontal lobe function, also well known as 'hypo-frontality', is one of the core features in schizophrenia and has been repeatedly confirmed in a plethora of functional imaging studies. A relative reduction of regional cerebral blood flow in the frontal cortex of chronic schizophrenic patients has first been reported by Ingvar & Franzén in 1974 (Ingvar & Franzén, 1974). In recent years, a dysfunction of prefrontal brain areas in schizophrenic illnesses has been demonstrated in various studies using fMRI (see, for example, Minzenberg, Laird, Thelen, Carter & Glahn, 2009), PET (Kim et al., 2003; Minzenberg, et al., 2009), EEG (e.g. Fallgatter, Bartsch, Zielasek & Herrmann, 2003), or NIRS (Ehlis, Ann-Christine, Herrmann, Plichta & Fallgatter, 2007; Ikezawa et al., 2009), whereby reduced frontal brain activation was most apparent in studies using cognitive activation tasks, such as verbal fluency tasks (Ehlis, Ann-Christine, Herrmann, Plichta, et al., 2007; Kubota et al., 2005), a continuous performance test (Zielasek, Ehlis, Herrmann & Fallgatter, 2005) or working memory tasks (Glahn et al., 2005).

Beyond these cognitive domains, it has been shown that patients suffering from schizophrenia are further impaired in action monitoring (Carter, C. S., MacDonald, Ross & Stenger, 2001; Firth & Done, 1989; Frith, Blakemore & Wolpert, 2000; Laurens, Ngan, Bates, Kiehl & Liddle, 2003; Malenka, Angel, Hampton & Berger, 1982). The ability to internally monitor erroneous responses to external stimuli plays a crucial role in human action monitoring and is associated with neural activity in the Anterior Cingulate Cortex (ACC) (Botvinick, Braver, Barch, Carter & Cohen, 2001; Botvinick, Cohen & Carter, 2004; Carter, Cameron S. et al., 1998; Kiehl, Liddle & Hopfinger, 2000; Michelet, Bioulac, Guehl, Goillandeau & Burbaud, 2009; van Veen, Cohen, Botvinick, Stenger & Carter, 2001), a heterogeneous brain structure within the medial frontal cortex. Neurobiological evidence for dysfunctional error monitoring in schizophrenia derives primarily from event-related potential research (Bates, Kiehl, Laurens & Liddle, 2002; Laurens, et al., 2003; Mathalon, Jorgensen, Roach & Ford, 2009; Morris, Yee & Nuechterlein, 2006). These studies usually target a fronto-central negative component, termed error negativity (Ne, not used hereafter) (Falkenstein, Hohnsbein, Hoormann & Blanke, 1990, 1991) or error-related negativity

(ERN), respectively (Gehring, Goss, Coles, Meyer & Donchin, 1993). The ERN occurs within the first 100 ms after the commission of an erroneous response and is usually followed by a positive component with a centro-parietal maximum peaking about 200-450 ms after the incorrect response (Error-positivity, Pe). Data from source localization analyses as well as neuroimaging studies confirm the ACC as neuroanatomical source for both the ERN (e.g. (Braver, Barch, Gray, Molfese & Snyder, 2001; Dehaene, Posner & Tucker, 1994; Kiehl, et al., 2000; van Veen & Carter, 2002)) and the Pe (Herrmann, Rümmler, Ehlis, Heidrich & Fallgatter, 2004; van Veen & Carter, 2002).

Previous research suggests an attenuated ERN in patients with schizophrenia. Kopp & Rist were the first to demonstrate diminished ERN amplitudes in paranoid schizophrenic patients who showed, at the same time, normal error correction performance. Mathalon et al. also reported ERN abnormalities in schizophrenic patients, while all subjects revealed normal post-error slowing and Pe (Mathalon et al., 2002). Moreover, these authors observed a negative wave on correct reaction trials in patients, but not in healthy control subjects, which resembled the ERN concerning amplitude, morphology, and topography. A similar electrophysiological pattern has been reported by (Alain, McNeely, He, Christensen & West, 2002) who further observed, in contrast to (Mathalon, et al., 2002) & (Kopp & Rist, 1999), a reduced error-related slowing of reaction times in patients compared to healthy controls. Morris and colleagues (Morris, et al., 2006) demonstrated that ERN abnormalities among schizophrenic patients occur even under conditions that normally maximize ERN amplitude. Taken together, disorder related ERN amplitude reductions have been reliably confirmed, whereas differences in CRN and post error slowing have been reported only in some studies.

Consistent with the idea that self-/ action- monitoring deficits in schizophrenia may be linked to alterations in dorsal ACC function (Carter, C. S., et al., 2001), neuroanatomical studies have indicated that the ACC and dorsolateral prefrontal cortex (DLPFC), both critical for error detection, are less activated in erroneous trials in patients with schizophrenia (e.g. (Kerns et al., 2005; Polli et al., 2008), see (Mathalon, et al., 2009) for an overview). Becerril et al. (Becerril, Repovs & Barch) emphasized the central role of the dorsal ACC in behavioral adjustment, as only activity in this specific area was predictive of individual differences in post-error

slowing. In addition, the authors reported on reduced connectivity between the dorsal ACC and cerebellar regions in schizophrenic patients.

Given its well-known neuroanatomic background and high intra- and interindividual stability (Olvet & Hajcak, 2009), the ERN can be considered a particularly useful tool to investigate ACC dysfunction in psychiatric disorders, such as schizophrenia. Moreover, it can be utilized to monitor distinct changes in frontal lobe function due to different antipsychotic treatment regimens, in order to further investigate the effects of typical/conventional (first generation) versus atypical (second generation) antipsychotics on the ACC. These two classes of antipsychotic medication constitute the mainstay for the treatment of schizophrenic disorders and rely on different neurobiological mechanisms of action. Although the exact cellular basis of their therapeutic action is not fully understood, resent research on both, animals and humans consistently suggests that typical agents, such as Flupentixol, primarily block a large proportion of subcortical dopamine D2 receptors, whereas atypical antipsychotics, such as Quetiapine, act on both, the dopaminergic (DA) as well as the serotonergic (5HT) systems, see (Abi-Dargham & Laruelle, 2005; Artigas) for an overview.

Although a superior effect of atypical over typical agents regarding clinical potency is still intensively discussed, the majority of studies support the finding that second generation antipsychotics positively affect the frontal lobe including the ACC and related neurocognitive function due to their capability to enhance the level of dopamine, serotonine and acetylcholine in prefrontal regions (see (Abi-Dargham & Laruelle, 2005). However, recent findings suggest a more sophisticated effect of antipsychotic medication on frontal lobe function. In a study conducted by Ehlis et al. 2011, baseline PFC function was differentially associated with the treatment response to first- and second-generation antipsychotics, with patients exhibiting pronounced PFC dysfunction showing significantly stronger symptom improvement under atypical than under conventional treatment, whereas patients with a relatively strong PFC function at the beginning of treatment improved more markedly under typical medication. The authors concluded that patients with strong PFC function, in contrast to patients with pronounced hypofrontality, show a major neurobiological pathology outside the frontal cortex, leading to a restricted effect of atypical antipsychotic treatment in this subgroup of schizophrenic patients, as atypical

medication is assumed to exert at least part of their pharmacological effect in frontal brain areas.

Aiming at the particular efficiency of Seroquel® (agent: Quetiapine) in enhancing neurocognition, functional neuroimaging studies could show a beneficial effect of this specific atypical antipsychotic on prefrontal activation and cognitive functioning in schizophrenic patients (Jones et al., 2004; Riedel et al., 2007; Stip et al., 2005). Riedel and colleagues specifically reported on a greater improvement in cognition, reaction quality and attention in schizophrenic patients treated with Quetiapine compared to patients medicated with Olanzapine. However, only very few controlled studies have been conducted and, to our knowledge, up till now there are no prospective studies directly examining the impact of Quetiapine on the ACC.

The present study therefore intended to investigate how the atypical antipsychotic drug Quetiapine affects ACC function and to further compare the effect of Quetiapine with one typical agent (Fluanxol®; agent: Flupentixol) in patients suffering from acute psychotic disorders. A facilitating treatment effect on prefrontal brain function would be expressed in a normalization of altered ERN/Pe amplitudes during an Eriksen Flanker Task.

Method

Study design & Participants

A total of 59 schizophrenia patients (age range: 19-69 years) were enrolled in this prospective, randomized, rater-blind treatment study.

Exclusion criteria were significant current comorbidities with other axis-I disorders, severe somatic or neurological conditions, pregnancy, or intolerance or lack of response to Quetiapine fumarate or Flupentixol. Patients were also excluded if they were currently posing an imminent risk of suicide or a danger to self or others. After complete description of the study to the participants, written informed consent was obtained. The study was approved by the Ethics Committees of the Universities of Wuerzburg and Tuebingen and all procedures were in accordance with the latest version of the Declaration of Helsinki.

41 patients were recruited at the University of Wuerzburg, Department of Psychiatry, Psychosomatics and Psychotherapy, and 18 patients were recruited at the University of Tuebingen, Department of Psychiatry and Psychotherapy, both Germany. Data from 3 patients were excluded because of equipment problems, noisy EEG data, or

an insufficient number of error trials throughout the experiment. Moreover, 4 patients were excluded from the study due to switch of drug category and another 13 patients discontinued study participation for personal reasons after the baseline assessment. Datasets of further 4 patients had to be excluded, either due to comorbid obsessive-compulsive disorder (n=2) or because patient's exceeded the predefined study age range (n=2), yielding a final sample of 35 patients.

The 35 remaining study patients were randomly assigned to one of two study groups; one group of patients was medicated with Quetiapine, the other with Flupentixol. All patients were investigated throughout a study period of approximately 30 days. Neurophysiologic investigations took place within one week after the first day of study medication (baseline measurement) and again approximately 30 days later after clinical stabilization (follow-up).

All patients were assessed with the Structured Clinical Interview for the *DSM–IV* (SCID; (Wittchen, Zaudig & Frydrinch, 1997)) and diagnosed with either paranoid (295.30; *n = 13*); disorganized (295.10; *n=5*), or catatonic schizophrenia (295.20, *n=3*), as well as schizoaffective disorder (295.70, *n=6*), brief psychotic disorder (298.80; *n=2*), delusional disorder (297.1; *n=1*), severe major depressive disorder, recurrent with psychotic features (296.34; *n=3*) or bipolar I disorder with psychotic features (296.44/296.54; *n=2*). With regard to psychiatric comorbidities, four patients were diagnosed with nicotine dependence (305.10), cannabis abuse (305.20) or cannabis dependence (304.30), respectively; one patient suffered from social phobia (300.23) and one patient suffered from borderline personality disorder (301.83). In addition to SCID, several psychopathological scales (Positive and Negative Symptom Scale, PANSS; Global Assessment of Functioning, GAF; Brief Psychiatric Rating Scale, BPRS; Hamilton Depression Rating Scale, HDRS and a German self-assessment scale for the subjective quality of life (Berliner Lebensqualitätsprofil, BLQP)), were applied four times throughout the study period of approximately 30 days (day1/baseline, day10, day20 and day30/follow-up). For the PANSS, four different measures including the three subscales "positive symptoms", "negative symptoms", "general psychopathology" and the total score were assessed. Concerning the BLQP, we regarded the two items "contentment with life in general" and "contentment with psychological health" as well as a quotient indicating general quality of life. Neuropsychological tests (Stroop Color Word Task; Trail Making Test,

TMT: Version A (just numbers) & B (numbers & letters); Verbal Fluency Test, VFT: letter version & category version) were conducted at baseline and again at follow-up.
Depending on former group assignment, patients were treated with either Quetiapine (*n=22*), or Flupentixol (*n=13*), respectively. The patients must not have been premedicated with one of these antipsychotics for at least three months prior to study enrolment. However, some patients additionally received at least one co-medication with low to medium doses of benzodiazepines (n=19), tri- or tetracyclic antidepressants (n=14), anti-epileptics (n=3), lithium (n=3) or biperiden (n=1).
The mean duration of the disease was 81.1 months (*SD*=89.57) in the Quetiapine group and 78.7 months (*SD*=105.16) in the Flupentixol group and the mean number of admissions to psychiatric hospitals was 1.8 (*SD*=2.79) in the Quetiapine group and 3.9 (*SD*=4.39) in the Flupentixol group. Only 2 patients (both Quetiapine group) had a positive family history for schizophrenia.
The groups did not differ in age, $t(33) = -0.99$, $p = .33$; years of education, $t(33)= -.07$, $p = .99$, or gender, $\chi^2 = .23$, $p = .63$. Detailed demographic characteristics of the groups are summarized in Table 1.

Experimental paradigm

Participants performed a flanker task similar to that used by Kopp, Matter and Rist (1994). At the beginning of each trial a combination of five arrow stimuli was presented for 125 ms, with the centrally displayed arrow serving as target pointing either right or left, and the four flanker stimuli (two at each side of the target arrow) either oriented in the same direction (congruent condition) or in the opposite direction of the target stimulus (incongruent condition). Subjects were instructed to press the right response button for target arrows pointing right, and the left response button whenever the target arrow was oriented to the left. After stimulus presentation the computer screen was cleared until the response was given. Directly after the button press, a symbol appearing for 500 ms on the screen indicated the correctness of the response (“+“ correct and fast response, “–” incorrect response, “!” response was too slow). To enhance error probability, subjects were instructed to adjust their reaction time every time they received a "too slow" feedback. The threshold that determined whether a correct response was fast enough was calculated on the basis of the median of the reaction times of the last 32 correct responses out of 42 practice trials during the training block at the beginning of the experiment. After the practice block,

participants performed a total of 400 trials with a short break after the presentation of the first 50 percent of experimental trials.

EEG recording

Measurements took place in a sound-attenuated, electrically shielded room at the University Hospital for Psychiatry and Psychotherapy Tübingen (Germany) and Wuerzburg (Germany), respectively. The EEG was recorded from 32 scalp electrodes embedded in an elastic cap and placed according to the International 10/20-System (Jasper, 1958). To identify eye movement artefacts in the EEG, EOG activity was recorded from three additional electrodes, one placed below the right eye, two placed at the lateral canthi of both eyes. The ground electrode was placed on the forehead and Fcz was used as recording reference. Electrode impedances were kept below 5 kΩ. Data were recorded with a 64channel DC-amplifier and the software “Vision Recorder” (Brain Products, Munich, Germany). All physiological data were digitalized at a rate of 1000 Hz. EEG and EOG were filtered online at 0.1-100 Hz.

Data Analysis

ERP data were analyzed using the software “Vision Analyser” (Brain Products, Munich, Germany). After a visual inspection of the EEG, all data were subsequently filtered using a high pass filter of 0.1 Hz (48db/oct) and a 70 Hz low pass (48db/oct). Further on, eye movement artifact correction was performed (Gratton, Coles, & Donchin, 1983) and data were transformed to an average reference. Response-locked epochs beginning 150 ms before and extending 750 ms beyond the response were then created for each trial. Segments containing amplitudes exceeding ± 70 µV or voltage-steps of more than 70 µV per ms as well as epoches with low activity of amplitude changes of less than 0.1 µV per 100 ms were excluded. Correct but slow responses were not further analyzed. In accordance with previous studies on the ERN (Pontifex et al., 2010) and common convention in ERN literature, data sets with less than 6 artifact-free segments per task condition were excluded from the analysis. Based on the response-locked grand average curves, two distinct components could be identified in the ERP: an early negative deflection with a frontocentral distribution that was solely present after response errors (ERN/Ne) and, attenuated, after partial response errors (i.e. trials in which subjects performed corrective behavior after an erroneous reaction), and a subsequent centroparietal positive peak (Pe). Peaks were individually determined in the respective averaged data of the three conditions within

defined time-windows (ERN/Ne: 0–100 ms; Pe: 100-210 ms) at Cz. Relative peak values, resulting from the difference of the negative ERN peak and the preceding positive peak occurring within a time window of -100 to +80 ms prior to the response, were used to quantify the ERN amplitude. To quantify Pe amplitudes, absolute peak values were used. The analysis was performed with a baseline correction (baseline from –200 to –100 ms before button press).

Statistical analyses were performed by IBM Statistics for Windows (version 19.0). In a first step of the analysis, 2x2 analyses of variance (ANOVAs) for repeated measures were conducted comprising the inner-subject factors ‘response type’ (correct vs. incorrect) and ‘time’ (baseline vs. 30-days follow-up) for reaction times, the ERN, and the Pe, as well as neuropsychological (VFT, TMT versions A and B, Stroop interference test) and psychometric variables (HDRS, BPRS, PANSS scales and total score) as well as self-reported quality of life (QoL) separately for both medication groups. Based on Ehlis et al. (2011) further 2x2x2 ANOVAs for repeated measures comprising the previously listed inner-subject factors as well as the between-subject factor 'hypofrontality' (low vs. high difference between ERN and CRN amplitude) were conducted in order to analyze ERP data (ERN & Pe). In a second step, behavioural variables were analyzed by means of 2x2x2 ANOVAs for repeated measures, including the inner-subject factors ‘response type’ (correct vs. incorrect) and ‘time’ (baseline vs. follow-up) and the between-subject factor ‘medication’ (Quetiapine vs. Flupentixol). Neuropsychological and psychometric variables were analyzed conducting 2x2 ANOVAs for repeated measures, including the within-subject factor ‘time’ as well as the between-subject factor ‘group’. Finally, electrophysiological data were analyzed by means of 2x2x2x2 ANOVAs for repeated measures comprising the inner-subject factors ‘response type’ and ‘time’ and the between-subject factors ‘hypofrontality’ and ‘medication’. This analysis included only a subgroup of the initial Quetiapine medication group (N=19) that was matched to the smaller Flupentixol group (N=13) in order to create an equal base level between both medication groups concerning the ERP data. To prevent alpha-error accumulation due to multiple testing, the Bonferroni correction method was applied to adjust the conventional significance level of $\alpha=.05$, leading to corrected alpha-levels of $p<.0083$ for the psychometric analyses (HDRS, BPRS, PANSS scales and total PANSS score), $p<.01$ for neurocognitive data (letter/category VFT, TMT-A & TMT-B, Stroop interfererence measure), and $p<.0167$ for the QoL. The Greenhouse–Geisser

procedure was used to correct the degrees of freedom whenever necessary. One-factorial ANOVAs and two-tailed *t*-tests for matched samples or for independent groups, respectively, were used for post hoc analyses. Equality of variances was tested by means of Levene's test and corrections for inequality were performed when necessary.

Results

1. General analysis separately for both medication groups

Behavioural Data

Behavioural data of both groups from measurement sessions 1 and 2 are presented in Table 1. Quetiapine medicated patients were faster on error compared to correct trials ($F(1,21)=19.87$, $p<.001$, $\eta^2=.49$) and reaction times decreased from session 1 to session 2 ($F(1,21)=5.57$, $p<.05$, $\eta^2=.21$). Moreover, accuracy increased from session 1 (M=.68, SD=.23) to time 2 (M=.75, SD=.22; $t(21)=-2.88$, $p<.01$).

Moreover, in the Quetiapine medication group, reaction times were significantly slower after erroneous trials (M=480.82 ms, SD=119.39 ms) compared to correct trials (M=458.36 ms, SD=106.06 ms) at baseline ($t(21)=-3.34$, $p<.01$), but there was no significant change in this post-error slowing (PES) effect over time ($t(21)=.99$, $p=.33$).

In the 13 Flupentixol medicated patients, 2x2 ANOVA neither revealed a significant effect of time nor a significant effect of response type on mean reaction times, although there was a trend to faster responses in error trials than in correct trials ($F(1,12)= 4.26$, $p=.06$) as well as a trend indicating faster responses at session 2 compared to baseline ($F(1,12)=387$, $p=.07$). There was no interaction "time x response type". As in the Quetiapine group, response accuracy increased over time in the Flupentixol group ($t(12)=-2.72$, $p<.05$, $M_{baseline}=.53$, $SD_{baseline}=.25$; $M_{follow\text{-}up}=.69$, $SD_{follow\text{-}up}=.23$). Furthermore, there was a trend towards an increase in post-error-slowing in the Flupentixol medicated group, although this effect did not reach statistical significance ($t(12)=-2.04$, $p=.06$).

Table 1. Overview over behavioural results in the group separated analysis.
*p<.05, **p<.01.

	Quetiapine group (N=22)					**Flupentixol group (N=13)**				
	Baseline		*Follow-up*			*Baseline*		*Follow-up*		
	Mean	Standard deviation	Mean	Standard deviation	*t-values (df=21)*	Mean	Standard deviation	Mean	Standard deviation	*t-values (df=12)*
N(correct)	299.77	102.86	329.82	96.74	*-3.26***	233.84	110.99	303.62	100.94	*-2.73**
N(error)	60.45	50.27	48.82	45.33	*1.64*	60.53	47.35	52.85	40.61	*.93*
RT(correct)	465.08	109.11	430.76	92.59	*3.36***	633.03	164.85	584.91	128.31	*2.71**
RT(error)	413.35	136.19	388.28	108.47	*.93*	596.49	178.30	552.40	196.81	*1.35*
RT(post-correct)	451.48	106.06	420.04	89.50	*2.70**	626.08	164.97	568.98	134.25	*3.17***
RT(post-error)	480.82	119.39	439.76	99.49	*2.85***	627.20	179.11	610.71	159.72	*.66*
accuracy	.68	.23	.75	.22	*-2.81***	.53	.25	.69	.23	*-2.72**

ERP Data

In the Quetiapine medication group (see figure 1), the 2x2x2 ANOVA revealed a main effect of time ($F(1,21)=9.07$, $p<.01$, $\eta^2=.31$), indicating higher mean ERN amplitudes at follow-up (M=-4.33 µV, SD=2.12 µV) compared to baseline (M=-3.70 µV, SD=1.97 µV), and a main effect of response type ($F(1,21)=73.53$, $p<.001$, $\eta^2=.79$) as well as a main effect of hypofrontality ($F(1,20)=9.27$, $p<.01$, $\eta^2=.32$). The effect of response type was further qualified by hypofrontality ($F(1,21)=24.27$, $p<,001$, $\eta^2=.55$). Subsequent t-tests revealed a significantly stronger effect of response type in patients with strong initial PFC function than in patients with weak initial PFC function ($t(15.59)=-4.01$, $p<.001$), with higher ERN values for error trials than for correct trials in both, the weak PFC function median group (M_{error}=-4.12 µV, SD_{error}=1.81 µV; $M_{correct}$=-2.22 µV, $SD_{correct}$= 1.39 µV) and the strong PFC function median group (M_{error}=-7.62 µV, SD_{error}=2.17 µV; $M_{correct}$=-2.34 µV, $SD_{correct}$=1.22 µV).

A similar ANOVA for the Pe revealed significant main effects of the factors response type ($F(1,22)=21.74$, $p<.001$, $\eta^2=.51$), and time ($F(1,21)=8.8$, $p<.05$, $\eta^2=.28$). Hence, Quetiapine medicated patients showed higher Pe values after errors (M=6.77 µV, SD=4.29 µV) than correct responses (M=3.22 µV, SD=2.95 µV) and Pe amplitudes increased significantly over time ($M_{baseline}$=4.04 µV, $SD_{baseline}$=3.19 µV; $M_{follow-up}$=5.95 µV, $SD_{follow-up}$=3.75 µV) in that group.

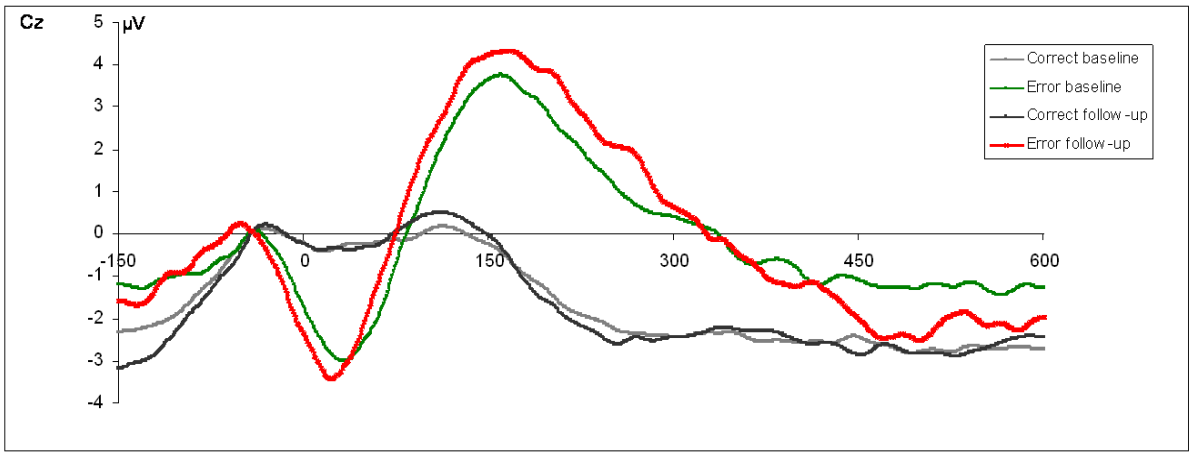

Figure 1. ERP waves for correct and error trials at baseline and follow-up measurement in Quetiapine medicated patients (N=22).

Unlike for Quetiapine medicated patients, in the Flupentixol group the 2x2x2 ANOVA revealed no significant effects on mean ERN amplitudes (.15<F<4.60, n.s.). Beyond that, there were no significant main effects or interactions of one of the included factors on mean Pe values, although there was a slight but non-significant trend suggesting more positive Pe amplitudes after errors than after correct reactions (F(1,21)=3.5, p=.09).

Psychopathology & Life Quality

The fourfold ANOVA for repeated measures for the PANSS scales, the BPRS, and HDRS score revealed the following findings: First, there was a significant attenuation of symptom severity over time for all mentioned symptom measures and subscales in the Quetiapine group (4.12<F<13.99, p<.01, .32<η^2<.48), except for the PANSS subscale “positive symptoms” for which only a trend of improvement was observable (F(3,45)=4.13, p=.05). Post-hoc comparisons indicated that severity of negative symptoms and general psychopathology were reduced between day 10 and day 20 as well as between day 20 and day 30/follow up (2.21<$t_{negative\_symptoms}$<3.05, p<.05; 2.21<$t_{general\_psychopathology}$<2.85, p<0.05) and the mean total PANSS score differed significantly between all four sessions (2.3<t_{PANSS_total}<3.39, p<.05). Mean HDRS scores appeared to be reduced between baseline and day 10 as well as day 20 and follow up (3.33<t_{HDRS}<3.66, p<.01); mean BPRS scores changed significantly only after day 20 (t_{BPRS}(15)=3.27, p<.01). Quetiapine medicated patients further showed an increase in global social functioning over time, with significant GAF score changes between day 10 and day 20 (t(14)=-4.38, p<.001). Finally, we observed a significant improvement in self-reported quality of life (F(3,36)=6.54, p<.01, η^2=.35), as signalled

by a significant improvement in “Contentment with psychological health” from day 10 to day 20 ($t(13)=-3.99$, $p<.01$) as well as a significant increase in the QoL quotient ($F(39,3)=5.32$, $p<.0167$, $\eta^2=.29$) from baseline measurement to day 10.

In the Flupentixol group, there was a significant improvement over time for all PANSS scores except for the subscale “negative symptoms” ($F<1$, n.s.) and the HDRS sum score ($5.50<F<22.37$, $p<0.0083$, $.31<\eta^2<.69$). Concerning the total PANSS value and general psychopathology, significant changes were observed between baseline and day 10 ($t_{PANSS\_total}(10)=4.39$, $p<.001$; $t_{general\_psychopathology}(10)=3.09$, $p<0.05$) as well as between day 20 and follow-up ($t_{PANSS\_total}(10)=2.68$, $p<0.05$). For the subscale “positive symptoms”, a significant improvement was found only between day 10 and day 20 ($t(10)=2.80$, $p<0.05$). HDRS values decreased significantly between baseline and day 10 and again between day 20 and follow-up ($2.57<t<2.82$, $p<.05$). As in the Quetiapine group, Flupentixol medicated patients exhibited significant improvement in global social functioning ($F(3,24)=9.23$, $p<.0001$, $\eta^2=.54$), expressed by an increasing mean GAF score from day 10 to day 20 ($t(8)=-1.30$, $p<.05$). However, there was no significant change in self-reported quality of life ($.96<F<2.88$, n.s.) in this group.

Neuropsychology

Concerning the letter version of the VFT, Quetiapine medicated patients showed a significant performance improvement from baseline (M=28, SD=13.35) to follow-up (M=33.2, SD=16.74; $t(20)=-3.06$, $p<.01$), but there was no effect of time for the category version ($t(20)=-0.87$, $p=.39$). A similar improvement effect was observed in TMT performance in both, TMT-version A ($M_{baseline}=18.14$ s, $SD_{baseline}=8.46$ s; $M_{follow-up}=14.49$ s, $SD_{follow-up}=7.76$ s; $t(21)=2.79$,$p=.05$,) and version B ($M_{baseline}=41.54$ s, $SD_{baseline}=25.54$ s; $M_{follow-up}=32.86$ s, $SD_{follow-up}=19.03$ s; $t(21)=2.32$, $p<.05$). Moreover, the Quetiapine group showed a significant effect of time in the Stroop interference measure ($t(20)=3.01$, $p<.01$), with faster performance at session 2 (M=95.95 s, SD=29.95 s) compared to the baseline assessment (M=108.48 s, SD=30.35 s).

In contrast to the Quetiapine group, Flupentixol medicated patients showed no significant improvement effects over time concerning the VFT ($t_{VFT\text{-}letter}(10)=.67$, $p=.52$; $t_{VFT\text{-}category}(10)=-.66$, $p=.53$), the TMT $t_{TMT\text{-}A}(12)=.38$, $p=.71$; $t_{TMT\text{-}B}(12)=-.23$, $p=.82$), as well as the Stroop interference test ($t(12)=1.46$, $p=.17$).

2. Direct medication group comparison

Behavioural Data

For the mean reaction times, the 2x2x2 ANOVA revealed significant main effects of response type ($F(1,30)=18.41$, $p<.0001$, $\eta^2=.38$), time ($F(1,30)=8.10$, $p<.01$, $\eta^2=.21$), and group ($F(1,30)=12.53$, $p<.001$, $\eta^2=.30$), whereas none of the possible interactions were significant (all $F<1$, n.s.). Mean responses were faster in erroneous than in correct trials ($M_{correct}=518.51$ ms, $SD_{correct}=139.73$ ms; $M_{error}=474.21$ ms, $SD_{error}=166.08$ ms), at follow-up compared to baseline ($M_{baseline}=512.52$ ms, $SD_{baseline}=165.36$ ms; $M_{follow\text{-}up}=480.21$ ms, $SD_{follow\text{-}up}=145.41$ ms), and in the Quetiapine group compared to the Flupentixol group ($M_{Quetiapine}=431.12$ ms, $SD_{Quetiapine}=106.16$ ms; $M_{Flupentixol}=591.71$ ms, $SD_{Flupentixol}=159.33$ms). Response accuracy changed significantly over time ($F(1,30)=16.79$, $p<.0001$, $\eta^2=.36$), with enhanced accuracy from baseline (M=.61, SD=.24) to follow-up (M=.73, SD=.21), but did not differ between groups at any time ($F<1$, n.s.). 2x2 ANOVA for post-error slowing revealed a significant interaction "time x medication" ($F(1,30)=5.21$, $p<.05$, $\eta^2=.14$). A subsequently conducted t-test between groups for PES difference measures from baseline to follow-up indicated a significantly greater improvement in PES over time in the Flupentixol group ($M_{baseline}=1.11$ ms, $SD_{baseline}=55.30$ ms, $M_{follow\text{-}up}=45.85$ ms, $SD_{follow\text{-}up}=63.47$ ms) compared to the Quetiapine group ($M_{baseline}=31.72$ ms, $SD_{baseline}=41.78$ ms, $M_{follow\text{-}up}=24.06$ ms, $SD_{follow\text{-}up}=37.01$ ms; $t(17.98)=-2.13$, $p<.05$).

ERP Data

For the ERN, the 2x2x2x2 ANOVA revealed significant main effects of the factors response type ($F(1,28)=$, $p<.0001$, $\eta^2=.42$) and time ($F(1,28)=4.51$, $p<.05$, $\eta^2=.14$). Furthermore, there were significant 2x2 interactions as follows: response type x medication ($F(1,28)=4.53$, $p<.05$, $\eta^2=.14$), time x medication ($F(1,28)=5.50$, $p<.05$, $\eta^2=.16$), and response type x hypofrontality ($F(1,28)=4.53$, $p<.05$, $\eta^2=.14$). The latter interaction was further affected by the factor “time” ($F(1,28)=5.45$, $p<.05$, $\eta^2=.16$). Subsequent 2x2 (response type x time) ANOVAS were conducted separately for each median group of hypofrontality. For patients with strong baseline PFC function, this analysis only revealed a significant main effect of response type ($F(1,15)=26.28$, $p<.0001$, $\eta^2=.64$), indicating higher ERP amplitudes on erroneous (M=-5.35 µV, SD=2.31 µV) compared to correct responses (M=-2.45 µV, SD=1.34 µV). In contrast, there was a significant effect of time ($F(1,15)=9.60$, $p<.01$, $\eta^2=.39$) as well as a

significant interaction “response type x time” ($F(1,15)=6.97$, $p<.05$, $\eta^2=.32$) in patients with weak baseline PFC function. Post-hoc t-tests showed a significant enhancement of ERP amplitudes after errors over time ($t(15)=3.25$, $p<.01$, $M_{baseline}$=-2.12 µV, $SD_{baseline}$=1.13 µV; $M_{follow\text{-}up}$=-4.46 µV, $SD_{follow\text{-}up}$=3.24 µV), whereas there was no time effect on ERP values in correct trials ($t(15)=-.16$, n.s., $M_{baseline}$=-2.41 µV, $SD_{baseline}$=2.04 µV; $M_{baseline}$=-2.34 µV, $SD_{baseline}$=1.71 µV).

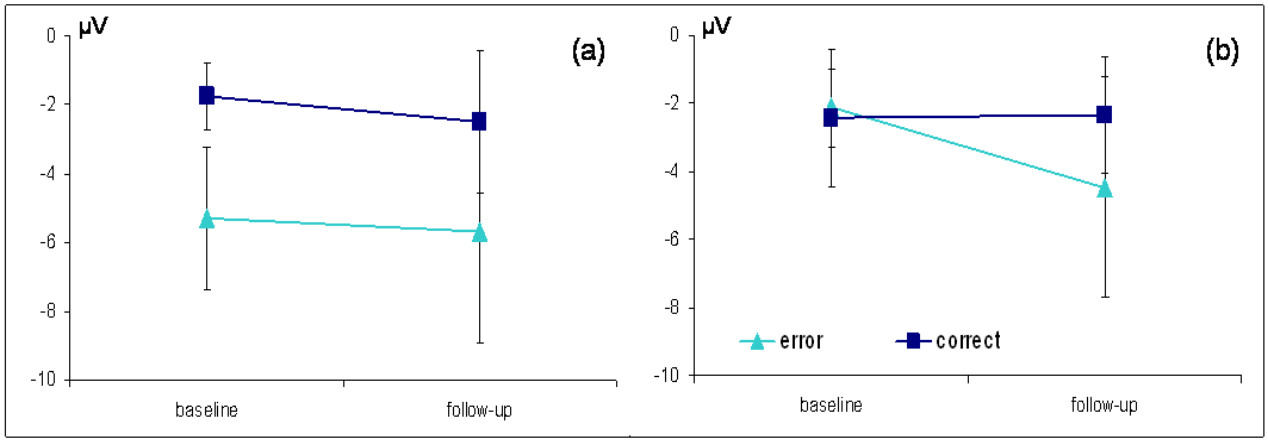

Figure 2. Graphic illustration of the three-way interaction “medication x time x hypofrontality” for mean ERN amplitudes. (a) Median group with weak baseline PFC function, (b) Median group with strong initial PFC function.

Subsequent group separated t-tests were further performed in order to analyze the response type x medication and time x medication interactions. First, post-hoc comparisons revealed significant ERP amplitude differences between correct and erroneous trials averaged over both measurements in the Quetiapine group ($t(18)=5.53$, $p<.0001$), with higher ERP values after errors (M=-5.22 µV, SD=2.30 µV) than after correct responses (M=-2.33 µV, SD=1.35 µV), whereas ERP amplitudes in the Flupentixol group were similar for both response types (M_{error}=-3.56 µV, SD_{error}=2.27 µV; $M_{correct}$=-2.67 µV, $SD_{correct}$=1.60 µV; $t(12)=1.40$, n.s.). Second, post-hoc results indicated a significant increase of mean ERN/CRN values in the Quetiapine group ($t(18)=4.24$, $p<.0001$; $M_{baseline}$=-2.93 µV, $SD_{baseline}$=1.43 µV; $M_{follow\text{-}up}$=-4.16 µV $SD_{follow\text{-}up}$=1.95 µV), but no change in ERN/CRN amplitudes over time in the Flupentixol group ($t(12)=.65$, n.s.; $M_{baseline}$=-2.81 µV, $SD_{baseline}$=1.61 µV; $M_{follow\text{-}up}$=-3.15 µV, $SD_{follow\text{-}up}$=1.97 µV).

For the Pe, the conducted 2x2x2 ANOVA revealed main effects of the factor response type ($F(1,30)=18.23$, $p<.001$, $\eta^2=.38$), indicating higher ERP amplitudes in erroneous (M=5.90 µV, SD=4.07 µV) compared to correct trials (M=2.88 µV,

SD=2.96 µV). Moreover, there was a significant interaction time x medication (F(1,30)=7.36, p<.01, η^2=.20). Whereas Pe values were generally higher at follow-up (M=5.63 µV, SD=4.10 µV) compared to baseline (M=4.08 µV, SD=3.14 µV) in the Quetiapine group (t(18)=-2.27, p<.05), there was no such effect of time in the Flupentixol group (t(12)=1.63, n.s.). In contrast, descriptive values rather indicated a slight decrease in Pe values in the Flupentixol group ($M_{baseline}$=4.44 µV, $SD_{baseline}$=3.13 µV; $M_{follow\text{-}up}$=3.01 µV, $SD_{follow\text{-}up}$=2.69 µV).

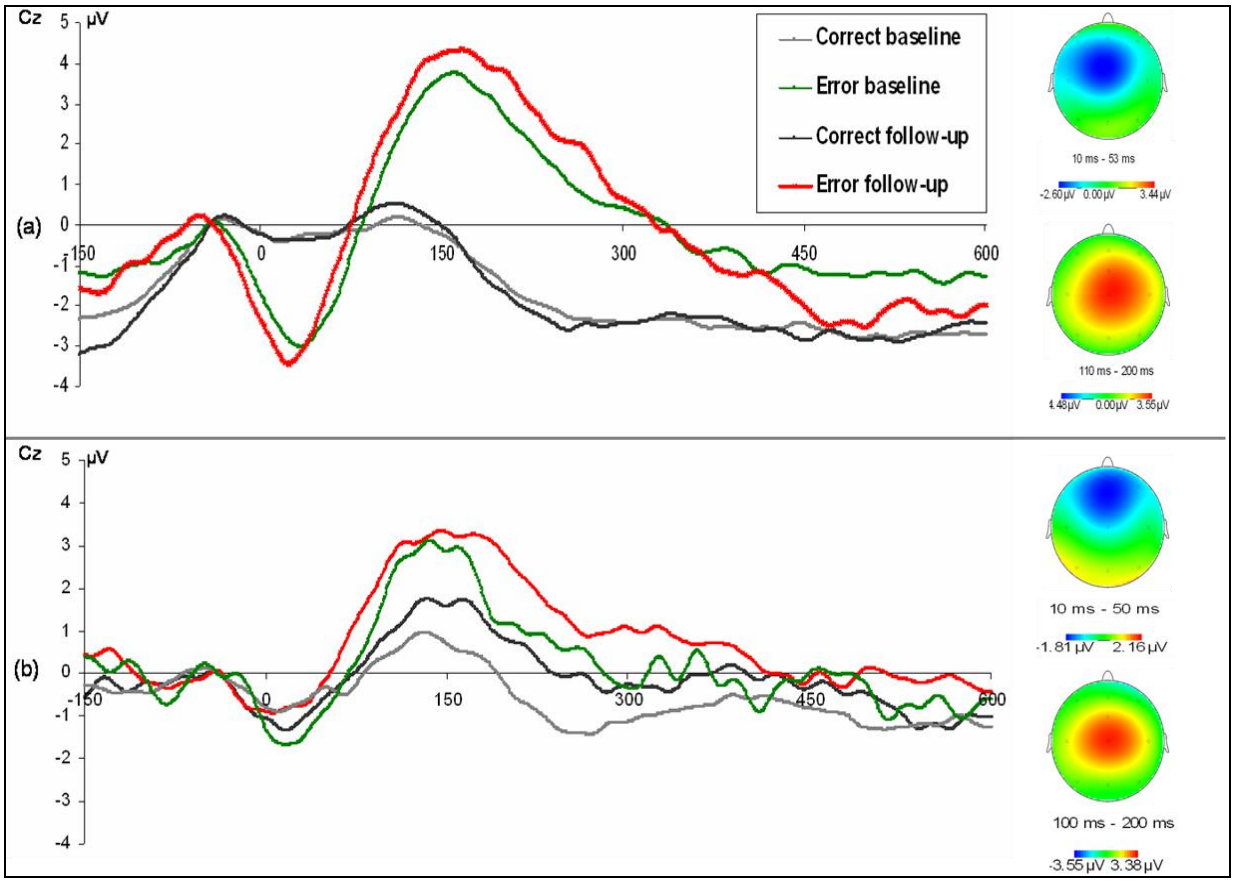

Figure 3. ERP waves for (a) the Quetiapine group, and (b) the Flupentixol group. Topographic maps of the ERN and Pe are illustrated on the right.

Psychopathology & Life Quality

The conducted 4x2 ANOVAs for repeated measures revealed significant effects of time for the PANSS subscales “positive symptoms” and “general psychopathology”, the PANSS total score, the BPRS, and HDRS score (9.55<F<32.0, p<.001, .31<η^2<.59). Concerning the PANSS subscale “negative symptoms”, the time effect was marginally significant (F(3,66)=3.78, p=.02). The effect of time was not qualified by medication for any of the psychopathology measures. We further observed a significant main effect of medication for BPRS scores (F(21,1)=9.47, p<.01, η^2=.32), indicating more severe symptomatology in the Flupentixol group (M=43.44, SD=8.67)

than in the Quetiapine group (M=37.13, SD=6.57). Figure 3 gives an overview of the time course of symptom severity in both groups.

Due to a relatively large number of missing QoL values at the two assessment time points between baseline and follow-up (day10 & day20) only 2x2 ANOVAs were conducted for the quality of life measures. There was a significant effect of time regarding the contentment with psychological health ($F(1,28)=9.69$, $p<.01$, $\eta^2=.26$), signalling an increase in life quality across medication groups. No other main effects or interactions were observed.

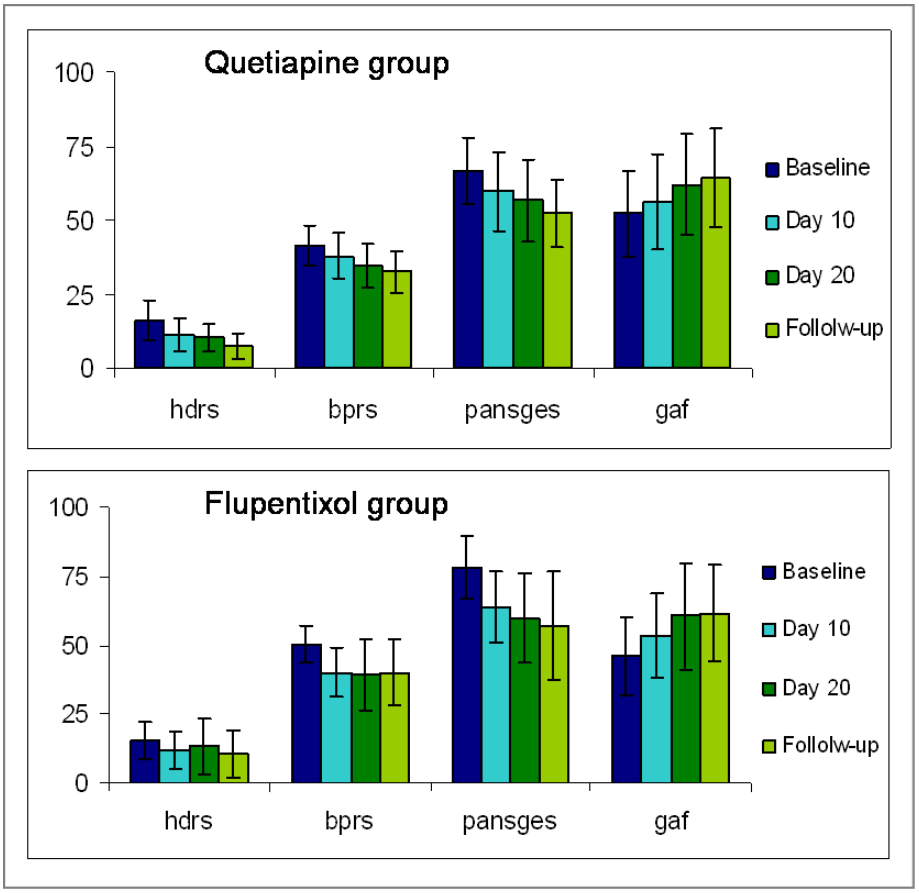

Figure 4. Illustration of time course in psychiatric symptoms separately for the two experimental groups.

Neuropsychology

2x2 ANOVAS for the two VFT and TMT measures did not result in significant main or interaction effects ($.01<F<3.33$, n.s.). However, there was a significant effect of time concerning the Stroop interference test ($F(1,29)=7.18$, $p<.01$, $\eta^2=.20$), indicating faster performance at follow-up (M=107.38 s, SD=28.99 s) compared to baseline (M=120.81 s, SD=31.38 s) measurement across experimental groups.

Discussion

The present study was conducted in order to a) directly investigate the effect of Quetiapine on ACC function and b) to further compare the effect of Quetiapine with the typical antipsychotic Flupentixol in patients suffering from acute psychotic disorders.

The reported results suggest that Quetiapine treatment of at least four weeks leads to a significant improvement in prefrontal brain function in patients suffering from psychotic disorders, indicated by an increase in ERN/CRN as well as Pe amplitudes from baseline assessment to follow-up. These ERP parameters have been repeatedly proved to reflect ACC/PFC function in a broad range of electrophysiological studies on healthy subjects and psychiatric illnesses (e.g. Ehlis, Herrmann, Bernhard & Fallgatter, 2005; Herrmann, et al., 2004; Mathalon, Whitfield & Ford, 2003; Stemmer, Segalowitz, Witzke & Schönle, 2004) . This interpretation is further supported by an additional improvement in cognitive function as reflected by a significant increase in processing speed in three different neuropsychological tasks, including one attention-based (TMT) and one verbal memory focussed (VFT) method as well as one task measuring mental flexibility and inhibition ability (Stroop-interference test). Beyond cognitive improvement, Quetiapine medicated patients reported a reduced severity of psychopathological symptoms that was further accompanied by an improvement in subjective quality of life. These findings are compatible with a plethora of previous studies suggesting a positive effect of atypical antipsychotics on prefrontal brain function (e.g. Braus, Ende, Weber-Fahr, Demirakca & Henn, 2001; Ehlis et al., 2007; Honey et al., 1999; Stip, et al., 2005) and cognitive performance (Keefe, Silva, Perkins & Lieberman, 1999; Riedel, et al., 2007; Woodward, Purdon, Meltzer & Zald, 2005). However, there are inconsistent findings concerning the question, whether atypical antipsychotics can be regarded as superior compared to typical agents regarding their impact on ACC activation and neurocognitive functioning (see Ehlis et al., 2011 for an overview). Aiming at this critical issue, we further compared a reduced Quetiapine medicated group of patients (N=19) with a patient group that was treated with Flupentixol for the same time period. A reduction of sample size concerning the quetiapine treated patients was necessary due to baseline differences regarding the PFC function parameter, which would have aggravated an interpretation of the results. In the global statistical test, our results indicate a significant improvement in psychopathology and cognitive

performance over time in both, the Quetiapine and the Flupentixol group. In contrast, the direct group comparison of the ERP data revealed a significant enhancement in error-related electrophysiological activation in Quetiapine medicated, but not in Flupentixol medicated patients, indicating a selective positive effect of atypical antipsychotic treatment with Quetiapine on the PFC. This finding is in line with studies reporting less pronounced (Ichikawa, Dai, O'Laughlin, Fowler & Meltzer, 2002; Li, Perry, Wong & Bymaster, 1998), or even negative effects of typical agents (Braus, et al., 2001; Miller et al., 2001) on prefrontal brain functions. However, Ehlis et al. (2011) demonstrated that treatment response to typical or atypical agents is mediated by baseline PFC function. The authors noted that patients with weak initial PFC function better responded on atypical antipsychotic medication, whereas patients with strong initial PFC function received more benefits under typical antipsychotics. Our present study, however, could not replicate this finding, as the three-way interaction “medication x time x hypofrontality” was not significant. Alternatively, we found a significant interaction “response type x time x hypofrontality” and post-hoc analyses indicated a differential increase in ERP values after errors but not correct responses in patients with weak initial PFC function, whereas patients with stronger PFC function did not show ERP amplitude enhancement over time. There was no effect of medication on this relation. In their study, Ehlis and colleagues concluded that in patients with weak PFC function, atypical agents, that exert at least part of their pharmacological effect in prefrontal brain structures, were more effective due to their additional affinity for 5-HT-receptors in the frontal lobe. In the present study, we compared Quetiapine to Flupentixol, a typical antipsychotic medication that has been also seen as a “partial atypical neuroleptic” (Kühn, Meyer & Maier, 2000) due to its antagonistic effect on 5HT2A receptors. Thus, our results can be interpreted in line with the findings and conclusion of Ehlis et al. (2011), considering an additional effect of Flupentixol in prefrontal brain areas beyond the typical agent effect on subcortical dopamine receptors. This effect may have been adumbrated in the significant Flupentixol induced improvement in post-error slowing which can be regarded as a behavioural parameter of error monitoring and behavioural control. However, this prefrontal effect of Flupentixol was not strong enough to produce a significant improvement in error monitoring over time. Regarding this specific ACC function, Quetiapine appeared to have a superior treatment effect.

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Tuebingen, 11/04/2012 A.J. Fallgatter