

## RESEARCH ARTICLE

# Effects of Blocking D2/D3 Receptors on Mismatch Negativity and P3a Amplitude of Initially Antipsychotic Naïve, First Episode Schizophrenia Patients

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## Abstract

**Background:** Reduced mismatch negativity and P3a amplitude have been suggested to be among the core deficits in schizophrenia since the late 1970s. Blockade of dopamine D2 receptors play an important role in the treatment of schizophrenia. In addition, there is some evidence indicating that deficits in mismatch negativity and P3a amplitude are related to increased dopaminergic activity. This is the first study investigating the effect of amisulpride, a potent D2-antagonist, on mismatch negativity and P3a amplitude in a large group of antipsychotic-naïve, first-episode schizophrenia patients.

**Methods:** Fifty-one antipsychotic-naïve, first-episode schizophrenia patients were tested in a mismatch negativity paradigm at baseline and after 6 weeks of treatment with amisulpride. We further examined 48 age- and gender-matched controls in this paradigm.

**Results:** At baseline, the patients showed significantly reduced P3a amplitude compared with healthy controls, but no differences in mismatch negativity. Although the treatment with amisulpride significantly improved the patients' psychopathological (PANSS) and functional (GAF) scores, it did not influence their mismatch negativity amplitude, while also their reduced P3a amplitude persisted.

**Conclusion:** Our findings show that antipsychotic naïve, first-episode patients with schizophrenia have normal mismatch negativity yet reduced P3a amplitude compared with healthy controls. In spite of the fact that the 6-week amisulpride treatment improved the patients both clinically and functionally, it had no effect on either mismatch negativity or P3a amplitude. This suggests that even though there is a dopaminergic involvement in global functioning and symptomatology in schizophrenia, there is no such involvement in these particular measures of early information processing.

**Keywords:** First episode schizophrenia, D2 blockade, psychophysiology, mismatch negativity

## Introduction

Psychophysiological measures, including mismatch negativity (MMN), have been intensively investigated over the last 30 years in the search for objective and reproducible methods to support a diagnosis of schizophrenia. MMN was first described in the 1970s (Naatanen et al., 1978) and later reported as deficient in schizophrenia patients in various stages of the disease (Shelley et al., 1991; Javitt et al., 1998; Light and Braff, 2005; Naatanen et al., 2005).

MMN is usually considered to be a reflexive response to the breach of sensory memory patterns, generated in cortical brain regions: temporal and frontal (Alho et al., 1994; Umbricht and Krljes, 2005; Oknina et al., 2005; Naatanen and Kahkonen, 2009). As such, it is often referred to as an “orienting reflex.” Generally, a so-called auditory odd-ball paradigm is used to assess MMN, where an occasional deviant sound (the “odd-ball”) is presented in a stream of frequently occurring (standard) sounds. In a healthy brain, the detection of the odd-ball triggers MMN: a negative deflection in the encephalogram (EEG) with maximum amplitude usually appearing at frontal sites. Both differences in pitch (frequency) and duration have frequently been used as characteristics to differentiate deviant from standard stimuli in MMN paradigms. Both have been found to be deficient in patients with schizophrenia (Baldeweg et al., 2002; Horton et al., 2011; Atkinson et al., 2012a; Fisher et al., 2012), although it has been suggested that duration deviants have more discriminative power to separate patients from controls than the frequency deviants (Magno et al., 2008; Todd et al., 2008a).

Another measure of attention that is often simultaneously assessed with MMN is the P3a amplitude: a positive deflection in the EEG succeeding MMN after presentation of a deviant stimulus. Similar to MMN, the P3a amplitude has frequently been found to be reduced in patients with schizophrenia (Kiang et al., 2007; Atkinson et al., 2012b).

There is some evidence for a dopaminergic involvement in MMN: aripiprazole appears to ameliorate MMN deficits in schizophrenia patients (Zhou et al., 2013), while haloperidol increases MMN in healthy volunteers (Kahkonen et al., 2001). Furthermore, it has been proposed that dopaminergic activity in the frontal parts of the brain modulates P3a amplitude (for review, see Polich 2007; Huang 2015). Indeed, sulpiride (dopaminergic antagonist) increases P300 amplitude in subjects with low amplitudes, yet decreases it in subjects with high amplitudes.

The current study was designed to investigate the involvement of dopamine on both MMN and P3a amplitude further. We previously reported on the influence of 6 weeks of treatment with amisulpride (a specific D2/D3 dopaminergic antagonist) on sensory and sensorimotor gating in initially antipsychotic-naïve, first-episode patients with schizophrenia (During et al., 2014). In the present study, we investigated amisulpride's effect on MMN and the P3a amplitude in this same cohort of subjects. Given the literature cited above, we expected deficient MMN and P3a amplitude in our patients compared with controls at baseline, while treatment with amisulpride would ameliorate both deficits.

## Methods

### Subjects

The study was approved by the Ethical Committee of the Capital Region Copenhagen (Registration: HD-2008-088) according to the ethical principles and guidelines for medical research as stated in the Declaration of Helsinki (amendment of Washington 2002).

The procedure has been described before (During et al., 2014). Written and oral information was given to the patients, and all patients signed informed consent. A total of 61 first-episode, antipsychotic-drug naïve schizophrenia patients between 18 and 41 years of age and 48 controls matched on gender, age, and parental socioeconomic status were recruited for the study. The patients were referred from psychiatric centers in the Capital Region of Copenhagen and completed the Schedule of Clinical Assessment, version 2.1 (Wing et al. 1990) performed by a trained physician (S.D.) and nurse (G.S.A.). All included patients met the ICD-10 criteria for schizophrenia and schizoaffective disorder. Controls were recruited from the community via an advertisement in [www.forsoegsperson.dk](http://www.forsoegsperson.dk). Participation was offered only to control subjects with no previous or current mental health issues (confirmed by the Schedule of Clinical Assessment, version 2.1 interview) and no known first-degree relatives with mental health disorders. Neither patients nor controls had ever participated in psychophysiological studies before. They were examined physically to exclude somatic illness.

The severity of psychopathological symptoms was assessed by the PANSS interview (positive and negative syndrome scale) (Kay et al., 1988). Exclusion criteria were previous impact-related unconsciousness, organic brain damage or disease, intellectual disability (IQ < 70), diseases or processes contraindicated with amisulpride treatment (allergy, prolactin producing tumor, etc.), and all patients treated involuntarily or under judicial ruling. Substance use and abuse were not exclusion criteria, but their extent and type were noted. Urine samples were collected to confirm self-report (benzodiazepines, cannabis, central stimulants).

At baseline, 51 patients and 48 controls completed MMN testing. Of the 10 patients who did not complete testing, 7 were too psychotic to participate in the examinations; 1 was excluded due to a brain lesion found on an MRI scan prior to testing, 1 dropped out due to physical obstruction to correctly fit the EEG cap, and 1 did not want to proceed after the first tests in the Copenhagen Psychophysiology Test Battery (CPTB) paradigm. The subjects were reassessed after 6 weeks following the baseline assessment: 33 patients and 43 controls agreed to be retested. The predominant dropout reasons were discomfort during the baseline assessment, insufficient treatment effect, side effects, and/or worsening of symptoms.

Between baseline and follow-up, patients were treated with amisulpride dosages according to their clinical needs (50–800 mg/d, mean 288 [SD: 170]).

### Procedure

All subjects were examined with the CPTB (Jensen et al., 2008; Wienberg et al., 2010a; Oranje and Glenthøj, 2013). The CPTB includes PPI, P50 suppression, MMN, and selective attention paradigms. Tests are always assessed in this fixed order. To keep this report focused, only results of the MMN paradigm are presented in the current article. Results of the other paradigms are published elsewhere (During et al., 2014). In addition, there were 3 other publications of our research group on this specific cohort (Nielsen et al., 2011a, 2011b; Nordholm et al., 2013a, 2013b). To avoid acute and/or withdrawal effects of nicotine, smoking was not allowed from 1 hour prior to testing. All subjects were requested not to drink any caffeinated beverages on a test day until all tests were completed. In addition, patients were asked to refrain from taking benzodiazepines from 11:00 PM onwards on the evening prior to

a test day. During testing, subjects were seated in a comfortable armchair in a room with a sound level <40 dB situated adjacent to the control room. They were instructed to avoid unnecessary movements and, since MMN is usually recorded without the subjects' attention drawn towards the stimuli, they were asked to ignore all stimuli and to watch a muted video on a screen in front of them (a nature documentary).

## Paradigm

### Stimulus Presentation

Auditory stimuli were presented by a computer running Presentation (Neurobehavioral Systems, Inc., Albany, NY) software (soundcard: Creative soundblaster 5.1, 2008 Creative Technology Ltd, Singapore, Singapore) and were presented binaurally through stereo insert earphones (Eartone ABR, 1996–2008 Interacoustics A/S, Assens, Denmark, C and H Distributors Inc, Milwaukee, WI). The soft- and hardware settings were calibrated by means of an artificial ear (Brüel and Kjær, type 2133, Odin Metrology Inc., Thousand Oaks, CA).

### MMN Paradigm

The paradigm consisted of 1800 stimuli that were presented binaurally. Four types were presented: standard tones with a frequency of 1000 Hz (50 ms) and a probability of 83%, deviant tones with a frequency of 1200 Hz and duration of 50 ms (probability 6%), deviant tones with a frequency of 1000 Hz and duration of 100 ms (probability 6%), and deviant tones with a frequency of 1200 Hz and duration of 100 ms (probability 6%). All stimuli were 75 dB. The stimuli were presented in 1 run, with an interstimulus interval randomized between 300 and 500 ms. The duration of the task was approximately 12 minutes.

## Signal Recording and Processing

EEG as well as electromyography recordings were performed with BioSemi hardware (Amsterdam, Netherlands), using a cap with 64 active electrodes. BESA software (version 5.2.4, MEGIS Software GmbH, Gräfelting, Germany) was used for further processing of the data. Besides assessing MMN and P3a amplitude from the electrodes where their maximum amplitudes were reached (electrode FCz), we assessed amplitudes at electrodes Fz and Cz. Processing of the data started with resampling from the original 4 kHz to 250 Hz to allow easier file handling. Second, the data were corrected for eye-artifacts by using the adaptive method of BESA. Third, the data were epoched (from 100 ms prestimulus to 900 ms poststimulus) and corrected for movement (or other paradigm unrelated) artifacts by removing those epochs from the database that contained amplitude differences of 75  $\mu$ V between maximum and minimum in a time window between 0 and 500 ms of these epochs. Subsequently, the data were filtered (low-pass set to 40 Hz, 24 dB/octave), after which MMN for each of the 3 deviant types was expressed as the average ERP of a subject to deviant stimuli, subtracted with the average ERP of this subject to standard stimuli. MMN amplitudes were scored as the maximum negative voltage within a window of 50 and 275 ms, while the P3a amplitude was scored as the maximum positive voltage within a window of 175 and 375 ms.

## Statistical Analyses

All analyses were performed with SPSS version 21.00 (SPSS). Gender and age were used as covariates throughout all analyses but were excluded if they did not reach statistical significance.

Both MMN and P3a amplitude data were normally distributed (Kolmogorov-Smirnov-test), although some values in the data were more than 3 SDs above or below the average, in which case they were excluded from analysis. Maximum amplitude was reached on electrode FCz for MMN as well as P3a amplitudes.

Baseline MMN and P3a amplitude data were analyzed with repeated measures ANCOVA. Within factors in the ANCOVAs were "lead" (amplitudes assessed at Fz, FCz, and Cz) and "deviant-type" (frequency, duration or the combination frequency-duration), while "group" (patients or controls) was used as a between factor.

Effects of time (which is equivalent to treatment in patients) was assessed by adding the within factor "time" (baseline or 6-week follow-up) to the above-mentioned analyses. To prevent alpha-inflation, further analyses with Student's *t* tests were performed only when the ANCOVAs indicated significance.

The effect of amisulpride on psychopathology (PANSS positive, negative, general and total scores) and functioning (GAF score) data were analyzed with paired samples Student's *t* tests (baseline to 6 weeks), while correlations between MMN and P3a amplitude, dose of medication, symptomatology, and functioning scores were investigated with Pearson's correlation test.

## Results

### General

Since patients and controls were matched, they did not differ in either age or gender composition. The patients were moderately to severely ill, as can be inferred from their PANSS scores, and were treated with low to moderate doses of amisulpride (Table 1). The patients who dropped out of the study (from baseline to 6-week follow-up) did not differ significantly in PANSS scores (total, general, positive, or negative, *P* value range: 0.061–0.58) from patients who completed the study. Neither did the baseline MMN [ $F(1,47) = 0.853$ ;  $P = .36$ ] or the P3a amplitudes [ $F(1,48) = 0.077$ ;  $P = .78$ ] differ between those who dropped out and those who completed the study.

### MMN

The baseline ANCOVA showed a significant main effect of deviant type only [ $F(2,95) = 36.78$ ;  $P < .001$ ]. Neither a significant main effect of group [ $F(1,96) = 0.371$ ;  $P = .544$ ] nor significant group interaction effects ( $P > .06$ ) were found. Neither splitting on deviants (frequency, duration, or their combination) nor on electrodes revealed any group effects ( $P > .131$ ), indicating that both patients and controls showed similar baseline levels of MMN.

Similar to the baseline data, no group effects were detected from baseline to follow-up, indicating similar levels of MMN in patients and controls, regardless of time (which equals treatment in patients), lead, or deviant stimulus.

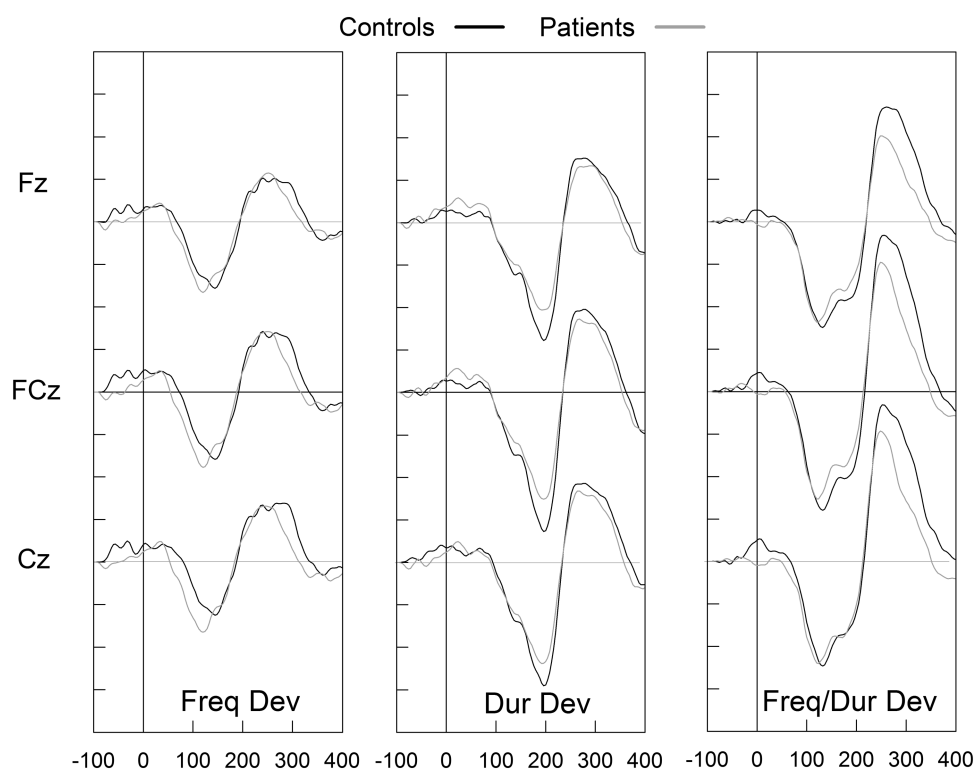
### P3a Amplitude

The baseline ANCOVA showed a significant main effect of group [ $F(1,94) = 3.97$ ;  $P = .049$ ], indicating that patients scored lower P3a amplitude than controls on all 3 electrodes and across all 3 deviants. To determine the origin of this effect, we split the ANCOVA on the 3 separate deviant trials. Neither the frequency [ $F(1,96) = 0.82$ ;  $P = .37$ ] nor the duration deviant [ $F(1,94) = 2.48$ ;  $P = .12$ ] showed any group effects. However, the combined frequency-duration deviant showed a group effect that reached a trend

**Table 1.** Demographics, PANSS Scores, and Medication

	Controls	Patients	Controls	Patients
	Baseline		Six-Week Follow-Up	
Subjects (N)	48	51	43	33
(male/female)	(31/17)	(31/19)	(30/13)	(22/11)
Mean age (SD)	25.8 (6.4)	24.9 (6.1)		
Average PANSS scores (SD)				
Positive		20.1 (3.8)		14.4 (4.0)**
Negative		21.4 (7.2)		19.4 (6.0)
General		42.6 (8.9)		31.5 (8.5)**
Total		84.1 (15.8)		65.2 (15.3)**
GAF score total		40.7 (9.1)		50.7 (14.4)**
Mean dosage antipsychotic medication				288.5 (170.0)

\*Significantly decreased compared with baseline,  $P < .05$ ; \*\*significantly decreased compared with baseline,  $P < .01$ .



**Figure 1.** Grand averages for both patients and controls at baseline, specified for each of the 3 electrodes (Fz, FCz, and Cz) and for each of the 3 deviant types (frequency, duration, and their combination). No significant group effects were found for mismatch negativity (MMN) amplitude, but significantly reduced P3a amplitude was found in patients compared with controls (see text for more details).

level of significance [ $F(1,94) = 3.56$ ;  $P = .06$ ], which appeared to be based on electrode FCz only, where patients scored significantly lower P3a amplitude than controls [ $F(1,94) = 4.77$ ;  $P = .03$ ]. This is also the electrode where maximum P3a amplitude was recorded, regardless of group or deviant type.

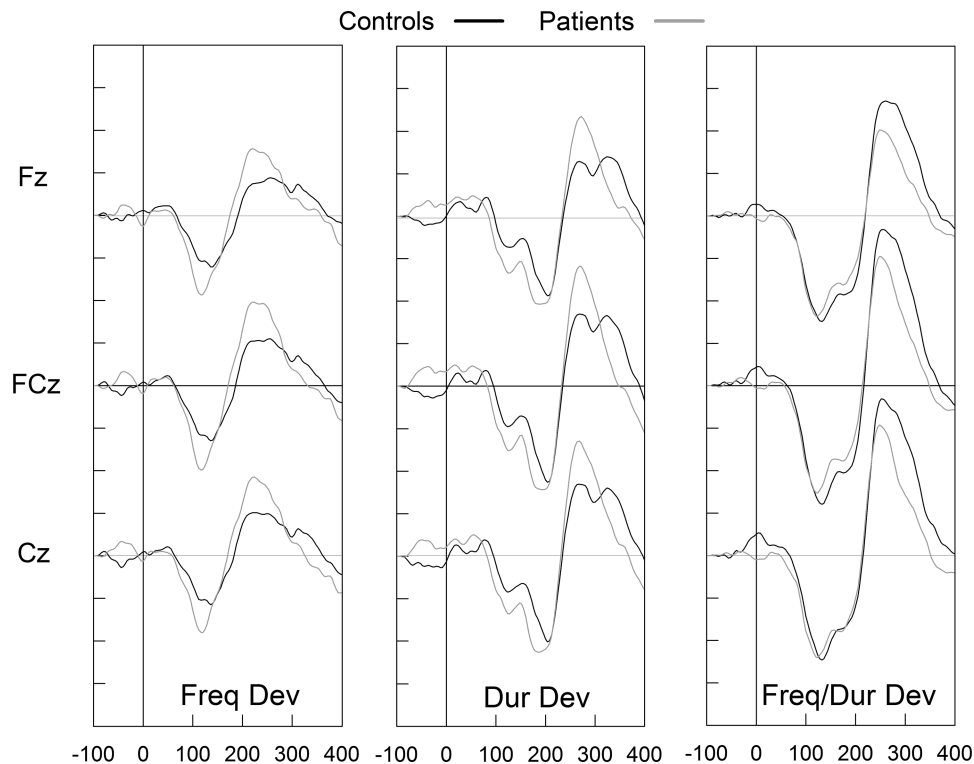
Baseline to (6 week) follow-up analyses also showed a significant main effect of group [ $F(1,71) = 4.52$ ;  $P = .037$ ], indicating that patients scored lower P3a amplitudes, regardless of time (treatment), lead, or deviant-type. To determine the origin of this group effect, we again split the ANCOVA on the 3 separate deviant stimuli. Similar to the baseline analyses, neither the frequency [ $F(1,73) = 0.437$ ;  $P = .51$ ] nor the duration deviant [ $F(1,71) = 3.13$ ;  $P = .082$ ] showed any group effects. However, the combined frequency-duration deviant showed a significant main group

[ $F(1,71) = 5.31$ ;  $P = .024$ ], indicating that patients scored lower P3a amplitude than controls, regardless of time (treatment). Neither patients [ $F(1,29) = 2.74$ ;  $P = .11$ ] nor controls [ $F(1,41) = 0.32$ ;  $P = .57$ ] showed a significant difference in P3a amplitude over time.

### Psychopathology/Functioning

A statistically significant reduction in PANSS positive ( $t = 8.1$ ,  $df = 36$ ,  $P < .001$ ), general ( $t = 7.8$ ,  $df = 36$ ,  $p < 0.001$ ), and total ( $t = 7.3$ ,  $df = 36$ ,  $P < .001$ ) scores, but not in PANSS negative score ( $t = 1.1$ ,  $df = 36$ ,  $P = .295$ ), was found in patients between baseline and 6-week follow-up. Furthermore, the patients' total GAF score increased significantly ( $t = 4.7$ ,  $df = 38$ ,  $P < .001$ ) in this same period of time (Table 1). No significant correlations were found between





**Figure 2.** Grand averages for both patients and controls at 6-week follow-up, specified for each of the 3 electrodes (Fz, FCz, and Cz) and for each of the 3 deviant types (frequency, duration, and their combination). Similar to baseline, no significant group effects were found on mismatch negativity (MMN) amplitude, but P3a amplitude was still significantly reduced in patients compared with controls (see text for more details).

the electrophysiological measures (MMN and P3a amplitude) and the psychopathological/functional measures (PANSS and GAF scores) at either baseline or at follow-up (see Figures 1 and 2).

## Discussion

This is the first study to selectively investigate the effect of D2/D3 blockade in a large cohort of antipsychotic-naïve, first-episode schizophrenia patients. We found no significant MMN differences between patients and controls either at baseline or at follow-up. However, we did find a significant difference between patients and controls in P3a amplitude both at baseline and at follow-up. Furthermore, PANSS (positive, general, and total, but not negative scores) and GAF-scores improved significantly during the course of 6 weeks amisulpride treatment.

In our previous study on MMN in a similar yet smaller cohort of antipsychotic-naïve, first-episode patients with schizophrenia, we found no significant MMN deficits in our patients either, using a typical, frequency-only based MMN paradigm; we did however find MMN deficits in these patients in a dichotic listening paradigm in which the same frequency deviants were used (Oranje et al., submitted). Our current results, showing neither frequency nor duration-based MMN deficits in our patients using a typical MMN paradigm, appear to be consistent with these previous findings. Other studies failed to show MMN deficits in first-episode schizophrenia as well (Salisbury et al., 2002a; Devrim-Ucok et al., 2008a; Magno et al., 2008), while other groups have found differences in chronically ill patients (Horton et al., 2011; Todd et al., 2013). This may indicate that MMN deficits are caused by either progression of the disease, for example, due to loss of cortical tissue in areas related to the regulation of attention and orienting (Rosburg et al., 2004; Todd

et al., 2013), or effects of medication. In general, however, it is important to realize that these studies have been performed with very different paradigms in which various types of deviant stimuli were used. As mentioned above, there are some reports suggesting that deviant stimuli based on duration have a higher discriminative power to separate schizophrenia patients from healthy controls than frequency deviants (Magno et al., 2008; Todd et al., 2008a), although this was not the case in our current study. Neither did we find effects of amisulpride treatment, suggesting that reducing dopaminergic-D2 receptor activity has no influence on MMN. Our previous study on a similar cohort of antipsychotic-naïve, first-episode patients with schizophrenia showed that 6 months of treatment with quetiapine normalized the (frequency-based) MMN deficits that we found in the dichotic listening paradigm only. Since quetiapine has a strong serotonergic influence, this could indicate serotonergic involvement in the regulation of MMN. This is in agreement with 2 other studies from our laboratory, where we found altered MMN in healthy volunteers following administration of 10 and 15 mg of the selective serotonergic reuptake inhibitor escitalopram (Oranje et al., 2008; Wienberg et al., 2010b). Nevertheless, other second generation antipsychotics with a high serotonergic affinity, such as clozapine, risperidone, and olanzapine, do not ameliorate MMN deficits (Umbricht et al., 1999; Korostenskaja et al., 2005).

Our patients did show significantly reduced P3a amplitude to the combined frequency/duration oddballs compared with controls. Amisulpride did not ameliorate this deficit, which in turn suggests that dopamine-D2 receptors are not involved in this particular deviant-based P3a deficiency. Alternatively, the absence of a treatment effect may be related to the dosages of amisulpride that were used in the present study, which were

relatively low due to the fact that we only included antipsychotic naïve, first-episode patients in our study: these patients are known to clinically improve with lower dosages of antipsychotics than patients suffering from more advanced stages of schizophrenia. Logically, this line of reasoning can also explain why we found no treatment effects on MMN amplitude.

We found a significant improvement in PANSS- and GAF scores, indicating a clinically sufficient effect of amisulpride in spite of its lack in ameliorating the deficiencies in our chosen measures. Most likely this also explains why we did not find any correlation between our current psychophysiological measures and these scores on psychopathology or daily functioning. Even though the basic information processes reflected by P3a amplitude and MMN in theory could underlie some features in the symptomatology in schizophrenia, our data do not suggest such a direct linkage. Other literature supports the absence of such a relationship with symptomatology (Salisbury et al., 2002b; Devrim-Ucok et al., 2008b), although there is some evidence that MMN amplitude correlates with a subclass of PANSS items (Todd et al., 2008b). Studies on the relationship between MMN and daily functioning suggest associations in chronic patients with schizophrenia (Light and Braff, 2005). However, similar to our data, no such relationships are found in recent onset patients or in individuals at risk for developing schizophrenia (Jahshan et al., 2012).

There are strengths but also limitations to our study. Obvious strengths are the rather large population of antipsychotic-naïve, first-episode schizophrenia patients and the longitudinal design of this study. Another strength of our study is that amisulpride is rather specific for the dopaminergic D2/D3 receptor system.

A limitation may have been that our patients had to go through a large battery of tests and as such were not as ill as this particular group of patients usually is. This, in combination with the fact that schizophrenia is such a heterogeneous disease, may have limited the representativeness of our results of this particular population in general. More severely ill patients might have shown more explicit psychophysiological deficits. Nevertheless, the average PANSS scores did indicate moderate to severe symptomatology, which is to be expected in first-episode patients (Boter et al., 2009; Wobrock et al., 2013). Another limitation may have been the relatively short treatment period and the low to moderate dosages of amisulpride within the recommended dosage for clinical treatment. However, many other treatment studies have used very similar periods; nevertheless, we cannot be certain whether our results persist over longer periods of time, or if higher dosages of amisulpride would have been used.

In conclusion, we found P3a amplitude to be reduced in a large cohort of antipsychotic-naïve, first-episode schizophrenia patients. Six weeks of treatment with amisulpride did not ameliorate this P3a amplitude deficit, suggesting that it does not improve by blockade of dopamine D2/D3 receptors. In contrast to what we expected, we found no MMN deficits in our patients. Since there are many reports on MMN deficits in patients with schizophrenia, our results may indicate that these deficits appear later in the disease, either due to progression of the disease or due to medical treatment.

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## Statement of Interest

None.

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