Acta Neuropsychiatrica 2009: 21: 26–33

DOI: 10.1111/j.1601-5215.2008.00337.x

ACTA NEUROPSYCHIATRICA

Effect of quetiapine on cognitive function in schizophrenia: a mismatch negativity potentials study

Yuan G-z, Zhou Z-h, Yao J-j. Effect of quetiapine on cognitive function in schizophrenia: a mismatch negativity potentials study.

Objective: The purpose of this study was to investigate whether the effects of quetiapine on abnormalities of early auditory processing in patients with schizophrenia were reflected by mismatch negativity (MMN).
Methods: Subjects were 23 patients with schizophrenia and 23 controls. Psychopathology was rated in patients with the Positive and Negative Syndrome Scale (PANSS) at baseline and after 4-week and after 8-week treatments with quetiapine. Auditory stimuli for event-related potentials consisted of 100 ms/1000 Hz standards, intermixed with 100 ms/1500 Hz frequency deviants and 250 ms/ 1000 Hz duration deviants. A stimulus onset asynchrony of each was 300 ms. Electroencephalograph was recorded at Fz. BESA 5.1.8 was used to perform data analysis. MMN waveforms were obtained by subtracting waveforms elicited by standards from those elicited by frequency- or duration-deviant stimuli.
Results: Quetiapine decreased all PANSS scores. Patients showed smaller mean amplitudes of frequency and duration MMN at baseline than did controls. A repeated measure analysis of variance with sessions (i.e. baseline and 4- and 8-week treatments) and MMN type (frequency versus duration) as within-subject factors revealed no significant MMN type or MMN type × session main effect for MMN amplitudes (for MMN type: $F = 0.704$, df = 1, $p = 0.403$; for MMN type × session: $F = 0.299$, df = 2, $p = 0.796$). Session main effect was significant ($F = 3.576$, df = 2, $p = 0.031$). Least square difference tests showed significant differences between MMN amplitudes at 8 weeks and those at both baseline ($p = 0.025$) and 4 weeks ($p = 0.020$). MMN amplitudes at 8 weeks were higher than those at baseline.
Conclusions: Quetiapine improved the amplitudes of MMN after the 8-week treatment. MMN offers objective evidence that treatment with the quetiapine may ameliorate preattentive deficits in schizophrenia.

Guo-zhen Yuan, Zhen-he Zhou, Jian-jun Yao

Department of Psychiatry, Wuxi Mental Health Center of Nanjing Medical University, Wuxi, China

Keywords: cognitive function; mismatch negativity; quetiapine; schizophrenia

Professor Zhen-he Zhou, Department of Psychiatry, Wuxi Mental Health Center of Nanjing Medical University, Wuxi 214151, China.
Tel: +86-510-13358118986;
Fax: +86-510-83015825;
E-mail: zhouzhenhe1970@sohu.com

Introduction

Schizophrenia often begins during adolescence or early adulthood and presents a broad impairment of cognitive or neuropsychological functions, including the executive functions, perceptual and motor processing, attentional skills, vigilance, verbal learning and memory, spatial working memory and verbal fluency (1,2). Cognitive dysfunction not only is a core syndrome but also is correlated with functional impairment of schizophrenia. Studies showed that the neurocognitive deficits appear predictive of social functioning, occupational functioning and the capacity for independent living in the community (3–5). Undoubtedly, the assessment of the level of cognitive functioning is regarded as a crucial dimension of the assessment of treatment outcomes in schizophrenia. Quetiapine is indicated for the treatment of schizophrenia. Its antipsychotic effect is thought by some to be mediated through antagonist activity at dopamine and serotonin receptors. Specifically, the D1 and D2 dopamine receptor, the alpha-1 and alpha-2 adrenergic receptor and 5-HT1A and 5-HT2 serotonin receptor subtypes are antagonised. Serial positron emission tomography scans evaluating the D2 receptor occupancy of quetiapine have showed that quetiapine very rapidly disassociates from the D2

receptor (6). Theoretically, this allows for normal physiological surges of dopamine to elicit their normal effects in areas such as the nigrostriatal and tuberoinfundibular pathways, thus minimising the risk of side-effects such as pseudo-parkinsonism as well as minimising elevations in prolactin. Common side-effects of quetiapine include constipation, headache, dry mouth and weight gain (or loss). However, those effects may occur to a lesser degree compared to some other atypical antipsychotics such as olanzapine or clozapine. Some studies reported that quetiapine improves impaired cognitive functions in schizophrenia, including verbal fluency, memory and executive functions (7–9). Two strategies have been used to evaluate the effects of quetiapine on cognitive functions in schizophrenia. First, neurocognitive and functional measures through the use of performance-based competence assessments as outcome measures in clinical trials were used to evaluate the effectiveness of quetiapine in improving cognitive and functional outcomes. Other studies reported that quetiapine had beneficial effects not only on cognitive skills but also particularly on verbal reasoning, fluency skills and immediate recall. An additional improvement in executive skills and visuomotor tracking and on the average of the six cognitive domains was also noted with sustained treatment by standardised neuropsychological measures (7). A cognitive function summary score improved in the quetiapine group relative to the group treated with conventional antipsychotics. Patients taking quetiapine did better with respect to both verbal fluency (initiation) and verbal memory. There were also statistically significant group differences with respect to quality of life favouring the quetiapine group (10).

Second, the functional magnetic resonance imaging (fMRI) studies showed that in the verbal fluency task, there was significantly increased activation in the left inferior frontal cortex in the quetiapine-treated patients compared with the drug-naive sample. During auditory stimulation, the stably treated patients produced significantly greater activation in the superior temporal gyrus than did the drug-naive sample. The conclusion was that quetiapine treatment is associated with altered responses in blood oxygen level dependence in both the prefrontal and temporal cortex that cannot be accounted for by improved task performance subsequent to drug treatment (11). In addition, it was concluded through fMRI assessment that the neuronal networks underlying working memory are clearly altered in schizophrenia (9).

Cognitive deficits in schizophrenia not only include deficient performance in higher cognitive domains but also extend to information processing at the sensory and preattentive levels (12). The event-related potential (ERP) mismatch negativity (MMN) is an effective measure of preattentive information processing by auditory change detection. MMN is a negative ERP component elicited by deviant stimulus, i.e. the standard sounds changed frequency, duration, intensity or location. Namely, the MMN is believed to be the outcome of a comparison process, commonly elicited when an incoming stimulus differs from the memory of repetitive tones (standards) occurring in the recent acoustic past. Because in the absence of such a memory trace, no MMN is generated, MMN generation indexes auditory sensory memory and reflects context-dependent information processing at the level of the auditory sensory cortex. There is no agreement to date regarding whether MMN reflects an attention-independent process. A previous study originally proposed that the MMN was unaffected by various attentional manipulations (13). The conclusion was based on evidence suggesting that it was the mismatch process between the neural trace of the standard (the repetitive sound) and the incoming deviant sound that generates the MMN response, which was unaffected. Several studies showed that MMN generation was affected by attention (14–16). In addition, MMN likely reflects *N*-methyl-D-aspartate channel current influx in cortical layers II and III based on animal and human experiments (17).

To date, there have been many studies on MMN in schizophrenia. Several studies reported that MMN amplitude in response to tone duration and tone frequency deviants was reduced in patients with schizophrenia (18,19). One study showed that the presence of MMN abnormalities was related to illness onset (20). However, another study displayed normal MMN generation in first-episode patients (21). Thus, whether MMN deficits are present at illness onset remains controversial. Furthermore, MMN deficits are not observed in other major mental illnesses such as bipolar disorder or major depression, suggesting that they may be fairly specific to schizophrenia (22). However, several studies had found that MMN amplitude diminished in dyslexia, aphasia, Asperger's syndrome and Alzheimer's disease (23–26). At this time, the data are not able to specify clearly the association between the diagnosis of schizophrenia and decreased MMN potentials involved in psychiatric illnesses.

Since changed MMN reflects abnormalities of early auditory processing in schizophrenia, we suppose that a sufficient treatment period (i.e. more than 8 weeks) with quetiapine may lead to the improvement of MMN. Up to now, no studies for the effects of quetiapine on MMN in

https://doi.org/10.1111/j.1601-5215.2008.00337.x Published online by Cambridge University Press

schizophrenia have been reported. The goal of the present study was to investigate whether the effects of quetiapine on abnormalities of early auditory processing in patients with schizophrenia were reflected by auditory MMN.

Materials and methods

Study subjects

Subjects were 23 patients with *Diagnostic and Statistical Manual of Mental Disorders* (4th ed, DSM-IV) diagnosis criteria for schizophrenia and 23 matched age and gender controls with no personal or family history of schizophrenia. Patients with schizophrenia were recruited from Wuxi Mental Heath of Nanjing Medical University in Jiangsu, China. Controls were recruited from the employees of Wuxi Mental Health Center of Nanjing Medical University. Subjects and controls were excluded from the study if they were smokers; had a diagnosis of alcohol or substance dependence, neurological disorders and all kinds of head injury or had received electroconvulsive therapy in the past 6 months. All participants were Chinese. They all gave written informed consent to participate and all were paid. The protocol for the research project was approved by the Ethics Committee of Nanjing Medical University, China.

Clinical assessments

All participants underwent a clinical assessment by a psychiatrist to collect information on medication and sociodemographic data and to confirm/exclude a DSM-IV diagnosis. On the day of the ERP recording, psychopathology was rated in patients with the Positive and Negative Syndrome Scale (PANSS) (27). Handedness was assessed using the Annett Handedness Scale (28). Ratings on this scale were recoded into the following definitions of handedness: Annett score 1 = right, 2–7 = mixed, 8 = left.

The demographic characteristics of the sample are detailed in Table 1.

Table 1. Demographic characteristics of the sample

	Patients	Controls
Sex ratio (male/female)	23 (12:11)	23 (12:11)
Mean age (SD)	34 (12)	34 (12)
Age range (years)	17–59	17–59
Handedness		
R/M/L	13/8/2	12/8/3
% R/M/L	57/35/8	52/35/13

L, left; M, mixed; R, right; SD, standard deviation.

Experimental procedure

Stimulation protocol and procedure ERP recordings were acquired during the presentation of auditory stimuli. Auditory stimuli consisted of 100 ms/1000 Hz standards intermixed with 100 ms/1500 Hz frequency deviants and 250 ms/1000 Hz duration deviants. All stimuli had a rise-fall time of 5 ms. Stimuli were presented in a fixed order (four standards, one frequency deviant, four standards and one duration deviant) with a stimulus onset asynchrony of 300 ms. The stimuli were presented through foam insert earphones at a nominal intensity of a 75-dB level. Stimuli were presented in four blocks with 1000 stimuli, each totalling 4000 stimuli including 3200 standards, 400 frequency deviants and 400 duration deviants. During presentation of the auditory test paradigm, subjects watched a silent self-selected video film to divert attention from the tones and to minimise boredom and reduce eye movement artefacts. Subjects were constantly monitored. Short breaks were offered to ensure full alertness and comfort during the recording session.

In order to detect the treatment effects on MMN, auditory ERPs were recorded at baseline, 4 weeks and 8 weeks of quetiapine treatment. For healthy controls, ERPs were recorded once. At baseline, 17 patients were neuroleptic naive and 6 neuroleptic free (2 for at least half a year and 4 for at least 1 month). After 2 weeks of follow-up, patients received quetiapine 600–800 mg/day (mean value 721.7, standard deviation 90.2).

Electroencephalographic recordings According to the 10/20 International System, electroencephalography (EEG) was recorded with the Stellate Harmonie EEG device (Physiotec Electronics Ltd., Montreal, Quebec, Canada) from Fz, left mastoid and right mastoid sites using Electro-Cap Electrode System (ECI™ Electro-Caps; Electrocap International, Eaton, OH, USA). Ear electrodes served as a reference, and the ground electrode was attached to the forehead. Eye movement artefacts were monitored by recording vertical and horizontal electro-oculogram from electrodes placed above and below the right eye and at the left outer canthus. Electrode impedance was kept below 5 kΩ. System band pass was 0.1–30 Hz and digitalised continuously at a sampling rate of 250 Hz. Digital tags were obtained for all auditory stimuli.

Data analysis

Brain Electrical Source Analysis (BESA) program (version 5.1.8, software) was used to perform data analysis. Epochs were constructed that consisted of

https://doi.org/10.1111/j.1601-5215.2008.00337.x Published online by Cambridge University Press

a 100-ms pre-stimulus baseline and a 500-ms post-stimulus interval. All epochs with amplitudes exceeding ±75 μV at any electrode were excluded automatically. Epochs were averaged offline for each subject and stimulus type and digitally filtered with a low-pass filter of 15 Hz (24 dB down). MMN waveforms were obtained by subtracting waveforms elicited by standards from those elicited by frequency- or duration-deviant stimuli. Frequency MMN amplitude was defined as the peak negativity within a 100- to 225-ms latency window, and duration MMN amplitude was defined as the peak negativity within the 200–300 ms range.

Statistical analyses

Data were analysed using SPSS (version 10.0). Comparisons of PANSS scores (PANSS total scores, Positive Symptom Scale scores, Negative Symptom Scale scores and Total Psychopathology Scale scores) and mean amplitudes and latencies of frequency and duration MMN between neuroleptic-naive and neuroleptic-free patients were done using independent-sample *t*-tests. Comparisons of amplitudes of MMN between healthy controls and patients were done using paired-sample *t*-tests. PANSS scores were analysed by one-way repeated measure analysis of variances (ANOVA) with session (baseline and 4- and 8-week treatments) as a within-subject factor. The effects of quetiapine treatment on amplitudes of MMN were analysed by repeated measure ANOVA with session (baseline and 4- and 8-week treatments) and MMN type (frequency versus duration) as within-subject factors. Least square difference (LSD) tests were performed as *post hoc* analyses if indicated. Correlation coefficients between MMN and PANSS scores were calculated by the Pearson test. Alpha values of 0.05 were considered significant throughout.

Results

Comparisons of PANSS, MMN between neuroleptic-naive and neuroleptic-free patients

No differences in PANSS, mean amplitudes and latencies of frequency and duration MMN at baseline and after 4- and 8-week treatments between neuroleptic-naive and neuroleptic-free patients were observed ($p > 0.05$) (Tables 2 and 3).

Comparisons of PANSS before and after quetiapine treatment

PANSS scores were analysed by one-way repeated measure ANOVA with session (baseline and 4- and 8-week treatments) as a within-subject factor revealing significant session main effect for PANSS scores (for PANSS total scores: $F = 255$, df = 2, $p = 0.000$; for Positive Symptom Scale scores: $F = 155$, df = 2, $p = 0.000$; for Negative Symptom Scale scores: $F = 50$, df = 2, $p = 0.000$; for Total Psychopathology Scale scores: $F = 20$, df = 2, $p = 0.000$). Quetiapine decreased all PANSS, Total Psychopathology, Positive Symptom and Negative Symptom Scale scores. There was no significant correlation between changes in amplitudes of frequency and duration MMN and changes in PANSS scores at baseline and follow-up periods (Table 4).

Comparison at baseline of patients and healthy controls

Patients showed smaller mean amplitudes of frequency and duration MMN at baseline than did controls (in frequency MMN, $t = 2.067$, $p = 0.045$; in duration MMN, $t = 2.263$, $p = 0.029$; df for all electrodes = 22). The mean amplitudes of frequency and duration MMN were reduced in patients at 8-week treatments compared to controls however, did not reach significance (in frequency MMN, $t = 1.649$, $p = 0.113$; in duration MMN, $t = 1.861$, $p = 0.091$; df for all electrodes = 22). No differences in latencies between patients and controls were observed (Table 5; Fig. 1).

Effects of quetiapine treatment

A repeated measure ANOVA with session (baseline and 4- and 8-week treatments) and MMN type (frequency versus duration) as within-subject factors revealed no significant MMN type or MMN type × session main effect for MMN amplitudes (for MMN type: $F = 0.704$, df = 1,

Table 2. PANSS scores [presented as mean (standard deviation)] before and after quetiapine treatment of neuroleptic-naive (naive = 17) and neuroleptic-free patients (free, $n = 6$)

	Baseline		After 4-week treatments		After 8-week treatment	
	Naive	Free	Naive	Free	Naive	Free
PANSS	93.2 (10.7)	94.6 (9.8)	68.1 (15.4)	67.3 (16.9)	60.9 (18.4)	61.6 (19.1)
Positive Symptom Scale	22.0 (12.5)	21.8 (13.0)	12.3 (5.0)	11.9 (6.3)	10.4 (5.2)	11.0 (4.3)
Negative Symptom Scale	26.0 (13.1)	25.8 (12.6)	18.7 (10.9)	18.0 (11.2)	17.2 (11.3)	17.9 (10.7)
Total Psychopathology Scale	47.2 (7.1)	46.7 (9.3)	37.1 (11.5)	36.8 (13.3)	31.0 (4.1)	30.8 (3.5)

https://doi.org/10.1111/j.1601-5215.2008.00337.x Published online by Cambridge University Press

Table 3. Amplitudes and latencies of MMN [presented as mean (standard deviation)] of neuroleptic-naive (naive, $n = 17$) and neuroleptic-free patients (free, $n = 6$) at baseline and 4- and 8-week treatments

Types	Frequency		Duration	
Components	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)
Baseline				
Naive	142.9 (10.9)	1.61 (0.8)	238.9 (21.3)	1.57 (0.9)
Free	143.1 (11.2)	1.62 (0.9)	236.8 (19.4)	1.59 (1.1)
After 4-week treatments				
Naive	143.5 (12.2)	1.60 (1.1)	240.0 (18.7)	1.58 (1.0)
Free	144.0 (12.0)	1.61 (0.7)	239.8 (18.3)	1.59 (0.7)
After 8-week treatments				
Naive	143.9 (12.1)	1.91 (0.8)	237.2 (20.1)	1.90 (1.1)
Free	143.0 (13.5)	1.89 (0.9)	238.0 (18.2)	1.87 (0.9)

$p = 0.403$; for MMN type × session: $F = 0.299$, df = 2, $p = 0.796$). Session main effect, however, was significant ($F = 3.576$, df = 2, $p = 0.031$). LSD tests were performed as *post hoc* analyses and showed significant differences between MMN amplitudes at 8 weeks and those at both baseline ($p = 0.025$) and 4 weeks ($p = 0.020$). However, the test did not show a significant difference between MMN amplitudes at 4 weeks and those at baseline ($p = 0.935$). MMN amplitudes at 8 weeks were higher than those at 4 weeks and those at baseline (Table 5; Fig. 2).

Discussion

This study is the first to use electrophysiological indices of automatic auditory information processing, i.e. MMN, to assess cognitive improvement in patients with schizophrenia treated by atypical neuroleptic quetiapine. Our trial results authenticate previous hypothesis that treatment with quetiapine leads to the improvement of MMN in schizophrenia. The atypical neuroleptic quetiapine not only is an effective 5HT2a and D2 receptor antagonist but also is a 5HT1a receptor partial agonist, increasing dopamine and acetylcholine release in the prefrontal cortex (6). Because MMN amplitude is highest in frontal channels

Table 4. PANSS scores [presented as mean (standard deviation)] before and after quetiapine treatment

	Baseline	After 4-week treatments	After 8-week treatments
PANSS	95.0 (11.5)*	67.3 (17.8)*	61.3 (19.0)*
Positive Symptom Scale	21.8 (11.2)	12.0 (4.7)	10.0 (4.4)
Negative Symptom Scale	26.6 (12.9)	18.3 (11.1)	16.6 (10.8)
Total Psychopathology Scale	46.4 (6.5)	36.7 (10.0)	30.3 (2.1)

*$p < 0.01$.

Table 5. Amplitudes and latencies of MMN [presented as mean (standard deviation)] of healthy controls ($n = 23$) and patients ($n = 23$) at baseline and 4- and 8-week treatments

Types	Frequency		Duration	
Components	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)
Controls	143.5 (12.0)	2.01 (0.4)	239.5 (23.4)	2.00 (0.6)
Patients (baseline)	141.7 (11.2)	1.57 (0.9)*	239.7 (22.0)	1.53 (0.8)*
Patients (after 4-week treatments)	142.2 (14.4)	1.65 (0.8)*	238.9 (21.5)	1.42 (0.7)*
Patients (after 8-week treatments)	141.0 (13.2)	1.94 (0.5)	240.2 (22.1)	1.88 (0.7)

*Patients, after 8-week treatments versus baseline and after 4-week treatments, $p < 0.05$.

(29–31), MMN amplitudes at Fz electrodes present the status of cognitive function. Our study showed that quetiapine improved the amplitudes of MMN after 8-week treatments, which proves that quetiapine has an effect on passive attention in patients with schizophrenia. From a neuroelectrophysical standpoint, MMN offers objective evidence that treatment with the quetiapine ameliorates preattentive deficits in schizophrenia.

A previous study showed reduced MMN in stable chronic patients with schizophrenia and deduced that chronic patients represent a more homogeneous sample concerning the genetics of MMN deficits (12). Another study displayed that MMN amplitude was reduced in patients with schizophrenia and relatives compared with controls, and there were no significant differences between patients and relatives; therefore, the results suggest that reduced MMN amplitude may be an endophenotype marker of the predisposition to schizophrenia (32). The above two studies support that MMN deficits may represent a trait marker. However, a study reported that the MMN has no significant familial influence and is normal among the unaffected relatives. The researchers concluded that although the MMN is abnormal in patients with schizophrenia, it is a weak or unreliable marker of vulnerability when applied to subclinical populations. Therefore, it is unlikely to be an endophenotype for the disorder (33). In our study, the mean amplitudes of frequency and duration MMN were reduced in patients at 8-week treatments compared to controls however, did not reach significance, which deduces that MMN abnormalities are state dependent. However, because of the small sample, our results have to be considered preliminary. As a matter of fact, whether MMN deficits represent a trait marker or state marker remains controversial. The probable reason for inconsistencies is that

https://doi.org/10.1111/j.1601-5215.2008.00337.x Published online by Cambridge University Press

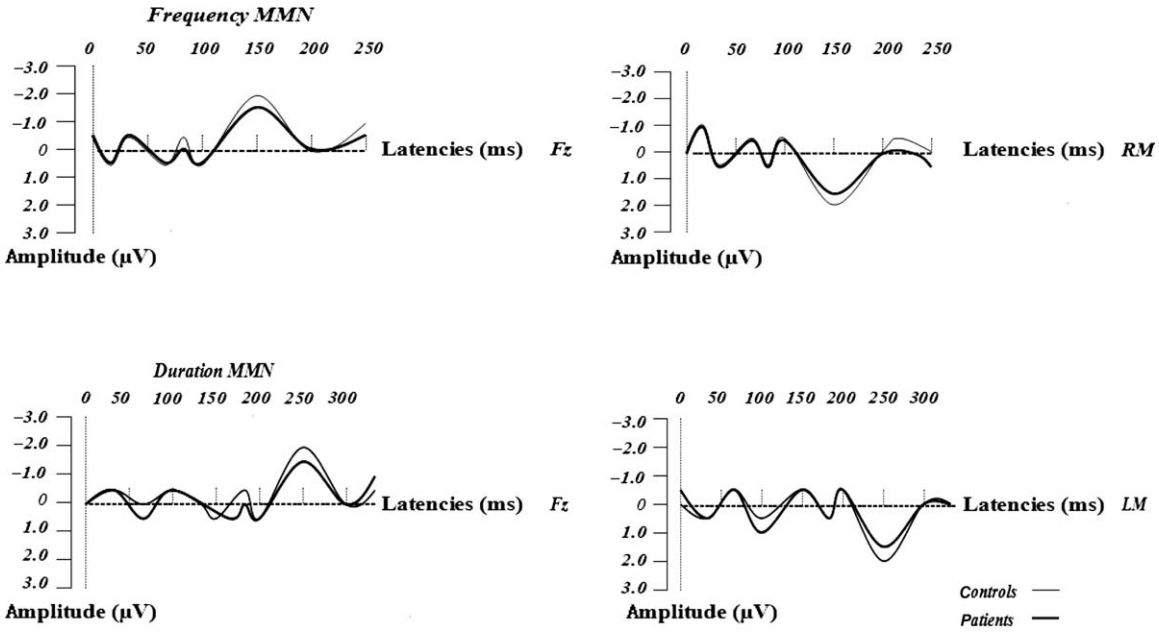

Fig. 1. Grand averages of frequency and duration MMN (MMN waveforms were obtained by subtracting waveforms elicited by standards from those elicited by frequency- or duration-deviant stimuli) in patients at baseline and controls. RM, right mastoid; LM, left mastoid.

different stimulus condition designs were used and insufficient numbers of subjects were recruited for these studies.

Neurocognitive impairment is now recognised as a fundamental symptom of schizophrenia (34,35). Improvement in cognitive function is increasingly recognised as an important goal of therapy. To some extent, the degree of neurocognitive impairment has been shown to be a much stronger predictor of community functioning than either positive or negative symptom severity (36). In this trial, quetiapine had no significant effects on amplitudes of MMN after 4-week treatments. It might be deduced that improvement in cognitive function during treatment with quetiapine in schizophrenia relies on a sufficient treatment period. Previous studies failed to show the effects of atypical antipsychotics such as clozapine, risperidone and olanzapine on MMN after a 4-week treatment (37–39). The probable reason for this failure is that the treatment period was insufficient.

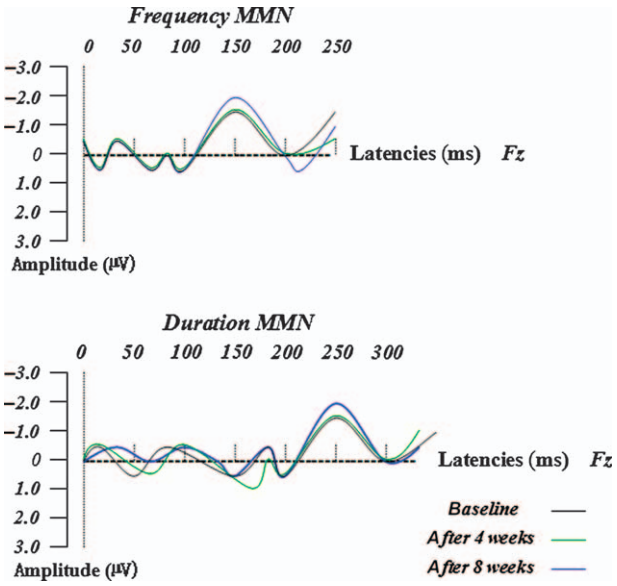

Fig. 2. Grand averages of frequency and duration MMN (MMN waveforms were obtained by subtracting waveforms elicited by standards from those elicited by frequency- or duration-deviant stimuli) in patients at baseline and 4- and 8-week treatments of quetiapine.

In the past, MMN for both duration and frequency deviants was investigated in patients with schizophrenia, and the results showed that patients with schizophrenia showed significantly smaller mean MMN than did healthy control subjects (22). Consistent with previous research, the present study showed that MMN amplitudes were significantly reduced in the patient group, which showed that MMN might be an abnormal index of preattentive automatic auditory information processing.

MMN is considered an index of the auditory sensory memory because MMN generation depends on the context in which a specific stimulus is presented. Namely, it is only generated when a memory trace of the regularity or invariance has been established against which any incoming stimulus is being compared. MMN provides a measure of cognitive deficits associated with

https://doi.org/10.1111/j.1601-5215.2008.00337.x Published online by Cambridge University Press

schizophrenia (40), being the first measurable brain response component that differentiates between frequent and deviant auditory stimuli and reflects the properties of an automatic, memory-based, comparison process.

We observed no significant correlation between changes in amplitudes of frequency and duration MMN and changes in PANSS scores at baseline and follow-up periods. The probable reason is that PANSS scores mainly reflect obvious symptoms, such as both positive and negative symptoms. Furthermore, few of the cognitive symptoms of automatic auditory information processing were reflected. Our results show that the MMN amplitudes at Fz reflect the degree of neurocognitive impairment. MMN amplitude improvement may be a possible biomarker of treatment efficacy. The improvement of this functional marker may indicate an important pathway towards new therapeutic strategies that target cognitive dysfunction in schizophrenia. It is important that clinicians understand the benefits and limitations of modern neuroimaging techniques and are also suitably equipped to appraise future developments (41). The use of MMN in evaluating psychopathology and therapeutic effects is helpful in the clinical management of schizophrenic patients. Therefore, it is necessary to validate this study effect using similar parameters in future studies.

In this study, during presentation of the auditory test paradigm, the attention of the subjects was diverted from the tones, and the results may exclude a practice effect. However, the limitation of this study is the failure to retest the control group at 4 and 8 weeks for further checking the validity.

In conclusion, MMN offers the ability to map the neuroelectrophysical response to treatment intervention within the brain and may enable improved understanding of the neuropharmacology of schizophrenia. Our study showed that quetiapine was useful for the treatment of schizophrenic patients, especially on improvement of abnormalities of early auditory processing, as assessed by MMN, a non-invasive technique with good temporal resolution.

Acknowledgements

This study was supported by the Key Technologies Research and Development Program of Nanjing Medical University, China (no. 20060587) .We thank Professor Helen Arnott for the English corrections.

References

1. Bilder RM, Goldman RS, Robinson D et al. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. Am J Psychiatry 2000;**157**:549–559.
2. Bema BK, Kfksal AA, Haluk A et al. Effects of quetiapine on cognitive functions in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2005;**29**:233–238.
3. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;**153**:321–330.
4. Meltzer HY, Thompson PA, Lee MA et al. Neuropsychological deficits in schizophrenia: relation to social function and effect of antipsychotic drug treatment. Prog Neuropsychopharmacol 1996;**14**:27S–33S.
5. Velligan DI, Miller AL. Cognitive dysfunction in schizophrenia and its importance to outcome: the place of atypical antipsychotics in treatment. J Clin Psychiatry 1999;**60**:S25–S28.
6. Sharma T. Quetiapine–efficacy in different domains. Eur Neuropsychopharmacol 2001;**11**:385–390.
7. Purdon SE, Malla A, Labelle A et al. Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. J Psychiatry Neurosci 2001;**26**:137–149.
8. Velligan DJ, Newcomer J, Pultz J et al. Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophr Res 2002;**53**:239–248.
9. Meisenzahl EM, Scheuerecker J, Zipse M et al. Effects of treatment with the atypical neuroleptic quetiapine on working memory function: a functional MRI follow-up investigation. Eur Arch Psychiatry Clin Neurosci 2006; **256**:522–531.
10. Velligan DI, Prihoda TJ. The effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings. J Clin Psychiatry 2003;**64**:524–531.
11. Jones HM, Brammer MJ, Toole M et al. Cortical effects of quetiapine in first-episode schizophrenia: a preliminary functional magnetic resonance imaging study. Biol Psychiatry 2004;**56**:938–942.
12. Daniel SG, Umbricht JA, Bates JA et al. Electrophysiological indices of automatic and controlled auditory information processing in first-episode recent-onset and chronic schizophrenia. Biol Psychiatry 2006;**59**:762–772.
13. Naatanen R. The mismatch negativity: a powerful tool for cognitive neuroscience. Ear Hear 1995;**16**:6–18.
14. Alain C, Woods DL. Attention modulates auditory pattern memory as indexed by event-related brain potentials. Psychophysiology 1997;**34**:534–546.
15. Dittmann-Balcar A, Thienel R, Schall U. Attention-dependent allocation of auditory processing resources as measured by mismatch negativity. Neuroreport 1999;**10**: 3749–3753.
16. Woldorff MG, Hillyard SA, Gallen CC et al. Magnetoencephalographic recordings demonstrate attentional modulation of mismatch-related neural activity in human auditory cortex. Psychophysiology 1998;**35**:283–292.
17. Lavoie S, Murray MM, Deppen P et al. Glutathione precursor N-Acetyl-Cysteine, improves mismatch negativity in schizophrenia patients. Prog Neuropsychopharmacol 2007;**11**:1–13.
18. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. Schizophr Res 2005;**76**: 1–23.
19. Anke BD, Indira T, Ralf P et al. Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. Schizophr Res 2005;**73**:297–310.
20. Javitt DC, Shelley AM, Silipo G et al. Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. Arch Gen Psychiatry 2000;**57**:1131–1137.

21. Salisbury DF, Shenton ME, Grigge CB et al. Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. Arch Gen Psychiatry 2002;**59**:686–694.
22. Umbricht D, Koller R, Schmid L et al. How specific are deficits in mismatch negativity generation to schizophrenia? Biol Psychiatry 2003;**53**:1120–1131.
23. Baldeweg T, Richardson A, Watkins S et al. Impaired auditory frequency discrimination in dyslexia detected with mismatch evoked potentials. Ann Neurol 1999;**45**:495–503.
24. Ilvonen TM, Kujala T, Tervanieme M et al. The processing of sound duration after left hemisphere stroke: event-related potential and behavioral evidence. Psychophysiology 2001;**38**:622–628.
25. Kujala T, Lepisto T, Nieminen-Von Wendt T et al. Neurophysiological evidence for cortical discrimination impairment of prosody in Asperger syndrome. Neurosci Lett 2005;**383**:260–265.
26. Pekkonen E, Hirvonen J, Jaaskelamen IP et al. Auditory sensory memory and the cholinergic system: implications for Alzheimer's disease. Neuroimge 2001;**14**:376–382.
27. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;**13**:261–271.
28. Annett M. A classification of hand preference by association analysis. Br J Psychiatry 1970;**61**:303–321.
29. Sato Y, Yabe H, Hiruma T et al. The effect of deviant stimulus probability on the human mismatch process. Neuroreport 2000;**11**:3703–3708.
30. Yago E, Escera C, Alho K et al. Cerebral mechanisms underlying orienting of attention towards auditory frequency changes. Neuroreport 2001;**12**:2583–2587.
31. Dittmann BA, Juptner M, Jentzen W et al. Dorsolateral prefrontal cortex activation during automatic auditory duration-mismatch processing in humans: a positron emission tomography study. Neurosci Lett 2001;**308**:119–122.
32. Michie PT, Innes-Brown H, Todd J et al. Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. Biol Psychiatry 2002;**52**: 749–758.
33. Elvira B, Croft RJ, McDonald C et al. Mismatch negativity in schizophrenia: a family study. Schizophr Res 2004;**67**:1–10.
34. Saykin AJ, Gur RC, Gur RE et al. Neuropsychological function in schizophrenia: selective impairment in memory and learning. Arch Gen Psychiatry 1991;**48**:618–624.
35. Gold JM, Harvey PD. Cognitive deficits in schizophrenia. Psychiatr Clin North Am 1993;**16**:295–312.
36. Velligan DI, Mahurin RK, Diamond DL. The functional significance of symptomatology and cognitive function in schizophre-nia. Schizophr Res 1997;**25**:21–31.
37. Umbricht D, Javitt D, Novak G et al. Effects of clozapine on auditory event-related potentials in schizophrenia. Biol Psychiatry 1998;**44**:716–725.
38. Umbricht D, Javitt D, Novak G et al. Effects of risperidone on auditory event-related potentials in schizophrenia. Int J Neuropsychopharmacol 1999;**2**:299–304.
39. Korostenskaja M, Dapsys K, Siurkute A et al. Effects of olanzapine on auditory P300 and mismatch negativity (MMN) in schizophrenia spectrum disorders. Prog Neuropsychopharmacol 2005;**29**:543–548.
40. Naatanen R, Paavilainen P, Alho K et al. Do event-related potentials reveal the mechanism of the auditory sensory memory in the human brain? Neurosci Lett 1989;**98**:217–221.
41. Malhi GS, Lagopoulos J. Making sense of neuroimaging in psychiatry. Acta Psychiatr Scand 2008;**117**:100–117.

https://doi.org/10.1111/j.1601-5215.2008.00337.x Published online by Cambridge University Press