Novelty-elicited mismatch negativity in patients with schizophrenia on admission and discharge

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Objective: Given recent reports of differences between mismatch negativity (MMN) elicited by always novel sounds (novelty-elicited MMN) and that elicited by repeated rare deviants (conventional MMN), we investigated novelty-elicited MMN and P3a in patients with schizophrenia before and after a nonstandardized inpatient treatment. **Design:** Electrophysiological and clinical assessment of patients on admission and discharge from hospital. Assessment of control subjects on 2 sessions. **Setting:** Inpatient treatment in a psychiatric university hospital. **Subjects:** 20 patients with schizophrenia and 21 healthy control subjects of similar age and sex. Selection of patients with first- to third-episode schizophrenia. **Outcome measures:** Early and late component MMN amplitudes and latencies, P3a amplitudes and latencies, Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning (GAF), Extrapyramidal Symptom Scale (EPS), Abnormal Involuntary Movement Scale (AIMS) and chlorpromazine equivalents. **Results:** In patients with schizophrenia, novelty-elicited MMN was unimpaired on admission, and there was a statistically significant reduction of the late MMN component with treatment. Improvements in symptom expression were associated with increased latencies of the early MMN component. **Conclusion:** Results indicate differences in information processing between conventional and novelty-elicited MMN. Some components of the novelty-elicited MMN might be more state dependent than those of the conventional MMN.

Objectif : Compte tenu des rapports récents sur les variations entre la négativité de discordance (MMN) provoquée par des sons toujours nouveaux (MMN provoquée par la nouveauté) par comparaison à la répétition de déviants rares (MMN classique), nous avons examiné la MMN provoquée par la nouveauté et le P3a chez les patients ayant connu un épisode de schizophrénie avant et après un traitement atypique de patients hospitalisés. **Conception** : Évaluation électrophysiologique et clinique de patients à leur admission et à leur sortie de l'hôpital. Évaluation de témoins pour deux séances. **Contexte** : Traitement de patients hospitalisés dans un hôpital universitaire psychiatrique. **Sujets** : 20 patients schizophréniques et 21 témoins

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en bonne santé de même âge et de même sexe. Sélection des patients ayant connu entre un et trois épisodes de schizophrénie. **Mesures des résultats** : Amplitudes et latences des composants hâtifs et tardifs de la MMN, amplitudes et latences de P3a, échelle des syndromes positifs et négatifs (PANSS), évaluation globale de fonctionnement (GAF), échelle des symptômes extrapyramidaux (EPS), échelle de mesure des mouvements involontaires anormaux (AIMS) et équivalents de la chlorpromazine. **Résultats** : Chez les patients atteints de schizophrénie, la MMN provoquée par la nouveauté était intacte à l'admission et il y a eu une diminution statistiquement significative des composants tardifs de la MMN avec traitement. On a associé des améliorations dans l'expression des symptômes à des latences accrues du composant hâtif de la MMN. **Conclusion** : Les résultats indiquent des variations dans le traitement de l'information entre la MMN classique et la MMN provoquée par la nouveauté. Certains composants de la MMN provoquée par la nouveauté pourraient davantage dépendre de l'état que ceux de la MMN classique.

Mismatch negativity (MMN) is an event-related potential derived by subtracting the waveform elicited by a frequent standard stimulus from that following a slightly deviant, rare nontarget stimulus.[1] MMN has been suggested to be a measure of preattentive auditory information processing.[2-5] MMN amplitude increases and latency shortens with the size of the deviation from the standard stimulus. MMN has some of the properties of a short-term echoic memory[6] and can be modulated by the direction of attention.[7-12] Additionally, MMN has been shown to be sensitive to memory processes.[12]

MMN amplitude is reduced in patients with schizophrenia,[13-21] and changes in MMN topography have been reported for subgroups of patients with schizophrenia.[20,22,23] Yet there have been occasional failures to find reduced MMN in first episode[24] or more chronically ill patients.[25,26] In some of the studies reporting impaired MMN in schizophrenia, unimpaired MMN was found in some definite conditions.[13,17,19] MMN peak latency prolongation in patients with schizophrenia was reported by Kathmann et al,[26] and 2 other studies reported significant correlations between MMN amplitude and ratings of negative schizophrenic symptoms.[17,21] Conversely, no correlations between MMN amplitudes and positive and negative symptoms were reported in Shelley et al[13] and Kasai et al.[20]

These studies on MMN in patients with schizophrenia differ with respect to the amount of stimulus deviance, stimulus intensity, interstimulus interval, stimulus duration and frequency. Differences in experimental designs (e.g., dichotic listening tasks and 2- or 3-tone oddball tasks with activation of intermodal or intramodal sensory channels) may contribute to the difficulties in the interpretation of inconsistencies among results. Tones with short durations (e.g., 50 ms) and low frequencies (e.g., 600 Hz) may make the detection of deviant stimuli more difficult, and high sound pressure levels may mask the detection of changes in pitch level. Javitt and colleagues systematically varied stimulus deviance, interstimulus interval and interdeviant interval in control subjects and patients with schizophrenia[19] and concluded that MMN reduction is largest under conditions when MMN is normally largest.

MMN in the context of novelty processing with rare, nonrepeated, nonidentifiable and highly deviant stimuli has attracted attention recently. Schroeder et al[27] found the novelty-elicited MMN sensitive to differences in memory performance in elderly subjects. In a recent magnetoencephalographic (MEG) study, Alho and colleagues[28] found evidence for neuronal generators contributing to the processing of novelty stimuli in the superior temporal plane. In a recent study combining electrophysiological and functional magnetic resonance imaging in the assessment of novelty processing, Opitz et al[29] found that the superior temporal gyrus is involved in the detection of novelty processing elicited through nonidentifiable sounds. Probable influences of additional unspecific and frontal generators are discussed in Escera et al,[30] a study comparing the impact of standard deviance and novelty deviance on reaction times and event-related potentials (ERPs). The authors argue that these might activate 2 different mechanisms of involuntary attention. The same idea was proposed in a recent review on novelty detection by Knight and Nakada[31] in which the authors propose a memory-dependent neocortical-limbic circuit that is activated by novel stimuli.

In patients with schizophrenia, symptom expression would be expected to change in the course of inpatient treatment. Studies by Schall et al[32] and Umbricht et al[33] confirmed a reduced MMN in patients with schizophrenia, as reported above, but reported no evidence for amplitude changes with treatment.

To our knowledge, there are no reports that focus on

the novelty-elicited MMN in patients with schizophrenia. Here, we assess the novelty information processing in control subjects and in young patients with schizophrenia within their first episodes on admission and before discharge from hospital. Our aim was to investigate probable differences in patients with schizophrenia and healthy subjects with respect to auditory novelty processing and the relation of changes in clinical symptoms to changes in novelty-elicited MMN in the course of a nonstandard inpatient treatment. A further feature of our analysis is the separate consideration of the earlier and later peaks in the MMN waveform. These will be termed early and late MMN, respectively, reflecting the hypothesis that they have separate functional correlates.[34,35]

Method

Twenty patients with schizophrenia, diagnosed according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, (DSM-IV) and based on consensus of 2 senior psychiatrists, and 21 healthy control subjects were assessed in a passive oddball task with 2 stimulus categories. From consecutive referrals, we selected those patients with a recent illness onset (1–3 episodes). Patients were measured within 1–5 days of admission to the clinic. At the time of the first assessment, 15 patients received neuroleptic medication, 10 patients received typical neuroleptics (e.g., haloperidol, flupenthixol, chlorprothixen) and 5 atypical neuroleptic medication (e.g., olanzapine, clozapine, risperidone) with a chlorpromazine equivalent (CPZ) of 355 (standard deviation [SD] 165) mg.[36,37] A second assessment was conducted of 15 control subjects and 12 patients with schizophrenia before discharge; the interval between recordings was 2–3 months for patients and controls.

The study was approved by the local ethics committee, and informed consent was obtained from patients before the assessments. Clinical symptoms were assessed by trained raters with the Positive and Negative Syndrome Scale (PANSS[38]), the Brief Psychiatric Rating Scale (BPRS) extracted from the PANSS, the Global Assessment of Functioning Scale (GAF[39]), the Extrapyramidal Symptom Scale (EPS[40]) and the Abnormal Involuntary Movement Scale (AIMS[41]). Mean scores of symptom expressions on admission and discharge are given in Table 1.

Subjects were comfortably seated in an electrically shielded room and read a book while 400 tones were presented in a randomized sequence of standard (86%, 1200 Hz, 65 dB, 50 ms, 10 ms rise–fall time) and deviant (14%, novelty stimuli, 65 dB, 50 ms) tones with an interstimulus interval of 1.1 s. Novel stimuli comprised tones of various frequencies between 300 Hz and 2800 Hz with rising or descending slopes (100 Hz/10 ms). ERPs were recorded from 19 sites (10–20 system electrocap) referenced to linked earlobes and filtered with a band pass filter of 0.3–70 Hz (24 dB/octave). Balanced impedance was kept below 2 kΩ. Data were recorded with a Siemens EEG21 amplifier and digitized for offline analysis on a PC with a sampling rate of 256 Hz. From the horizontal and vertical electro-oculogram sweeps with artifacts greater than 50 μV were eliminated from analysis. Artifact-free trials were averaged for standard (std) and deviant (novel) tones (std controls 272.8 (SD 36.1) trials and std patients 246.5 (SD 64.8) trials [ns]; novel controls 40.8 (SD 5.3) trials and novel patients 36.3 (SD 10.0) trials [ns]). MMN was analyzed for the early and late peak amplitudes and latencies on electrodes F7, F3, Fz, F4, F8, T3, C3, Cz, C4 and T4. The peak for the early component was scored in the latency range of 80–140 ms, and the peak of the late component in the range of 140–300 ms. The novelty-elicited P3a was scored from the deviant stimulus average curve at Fz, Cz and Pz in the latency range of 240–540 ms.

ERPs were compared between groups on the first recording session by means of multivariate analysis of variance (MANOVA). To validate ERP scalp distribu-

Table 1: Clinical symptom ratings for patients with schizophrenia on admission and discharge

	Mean rating (and SD)		
Scale	Admission $n = 20$	Admission $n = 12$	Discharge $n = 12$
PANSS			
Positive	21.1 (6.3)	21.8 (6.5)*	12.0 (3.9)*
Negative	19.9 (6.6)	20.5 (4.5)*	15.7 (5.5)*
General	44.9 (12.7)	45.2 (11.8)*	30.7 (9.1)*
BPRS	49.6 (13.5)	50.8 (13.1)†	33.1 (9.2)†
GAF	37.0 (12.0)	38.2 (11.3)‡	58.6 (14.8)‡
AIMS	7.8 (1.7)	8.0 (2.1)	7.1 (0.5)
EPS	3.3 (4.5)	3.4 (4.9)	3.4 (3.8)

Note: SD = standard deviation, PANSS = Positive and Negative Syndrome Scale, BPRS = Brief Psychiatric Rating Scale, GAF = Global Assessment of Functioning, AIMS = Abnormal Involuntary Movement Scale, EPS = Extrapyramidal Symptom Scale.
*Main effect session ($F = 71.8$, $p < 0.001$), session × scale ($F = 6.8$, $p = 0.005$).
†Main effect session ($F = 28.2$, $p < 0.001$).
‡Main effect session ($F = 19.1$, $p < 0.001$).

tion effects, raw data were adjusted by means of Min-Max transformation[42] and submitted to MANOVA. Changes in ERPs between sessions were assessed by MANOVA. Difference scores of ERPs and clinical data were computed between session 1 and session 2. Correlations between MMN and clinical data were computed. Pearson correlation coefficients were used when both variables showed normal distributions as indicated by the Kolmogorov-Smirnov Test. Otherwise, Spearman's rhos were calculated. To account for multiple comparisons, α level for correlational analyses was adjusted to $p = 0.01$.

Results

The mean age of the 20 patients with schizophrenia (8 women, 12 men) was 25.9 (standard deviation [SD] 9.9) years and of the 21 healthy control subjects (10 women, 11 men) was 26.3 (SD 7.6) years. Patients were in education for 13.2 (SD 5.4) years and control subjects for 16.1 (SD 3.7) years. Number of years in education tended to differ between groups ($F = 3.94$, $p = 0.054$), but groups did not differ with respect to age ($F = 0.02$, $p = 0.86$) or sex ($\chi^2 = 0.24$, $p = 0.62$). The neuroleptic dose for the 12 patients who were assessed a second time was CPZ = 336 (SD 189) mg on admission and CPZ = 346 (SD 173) mg at discharge.

Group differences of MMN peaks on the first session

Peak amplitudes and latencies of the early and late component were compared between control subjects ($n = 21$) and patients ($n = 20$, Fig. 1 and Fig. 2). Electrode (10) × group (2) MANOVAs revealed no differences between groups with regard to the amplitudes and latencies of the early and late components. As expected, the main effect of electrode was highly significant ($p < 0.01$) in all 4 analyses. With Min-Max transformed amplitude data, we found a significant electrode effect in the analysis of the early component ($F = 17.5$, $p < 0.001$) but not the late component ($F = 1.0$, $p = 0.42$).

MMN peak changes between sessions

To assess changes in the novelty-elicited MMN over time, we analysed the early and the late MMN amplitudes and latencies by means of electrode (10) × group (2) × session (2) MANOVAs in patients ($n = 12$) and controls ($n = 15$). As expected, the main effect of electrode was significant ($p < 0.01$) with respect to amplitudes and latencies of the early and late component. The main effect of session was significant for the amplitudes of the early and late components (early $F = 5.18$, $p = 0.03$; late $F = 4.85$, $p = 0.03$). Mean MMN amplitudes were reduced on the second session in both groups. Effects involving the group factor were significant only for the late component amplitude interaction of group × session ($F = 4.59$, $p = 0.04$). Amplitudes were reduced in patients with schizophrenia on the second session. Additionally, a trend emerged for the 3-way interaction (group × electrode × session) for the amplitudes of the late component ($F = 1.82$, $p = 0.06$). Regarding latency, no 3-way interactions were found for the early and late components (Fig. 2B and Fig. 2C).

Subsequent group (2) × session (2) MANOVAs were conducted separately for the 10 electrode sites. Amplitudes of the late component were reduced in patients with schizophrenia on session 2 on the left site and in the midline: F7 ($F = 7.75$, $p = 0.010$), F3 ($F = 9.55$, $p = 0.005$), Fz ($F = 5.90$, $p = 0.023$), T3 ($F = 13.53$, $p = 0.001$), C3 ($F = 8.13$, $p = 0.009$). In control subjects, amplitudes of the late component remained stable (Table 2).

Significant main effects for session were found for the early component at electrode F7 ($F = 17.26$, $p < 0.001$), Fz ($F = 6.22$, $p = -0.020$), T3 ($F = 10.40$, $p = 0.003$) and C3 ($F = 6.27$, $p = 0.019$). Amplitudes decreased between sessions. Main effects of amplitude reduction between sessions were found for the late component: F7 ($F = 7.75$, $p = 0.010$), F3 ($F = 9.55$, $p = 0.005$), Fz ($F = 5.91$, $p = 0.023$), T3 ($F = 13.53$, $p = 0.001$), C3 ($F = 8.13$, $p = 0.009$). Use of chlorpromazine equivalents as a covariate did not alter the results.

In the analysis of Min-Max transformed data for the early component, we found a significant electrode main effect ($F = 8.1$, $p < 0.001$) and an electrode × session interaction ($F = 5.29$, $p < 0.001$). The analysis of Min-Max transformed data for the late component MANOVA revealed a significant electrode main effect ($F = 3.68$, $p < 0.001$) and an electrode × session interaction ($F = 5.29$, $p < 0.02$). No effects were found regarding the group factor.

Treatment effects

A PANSS subscale (positive, negative, general [3]) × session (2) MANOVA indicated significant reductions in all 3 subscales ($F = 71.84$, $p < 0.001$, Table 1) to differ-

ent degrees ($F = 6.75$, $p = 0.005$). A comparison of negative and positive symptom subscales indicated a trend for a more pronounced reduction of positive than negative symptoms ($F = 3.77$, $p = 0.078$). BPRS and GAF symptom scores improved significantly with treatment (BPRS $F = 28.17$, $p < 0.001$; GAF $F = 19.1$, $p < 0.001$). Neither the scores on the EPS and the AIMS nor the chlorpromazine equivalents changed significantly between sessions.

Correlations between symptom expression in patients and ERPs on admission

There were no significant correlations between amplitudes of the early component and clinical symptom expressions in patients with schizophrenia. The amplitude of the late component at F7 was correlated with negative symptoms ($r = -0.55$, $p = 0.01$); the amplitude was elevated in subjects with high negative symptom

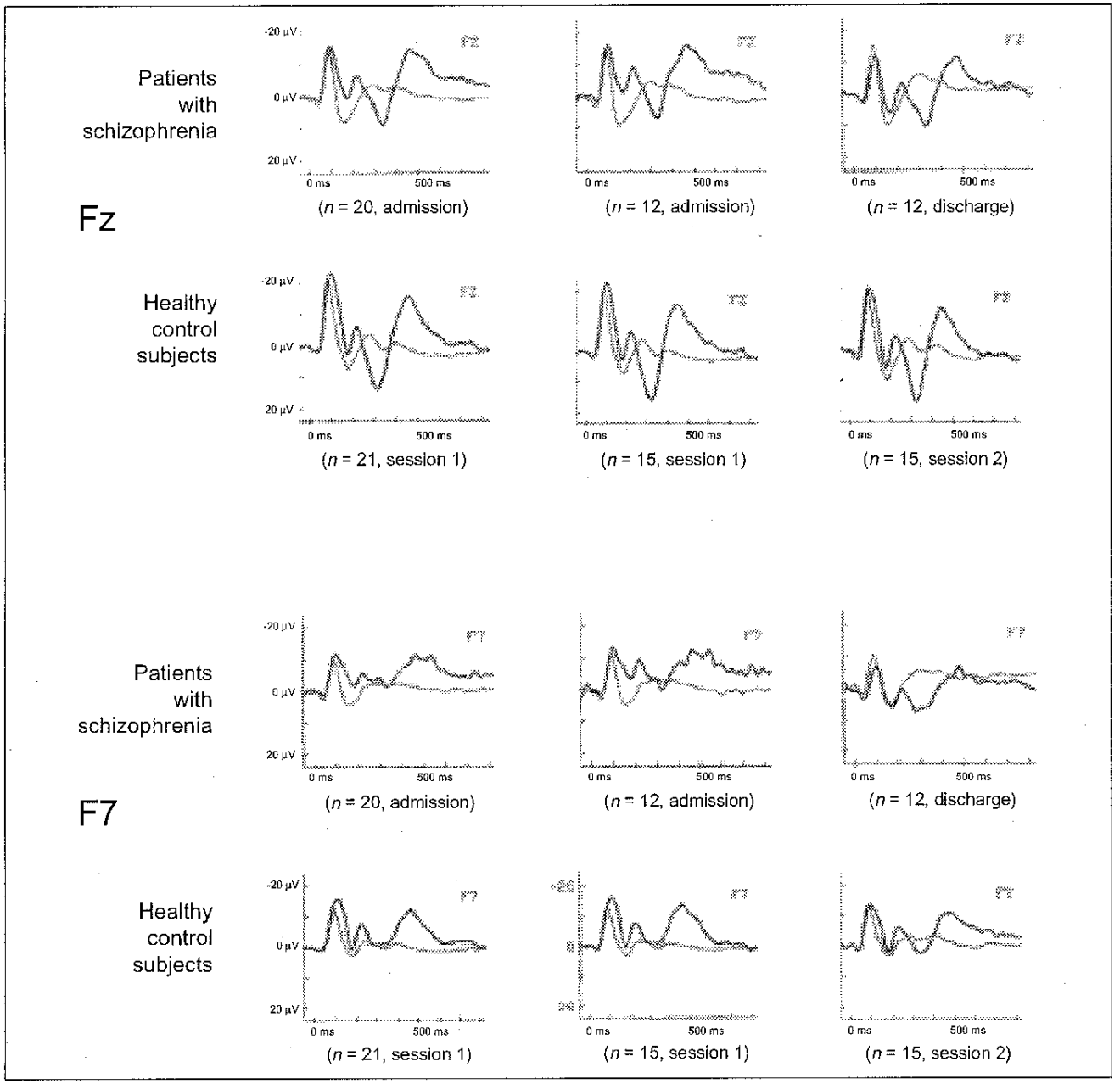

Fig. 1: Event-related potentials (ERPs) to standard (thin line) and novel (bold line) stimuli on Fz and F7 in patients with schizophrenia and healthy control subjects on admission and discharge.

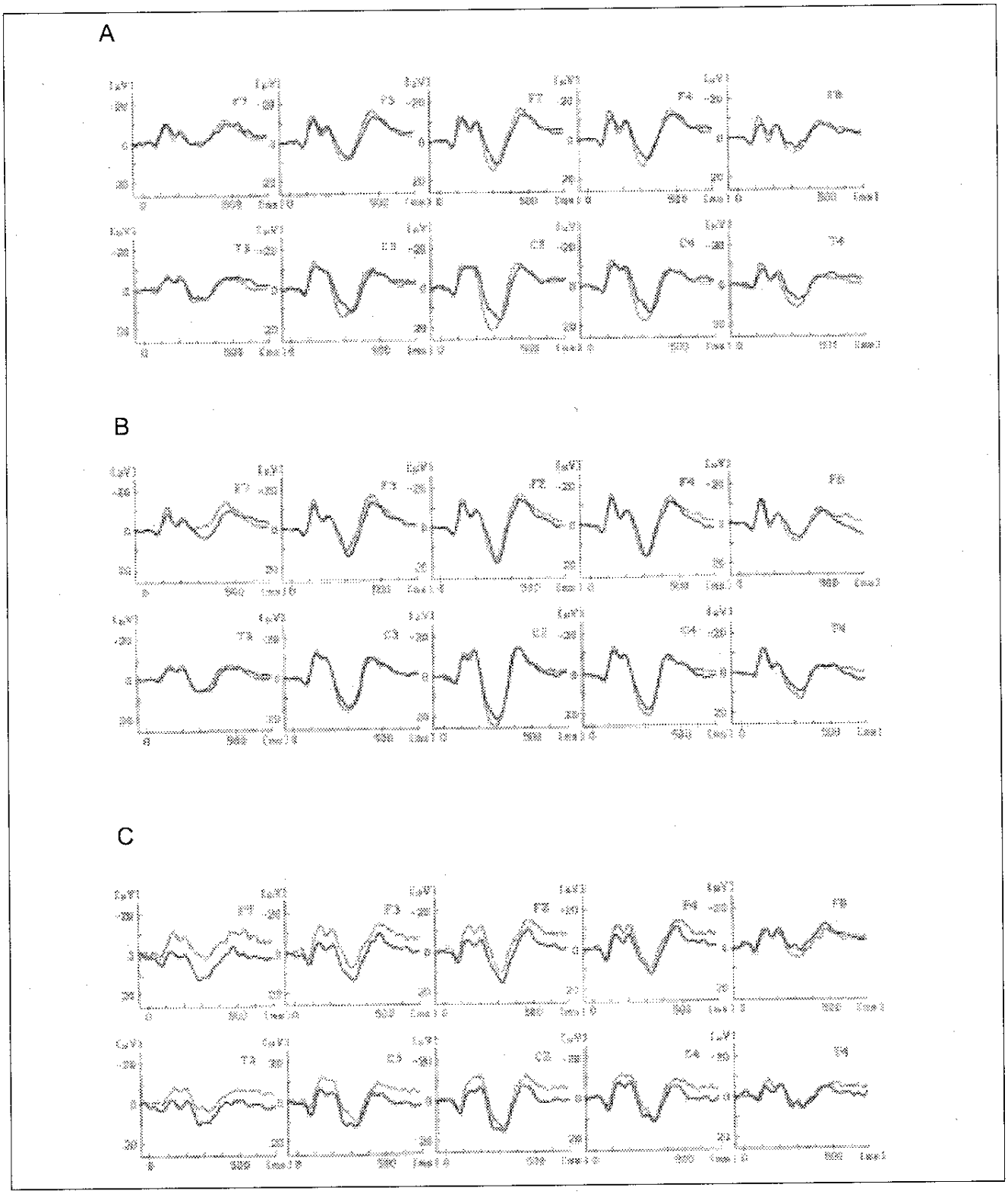

Fig. 2: Novelty-elicited mismatch negativity (MMN) difference waves. A: Comparison of 20 patients (bold line) and 21 controls (thin line) on admission. B: Comparison of 15 control subjects on test (thin line) and retest (bold line). C: Comparison of 12 patients with schizophrenia on admission (thin line) and discharge (bold line).

expressions. Latencies of the late component were negatively correlated with positive symptoms at T3 ($r = -0.65$, $p = 0.002$, Fig. 3A); patients with high expressions of positive symptoms showed shortened late-component latencies.

Correlations between difference scores of clinical symptoms and MMN over time

Positive symptoms correlated negatively with latencies of the early component at Cz ($r = -0.70$, $p = 0.01$) and C4 ($r = -0.72$, $p = 0.008$, Fig. 3B) and PANSS total scores correlated negatively with the latencies of the early component at Cz ($r = -0.65$, $p = 0.01$) and C4 ($r = -0.70$, $p = 0.01$). BPRS scores correlated negatively with latencies of the early component at Cz ($r = -0.67$, $p = 0.01$) and C4 ($r = -0.72$, $p = 0.008$). These data indicate that improvements in clinical symptoms were associated with prolonged latencies of the early component in patients with schizophrenia.

P3a

Group (2) × electrode (3) MANOVAs at session 1 involving 20 patients and 21 control subjects showed a trend for reduced P3a amplitudes in patients with schizophrenia (Fz 12.27 [SD 8.6] μV, Cz 16.04 [SD 12.0] μV, Pz 16.9 [SD 12.8] μV) as compared with healthy controls (Fz 19.27 [SD 14.7] μV, Cz 23.90 [SD 15.7] μV, Pz 24.31 [SD 12.5] μV; $F = 3.73$, $p = 0.06$). In follow-up analyses for electrodes Fz, Cz and Pz, no significant results were obtained. For P3a latency data, we found prolonged P3a latencies in patients with schizophrenia (Fz 336.0 [SD 18.6] ms, Cz 332.2 [SD 25.1] ms, Pz 346.2 [SD 25.7] ms) as compared with controls (Fz 328.7 [SD 27.3] ms, Cz 318.6 [SD 40.2] ms, Pz 322.9 [SD 34.4] ms; $F = 4.3$, $p = 0.05$). This effect was due to significant latency differences at electrode Pz ($F = 5.9$, $p = 0.02$).

The analysis of retest data with group (2) × electrode (3) × session (2) MANOVAs revealed significantly reduced P3a amplitudes in patients over both sessions ($F = 6.02$, $p = 0.02$). This was due mainly to amplitude differences at electrodes Fz (session 1/2 patients 9.8/14.1 [SD 7.7/10.1] μV, controls 20.2/20.1 [SD 15.6/10.9] μV, $F = 4.2$, $p = 0.05$) and Cz (session 1/2 patients 12.6/17.1 [SD 9.3/8.9] μV, controls 26.3/21.8 [SD 17.4/11.4] μV; $F = 4.7$, $p = 0.04$). No significant effects were found for latency data in the analysis of treatment effects or in correlation analyses of P3a amplitude and latency data.

Table 2: Amplitudes and latencies of the early and late mismatch negativity component in control subjects and patients with schizophrenia on admission and discharge at electrodes F7, Fz and Cz

	Group, mean amplitude or latency (and SD)					
MMN amplitude or latency	Controls, session 1 $n = 21$	Patients on admission $n = 20$	Controls, session 1 $n = 15$	Patients on admission $n = 12$	Controls, session 2 $n = 15$	Patients on discharge $n = 12$
Early component amplitude, μV						
F7	12.26 (5.96)	11.93 (7.70)	13.58 (6.06)	12.65 (9.36)	10.30 (7.22)	3.72 (11.03)
Fz	15.24 (8.54)	13.24 (8.02)	15.20 (8.00)	14.88 (9.58)	13.85 (7.30)	7.87 (9.35)
Cz	13.39 (7.40)	11.25 (6.09)	12.99 (7.08)	10.98 (7.29)	11.85 (6.43)	6.90 (6.20)
Early component latency, ms						
F7	128.19 (11.06)	127.60 (18.80)	129.87 (9.78)	127.67 (21.87)	135.73 (12.69)	127.67 (15.67)
Fz	129.90 (9.26)	133.40 (15.21)	130.93 (8.34)	131.67 (17.93)	132.80 (11.63)	132.33 (14.72)
Cz	128.19 (13.41)	128.80 (19.49)	127.73 (14.06)	125.33 (22.13)	129.87 (13.68)	131.67 (15.30)
Late component amplitude, μV						
F7	9.78 (7.07)	8.45 (9.61)	9.32 (6.73)	10.07 (8.34)	10.42 (7.40)	2.17 (11.24)
Fz	13.67 (12.08)	11.14 (13.59)	13.47 (10.61)	15.62 (12.19)	13.19 (11.09)	8.21 (12.35)
Cz	13.97 (10.79)	10.19 (12.17)	13.67 (11.24)	13.19 (11.49)	12.63 (13.64)	6.85 (11.59)
Late component latency, ms						
F7	221.52 (18.91)	223.20 (29.92)	219.73 (16.80)	227.67 (18.49)	232.80 (34.75)	222.00 (27.63)
Fz	224.76 (28.22)	230.00 (27.27)	223.73 (31.62)	225.33 (16.65)	221.07 (25.94)	212.00 (11.94)
Cz	203.05 (31.57)	217.20 (31.8)	200.53 (34.34)	210.00 (21.74)	201.33 (25.28)	207.33 (30.60)

Discussion

MMN on admission

In our study, novelty-elicited MMN was not reduced in patients with schizophrenia on admission. This is in line with results on conventional MMN reported by O'Donnell et al[25] and Kathmann et al,[26] but not with those of many others, among them Shelley et al,[13] Javitt et al[19] and Oades et al,[22] who reported reduced MMN in patients with schizophrenia. These studies used rare, repeated, low deviant stimuli and shorter interstimulus intervals that may be characterized as conventional MMN.[1,43] In contrast, we used rare, nonrepeated, nonidentifiable and highly deviant stimuli with a long interstimulus interval (novelty-elicited MMN).

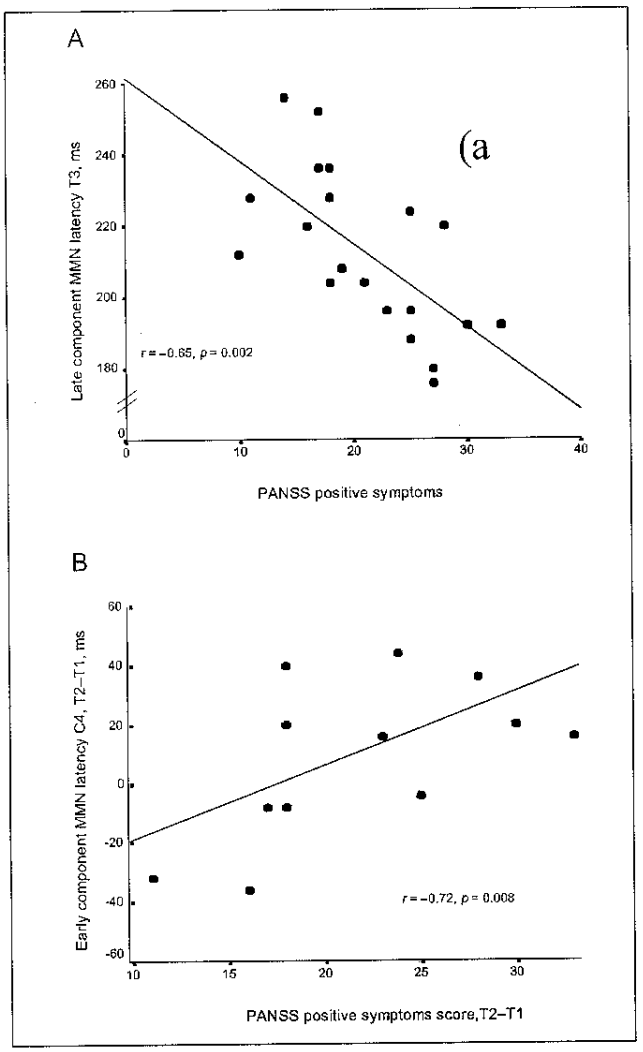

Fig. 3A: Scatterplot of late-component MMN latency at T3 with PANSS positive symptoms.
Fig. 3B: Scatterplot of early-component MMN latency difference score at C4 (session 2 – sesssion 1, T2–T1) with PANSS positive symptom difference score (T2–T1).

These differences in stimulus characteristics and interstimulus interval length raise the question of whether our experimental procedure to induce novelty-elicited MMN can be considered "MMN" as it has been established by Näätänen and colleagues.[1,43] As reported above, some evidence for equivalence of conventional and novelty-elicited MMN primary generators has been reported by Alho et al.[28] Visual inspection of the averages of standard and deviant stimuli show the peak amplitude of the MMN in the descending part of the N1 to the standard tone (Fig. 1). In schizophrenia research, large interstimulus intervals have been used by several authors, for example Javitt et al[16] (1300 ms), O'Donnell et al[25] (1200 ms) and Kreitschman-Andermahr et al[44] (1000 ms). Recently, Shelley and colleagues[45] studied the influence of different interstimulus intervals (between 250 ms and 4 s) on MMN and N1 in patients with schizophrenia; they found that alterations of the interstimulus interval affected the amplitude reduction in patients with schizophrenia with regard to the N1 but not the MMN.

We suggest that the difference wave elicited by novel sounds shares major characteristics with the conventional MMN that are further modulated by novelty-specific generators. This modulation might be comparable to that seen with the influence of attention on the major attention-independent characteristics of the MMN.[7-11] Escera et al[30] and Knight and Nakada[31] proposed that novelty-elicited MMN is modulated by neuronal generators that specifically process novelty-related information. Saigusa et al[46] related novelty-specific processing to the functioning of mesolimbic structures. Our results indicate that this form of novelty-elicited MMN is not impaired in patients with schizophrenia on admission.

MMN in the course of treatment

We found reduced early and late MMN components at retest in both groups. Although patients showed a reduction of MMN with regard to early and late MMN, the interaction effect between group and session was significant only for the late MMN component. This effect was due to a different amount of amplitude change over time in control subjects. It is of interest that the MMN in patients on admission was associated

with a negative shift which emerged with the early component of the MMN and did not return to baseline with the end of the late MMN component. It may be suggested that the cortical processing of the novel stimuli triggered some MMN-dependent processing that did not stop with the end of the late MMN in our young patients with schizophrenia on admission. Regarding the 2 MMN components, Sussman et al[35] reported in a recent study on MMN that the appearance of the early and the late component depended on the length of the stimulus interval, and Baldeweg et al[34] found support for the hypothesis that the functional significance of the early component might be attributed to early feature-detection processes located in the temporal cortex, whereas the late component might depend more on attentional processes probably mediated by frontal lobe function.

In the 2 reports on conventional MMN in the course of treatment in patients with schizophrenia, Schall et al[32] and Umbricht et al[33] found no changes with treatment. The major methodological difference between those studies and ours was their use of a conventional MMN procedure, defined by repeated low deviant stimuli and considerably shorter interstimulus intervals.[1,43] Catts et al[17] proposed that a low conventional MMN amplitude might be a marker of an underlying biological deficit in patients with schizophrenia. In contrast, our results on novelty-elicited MMN indicate that it might be modulated by state-dependent symptoms in schizophrenia. In previous studies, the assessment of patients with a long illness was associated with a reduction of the early MMN component.[17,32] In contrast to these results with conventional MMN, with novelty-elicited MMN we found that elevated amplitudes of the late component were correlated with high negative symptoms on admission.

MMN and N2b

The appearance of the late MMN in the latency range of the traditional N2b component at about 200–220 ms in control subjects suggests that the late component is functionally equivalent to the N2b component, which has been associated with stimulus categorization in the context of behaviorally relevant stimuli.[47–49] It can be argued that more novelty induces an attention switch that involuntarily assigns active resources to the analysis of the novel stimulus. This analysis may then result in the occurrence of the N2-like component. Reduced N2 amplitudes in patients with schizophrenia have been reported by several authors, including Umbricht et al,[33] Potts et al[50] and Kasai et al.[20] Umbricht and colleagues[33] assessed the influence of traditional (haloperidol) and new (clozapine) neuroleptic treatment on MMN, N2 and P3 and found only the P3 to be affected by the treatment. They argued that the N2b component may be more closely related to the MMN than to the following P3 component, a suggestion which has been supported by Kasai et al,[20] who reported evidence for a common underlying mechanism in the generation of the MMN and the N2b component and suggested a strong contribution from the preattentive system (MMN) to the controlled mismatch processing (N2b). According to this view, our (nonsignificant) early MMN reduction at session 2 may have had some impact on the significantly reduced late N2b-like MMN component. However, it remains unclear why we found no reduced early and late MMN components on admission. According to our results, first- to third-episode patients with schizophrenia may generate unimpaired early and late N2b-like MMN components when large deviant novel stimuli are applied.

MMN topography

Results of the numerous studies of MMN topography in schizophrenia[20,22,23,44,51,52] have been incongruous. Our results are comparable to those of Hirayasu et al[52] and Kreitschmann-Andermahr et al.[44] They reported reduced MMN amplitudes, especially over the left hemisphere of patients with schizophrenia. However, with Min-Max transformed data we found no evidence for a relevant topographic shift in patients compared with control subjects. For this reason, the interaction effect of topography, group and session in the raw data analysis must be interpreted with caution. The successful identification of probable laterality effects will have to rely on larger patients samples.

Latency correlations

Correlational analyses indicated that high positive symptom expressions were associated with shortened MMN latencies. Overall clinical improvements measured by PANSS were associated with latency prolongation. Kathmann et al[26] found prolonged MMN latencies in patients with schizophrenia and those dependent upon alcohol. Increased latencies were

interpreted in terms of a slowing of automatic information processing in both patient groups. The sensitivity of the MMN latencies to clinical symptoms in our study are in line with results suggesting difficulties of patients with schizophrenia in separating stimuli. These data emerged from experiments on sensory gating.[53] Difficulties in temporal discrimination of stimuli in patients with schizophrenia have also been associated with a dysfunction in the fronto-thalamo-cerebellar circuit, as proposed by Andreasen et al.[54] Our data suggest that patients with schizophrenia need to take more time with the first analysis and evaluation of auditory stimuli. An overly rapid stimulus evaluation may be associated with errors in stimulus processing and with errors in the integration of processing results into existing neuronal networks.

P3a results

In previous studies with patients with schizophrenia, the processing of auditory novel nontarget sounds has been assessed with respect to the P3a component. Our results are consistent with those of Grillon et al,[55] who found reduced P3a and P3b components in patients with schizophrenia and those of Mathalon et al,[56] who reported a reduction of the P3a amplitude in patients that was similar to that of the P3b and an association between P3a and symptoms of anxiety and depression. Amplitude reductions of the frontal P3a-like component have been associated with deficits in orienting to auditory stimuli, with dysfunction of the anterior cingulate[57,58] and with prefrontal and medial temporal lobe lesions.[31] Our result of prolonged P3a latencies in patients at session 1 are in line with recent reports on P3a latency prolongation.[57,59–61] Mathalon et al[57] reported evidence for an increased age-dependent latency prolongation of the P3 in patients with schizophrenia compared with that of healthy control subjects. In our study, we assessed first- to third-episode patients, which limits the amount of variance in our sample. Because of this factor and our limited sample size, we are not able to report significant correlations between P3 prolongation and illness duration.

Limitations

The interpretation of our results is limited by the 2-stimulus condition design; we therefore cannot compare conventional and novelty-elicited MMN directly. Our data indicate that there might be differences in the processing of novelty-elicited and conventional MMN in patients with schizophrenia and that both might be related differentially to clinical symptom expression. However, this study was intended as a pilot study to assess whether there might be abnormalities in the processing of the novelty-elicited stimuli. Only a study comparing the interaction of conventional- and novelty-elicited MMN in passive and active conditions can give direct evidence of the difference between conventional- and novelty-elicited MMN in subjects with schizophrenia and clarify the relation between the novelty-elicited MMN and the N2b.

Another limitation of this study is the small number of subjects in the retest part of our study which limits the power of detecting relevant deviances in ERPs and their associations with clinical data. Concerning the stability of novelty-elicited MMN, we recently conducted a method-oriented comparison of the novelty-elicited MMN and the conventional MMN in healthy subjects in a test–retest design. In this study, amplitudes in the novelty-elicited MMN condition were higher than those in the conventional MMN condition. Additionally, retest coefficients were highest for the novelty-elicited MMN as compared with the MMN difference waves elicited by conventional duration decrement and frequency deviance.[62] In this study, we averaged about 50 trials per condition and found retest coefficients of about $r = 0.8$ in the novelty condition. Thus, we have shown that the novelty-elicited MMN can be assessed reliably with a similar number of trials as reported here.

Conclusion

Our data provide indirect evidence for the suggestion that novelty-elicited MMN and conventional MMN measure different aspects of early auditory information processing. In contrast to previous results on conventional MMN, we found novelty-elicited MMN to be associated with state-dependent clinical symptom expressions in patients with schizophrenia. However, because of the small sample our results have to be considered preliminary. To our knowledge, this is the first report on novelty-elicited MMN in patients with schizophrenia; our data suggest that it may be useful to compare the differential effects of standard and novelty-elicited MMN in patients with schizophrenia in the course of treatment.

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