Impaired Attention-Dependent Augmentation of MMN in Nonparanoid vs Paranoid Schizophrenic Patients: A Comparison with Obsessive-Compulsive Disorder and Healthy Subjects

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Mismatch negativity (MMN), in the deviant-minus-standard event-related potential (ERP) difference-waveform, may represent a working memory trace of the tone difference. Most but not all studies find MMN reduced in schizophrenic patients. This report investigates if differences may be attributable to experimental condition (diffuse vs focused attention), component identification (N1-like vs N2-like), topographic distribution, and clinical condition (with/without paranoid-hallucinatory symptoms, PH/NP). Comparisons were made for 12 PH, 12 NP schizophrenic patients with 13 obsessive compulsive and 25 normal control subjects. Frontal MMN reduction in schizophrenics largely resulted from an absence of an increase in focused attention conditions as in comparison groups. But there was a marked temporal activity locus in NP patients. These features were not reflected in other components except for a visible but nonsignificant N1-like temporal locus in NP patients. Further, schizophrenic patients did not show an increase in late positivity with focused attention like the comparison groups. The results show that so-called automatic processing deficits (amount and locus of MMN) are best seen in situations requiring the activation of controlled attentional processes. It is suggested that impaired processing of irrelevant stimuli and reduced frontal MMN in NP patients may reflect reduced dopaminergic responsivity. © 1997 Society of Biological Psychiatry

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Introduction

Mismatch negativity (MMN) can be seen after subtracting the event-related potential (ERP) obtained after a common

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(standard) stimulus from that elicited by a deviant stimulus. It is a negative-going waveform with a peak latency between 100 and 250 ms depending on stimulus modality and the parameters of presentation. MMN has been studied mostly in the auditory modality and is regarded to represent a perceptual trace (Näätänen 1990) or working memory (Cowan et al 1993) for the difference between the two types of stimuli. It may usually arise as a result of

involuntary automatic processing of information, but the direction of focused attention can affect its size (Paavilainen et al 1993; Oades and Dittmann-Balcar 1995).

Schizophrenia has long been recognized as an illness that includes impairments of controlled (voluntary) attentional processing (Callaway and Naghdi 1981; Straube and Oades 1992). More recently consensus has emerged that the automatic processing of information can also be impaired (Hemsley 1994). Nonparanoid psychotic patients may experience difficulty in carrying out automatic processing (e.g., covert orienting of attention, Carter et al 1994), while paranoid schizophrenics may have problems in monitoring automatic processing and hence controlling it (Frith 1992; Strauss 1993). The question therefore arises whether schizophrenics show illness-specific MMN impairments and if so, are these impairments associated with a particular type of psychotic process or group of symptoms?

MMN as a function of tone-pitch and presentation rate was first reported to be attenuated in male schizophrenics (mixed subtype and illness duration) with respect to age- and gender-matched healthy subjects by an Australian group (Shelley et al 1991). This group replicated this finding with auditory stimuli varying in duration and with unmedicated patients (Catts et al 1992, 1995). They showed that even though the controls' MMN varied with stimulus duration, MMN amplitude was approximately halved in patients (respectively -4.5 uv and -2.5 uv). Oades et al (1992b, 1993) reported a severe MMN reduction in young acutely ill psychotic patients diagnosed with paranoid or other nonparanoid forms of schizophrenia where the stimuli varied in pitch and presentation frequency. Javitt et al (1993) also confirmed an attenuation of MMN in a mixed group of chronic schizophrenics of a similar age to those studied by the Australian group with stimuli varying in pitch.

Intriguingly, Oades (1995) represented his analysis in terms of patients with and without active paranoid-hallucinatory symptoms (PH from SANS and SAPS ratings, Andreasen 1983, 1984). While *frontal* MMN in normal healthy subjects averaged about 4.5 μV, PH patients showed a significant reduction to about 2.2 μV and nonparanoid patients (NP) showed virtually no frontal MMN. In contrast, the raw data showed NP patients with posterior *temporal* peaks.

These data imply that there was both a trait (schizophrenia) and a state (active symptoms) contribution to MMN reduction. The aspect of trait-dependency has since been emphasized by Javitt et al (1995a) who reported similarly attenuated MMN from remitted and hospitalized subchronic patients; however this group has recently suggested that lower MMN amplitude correlates with less

severe negative symptoms (Umbricht et al 1995). This implies a state-dependency albeit apparently opposite to that of Oades (1995). Further, problems of generalization and interpretation also arise since two groups have reported not being able to detect reduced MMN in schizophrenia (O'Donnell et al 1994; Kathmann et al 1995).

Catts et al (1992) obtained their results while subjects were distracted from actively attending to the tones by the simultaneous performance of a visual reaction time task, rather like Kathmann et al (1995) O'Donnell et al (1994) found no significant attenuation in chronic schizophrenics who were distracted by reading at the time of being presented with tones varying in pitch, rather like Javitt et al (1993). Thus the reported differences are not easily explained by methods (stimulus feature varied, accessory activity) or the age of the patients.

It seemed however, that this apparent paradox might be resolved by comparing MMN derived in a passive presentation (diffuse attention) with that derived from the same two types of tone irrelevant to the active discrimination of a third tone (compare accessory task above). Further we analyse such data in a) an extended patient group, and with b) raw and vector normalized data in order to emphasize symptom-group specificity of the purported amplitude impairment between psychiatric groups and the topographic differences within the schizophrenic group.

Between-group specificity was achieved by studying a group of patients with obsessive-compulsive disorder (OCD). As argued elsewhere (Oades et al 1994) this group is of interest for etiological reasons (the reported incidence of an obsessive phase in the ontogeny of psychosis), putative anatomical and biochemical functional impairment (orbito- vs dorsolateral frontal cortex, serotonin vs dopamine), and anomalous attentional function. The within-group specificity was examined by normalizing topographically recorded data with a vector taking account of the potentials recorded at all sites. The intention here was to see if the distinction previously drawn from raw data could be an artifact (see Methods below).

As a subsidiary goal other positive and negative deflections found in the difference waveform are described to explore their potential for either mirroring the schizophrenic impairment or, under different conditions, possibly expanding differentially to obscure the MMN impairment. (For example, one could posit that an enlarged positive component with a P2-like latency could overlap and obscure preceding or succeeding negative components). It should here be noted that there are reports in difference-waves of N1-like (early Nd, Woods et al 1993), P2-like and P3-like components (Yamaguchi et al 1995) and of their scalp topography (Oades et al 1995). Indeed O'Donnell et al (1994) did report on a "P2b" component in passive and active MMN measures, reminiscent of the

Table 1. Characteristics of Subject Groups (Means and Range for Data) and Discrimination Performance in the Active ERP Session

	Gender m/f	Age (y) range	BPRS/Q	CPZ equiv.	Biperidene	IQ (SPM)	Educ (y)	Hit/false alarm (%) SD	RT ms
PH	8/4	18.5	3.5	705	3.7	90	11.4	51[a]/6.4	603
		14–24	2.9–4.5	56–1630	2–4	75–120	8–16	17/9	116
NP	6/6	18.9	2.8	1246	6.4	91	10.0	64[a]/7.0	613
		14–24	1.8–4.1 YBOCS	217–3000	4–8	77–104	7–13	24/7	108
OCD	9/4	16.3	23.4	—	—	115	9.8	77/1.8	612
		11–19	14–40 (n = 8) MMPI 2–7–8			75–144	5–13	20/2	110
CON	14/10	18.5	49.1	—	—	116	12.0	88/1.6	545
		11–24	40–68 (n = 14)			95–144	6–16	12/1	95

PH = paranoid (1 neuroleptic- and 5 biperidene-free); NP = nonparanoid (2 neuroleptic- and 7 biperidene-free); CPZ = chlorpromazine equivalents (NP received nonsignificantly more medication; Rey et al 1989); OCD = obsessive-compulsive disorder (all medication-free); CON = healthy controls, BPRS (brief psychiatric scale of 7, score per question (18)); YBOCS (Yale-Brown scale for assessment of obsessive compulsive symptoms); MMPI (Minnesota multiphasic personality inventory, schizotypal scales 2–7–8 (40–60 = normal, subjects > 16 yr)); IQ from Raven's standard progressive matrices, educ (years of schooling and study); RT (reaction time to auditory target stimulus).

[a] Both schizophrenic groups were less accurate than OCD and CON groups (both measures; F(6,130) = 7, p < 0.0001) but there were no reaction time differences.

paradigm described here, that was specifically attenuated in the active measure in schizophrenic patients. Further Javitt et al (1995b) confirmed their findings of a reduced MMN in schizophrenics, but analyzed data for the *earlier* of two negative going components in the difference waveform which showed positive deflections before, between, and after the potential MMN components. Hence the analysis in the current report was briefly expanded to these other deflections.

In summary we expected to confirm MMN amplitude reduction in schizophrenics and predicted that it would not increase as in controls in the focused attention condition; in addition it was expected that the topographic analysis would confirm decreased frontal MMN (N2-like) activity seen in the raw data of nonparanoid schizophrenics and that this would be reflected in the earlier N1-like component (coinciding with the reported start of MMN) as well as in the subsequent P3-like late positivity.

Methods

Subjects

From 31 newly admitted patients diagnosed with a schizophreniform psychosis (DSM-IIIR and ICD-9) 24 provided ERP data. Diagnosis by a clinical psychiatrist was confirmed by a clinician and three psychologists (after rating a semistructured clinical interview; Spearman rho 0.64– 0.75 for 64 questions, Andreasen 1983, 1984). (Patients were excluded on diagnostic grounds (two) or if they did not discriminate between the tones (two) and provide

artifact free data (three).) Schizophrenic patients (SCH) were divided into paranoid hallucinatory (PH) and nonparanoid (NP) groups according to a median split on the SAPS scale (Andreasen 1984).

At the same time 13 medication-naive OCD patients were rated on the Yale-Brown Obsessive-Compulsive scale and tested. From a pool of 40, 25 young healthy case-controls were matched pair-wise to the psychotic patients for gender and age within 6 months. (One extra was added for a young OCD patient.) They reported themselves free of past or present psychiatric illness, organic disorder, or substance abuse (urine samples were taken) and medication, except contraceptive substances. This design along with our reports on ERP development from 8–22 yr (Oades et al 1996b) preclude explanations of differences in terms of age (Table 1, demography). Testing followed approval of the protocol by the clinic management, agreement of the therapists and nursing staff to the tests in principle and the time-point in each case, and the cooperation, understanding, and consent of the patient and the legally responsible adult.

Recording Procedure

A three-tone oddball was presented in successive passive and active discrimination sessions (diffuse vs focused attention: details in Oades et al 1995). Tones, from an exact gate-function-generator were played over DT48 (Beyer Dynamics) earphones. A hundred tones per trial-block were presented in a Bernoulli sequence with the proviso that a deviant tone should not follow a deviant

tone (0.8, 1.4, and 2.0 KHz tones, $p = 70\%$, 15%, and 15% respectively, at 65 dBspl with 50 ms duration, rise/fall time = 10 ms, SOA = 1.2–1.7 sec). Prior to recording, normal hearing thresholds up to 7 KHz were ascertained for all subjects with an Audio-Med audiometer BCA3: where any left/right hearing thresholds varied by 5dB or more, levels were adjusted accordingly.

Subjects, comfortably seated in a Faraday-room were asked to fixate on a small cross on the wall to help reduce eye movement during recordings. They were told that first there would be a baseline recording with nothing to do (passive session). Afterwards they were asked to discriminate between the tones by raising a finger from a metal contact as fast but as correctly as possible after the 1.4 KHz tone. This was practiced before recording in the active session. The accuracy of schizophrenic patients was worse than the OCD or control subjects, but reaction times did not differ significantly (Table 1).

Recordings were made from 19 sites (10:20, Electrocap) using linked ear reference with a balanced impedance of < 2 KOhm at all sites. Fpz and Oz were used as separate ground electrodes as required for data collection on the Siemens EEG 21 and Compaq 386 pc (sampled at 250 Hz for 1024 ms including 50 ms pretrigger time). Amplification by 12 K used a band pass 0.3 to 70 Hz (6dB/octave). Electrooculographic (EOG) artifact (> 65 μV) recorded above the eye was eliminated. Data were evaluated offline with gross electromyographic (EMG) interference reduced by the low pass filters and, when necessary, a digital low-pass, rectangular filter. The sampling rate and the normalization of latency data reduced problems of aliassing and hardware induced delays in the topographic analysis of latencies (Pivik et al 1993). The mean proportion of trials (SD) removed for artifact was CON 22% (10), OCD 35% (19), PH 38% (21), NP 29% (14). Only artifact- and error-free trials were evaluated; accepted common/rare tones per group averaged CON 205/67, OCD 199/67, PH 256/57, NP 210/57.

ERP Measures and Statistical Methods

ERPs were evaluated at F7, F3, Fz, F4, F8; C3, Cz, C4; P3, Pz, P4; T3, T4, T5, and T6. From these data and data from two Fp and two O sites on a 5×5 grid along the axes of the 10:20 system, topographic maps were made using a horizontal and vertical linear interpolation algorhythm to establish a matrix of 180×180 points.

Difference-waves were derived from ERPs after the deviant (2 KHz) minus the standard tones (0.8 KHz). Peaks were identified relative to the first large negative peak (N1-like, occurring 80–140 ms poststimulus) and the start of the earliest but largest positive P3-like deflection

(window 240–540 ms). A P1-like component (30–100 ms) was the largest positive-going dip before the first large negative peak, with a P2-like positive deflection (120–240 ms) following this negativity and preceding the window for the P3-like component. MMN (N2-like) was the largest negative peak: it occurred between the P2- and P3-like peaks (140–300 ms).

Data Analysis

A three-way multivariate analysis of variance (MANOVA) was performed with the four groups (PH, NP, OCD, and CON) as between subjects factor and the two conditions (passive and active, repeated measures) along with the recording sites (not Fp and O sites) as within subjects factors (repeated measures). Raw (Fz, Cz, Pz) and vector normalized data (15 sites) were analyzed for quantitative and topographic analysis, respectively. The vector was the mean of each component measure at each site, divided by the square root of the sum of the squared mean measures for the 15 recording sites (Naumann et al 1992). Significant results are reported after Hotelling's T^2 test as an assessment of potential between-measure differences (Faux and McCarley 1990) *and* SPSSX "averaged" tests for 15 sites after correction with the appropriate Greenhouse-Geisser e-factor. A significant T^2 result preceded further analysis (in terms of SPSS-averaged tests and progress from two- to three-way analyses). As the focus of the report is on the size and topography of group specific changes with attention condition the analysis concentrates on the three-way interaction (Table 2); however, changes of size and topography with condition, independent of group (two-way interaction, SPSSX-averaged tests) are also reported in the text.

To determine the locus of the effect of each condition a significant group-by-condition-by-site interaction was followed by a one-way analysis of variance (ANOVA) and a post-hoc Scheffe test at Fz/Cz *between groups*. (The ANOVA is cited and use of the term *Scheffe* denotes an alpha significance level of 5% was exceeded.) To find where the topographic effect lay paired Student t tests were performed *within each group* between the conditions at the three midline and six most lateral sites. The Bonferroni procedure then cautions adjustment of alpha to 0.14%.

Results

Figure 1 shows a major negative component in the passive difference waveform (MMNp) with an N2-like latency (mean 204 ms SD 39 (CON) to 253 ms SD 47 (PH) at Fz) followed by a major late positive deflection with a P3-like

Table 2. Summary of MANOVA for Subject-Group × Condition (Diffuse/Focused Attention) × Site Interactions for Five ERP Peak Amplitudes (and MMN and P3-like Peak Latencies) in the Deviant-Minus-Standard Waveform

Peak	Data	Hotellings T² Test df	F	p	Site-Averaged Tests df	F	p	Epsilon	Sig
P1	Raw	42,131	2.3	0.000	42,812	1.6	0.013	0.405	a
	Norm	42,131	2.2	0.000	42,812	1.9	0.000	0.409	c
N1	Raw	"	1.4	0.069	"	1.4	0.042	0.501	a
	Norm	"	1.2	0.203	"	1.1	0.355	0.466	NS
P2	Raw	"	1.2	0.257	"	1.8	0.001	0.448	b,d
	Norm	"	0.9	0.586	"	1.5	0.019	0.451	a,d
MMN	Raw	"	1.9	0.003	"	2.3	0.000	0.483	c
	Norm	"	2.1	0.001	"	1.7	0.007	0.450	b
Raw	Latency	"	1.1	0.285	"	1.1	0.270	0.532	NS
Norm		"	1.0	0.465	"	1.1	0.332	0.542	NS
P3	Raw	"	1.8	0.006	"	2.9	0.000	0.459	c
	Norm	"	1.1	0.370	"	1.2	0.222	0.430	NS
Raw	Latency	"	1.3	0.133	"	1.6	0.008	0.534	a
Norm		"	1.4	0.095	"	1.5	0.022	0.552	a

Norm = vector normalized data; df = degrees of freedom; p = statistical probability of test; sig = overall significance after correction with Greenhouse-Geisser epsilon factor ([a] $p < 0.1$, [b] $p < 0.05$, [c] $p < 0.01$, [d] = Hotellings/averaged test conflict over decimal place for significance, NS = not significant).

latency (mean 331 ms SD 71 (OCD) to 369 ms SD 72 (PH) at Pz). These two components are the focus of this study. This analysis extends our reports of decreased frontocentral MMN and reduced late positivity in the two schizophrenic groups (Oades et al 1993, 1996a). Here we concentrate on the changes recorded between passive and active conditions (MMNp and MMNa) and then their topography.

N2- & P3-like Difference-Wave Components

For the N2-like MMN component, condition × site interactions for raw and normalized data showed a general trend for an increase of negativity with increased focused attention across groups (F(14,812) = 2.8/2.6, e = .483/.450, corrected $p < .01/.05$) which was confirmed for Cz posthoc ($t = -2.11$, $p = .039$). Significant group × site ANOVAs on raw and normalized data further allow an inspection of the role of group in group × condition × site interactions (F(14,131) = 2.04/2.12, $p < .003$, Hotellings T²).

Significant three-way interactions for raw data (Table 2) were attributable to increases in the focused attention condition in the controls at Fz and Cz ($t = -2.68--2.98$, $p = .013-.007$). In the patient groups nonsignificant increases and decreases were registered at midline sites. Thus in the active (but not the passive) condition a much larger MMN amplitude was recorded in the controls at Fz vs the NP group (4.62 vs 1.76 μV) and at Cz vs the PH group (4.84 vs 0.55 μV; F(3,61) = 4.22/5.82, $p = .009-.002$ Scheffe).

The significant three-way interaction with normalized data (Table 2) reflected a) the decrease over frontal areas

in the NP group from passive to active conditions (where other patients increased and controls showed no change, Figure 2) and b) the increase at temporal sites in the NP and OCD groups from passive to active conditions ($t = -2.92$, $p = .013$) where controls showed no change and PH patients a decrease ($t = +2.17$, $p = .05$). Thus frontal MMN in NP patients was between half and a quarter of that in other subjects (e.g., F8, F(3,61) = 4.59, $p = .006$, Scheffe) while temporal MMN amplitude in NP patients was three times that in PH or OCD subjects (e.g., T6, F(3,61) = 8.14, $p = .0001$, Scheffe; Figure 2). There were no significant effects for latency measures.

An increase of late P3-like positivity in the difference waveform with increased focused attention was shown by the condition × site interaction for raw and normalized data (F(14,812) = 41/31, e = .459/.430, corrected $p < .001$). The group × site ANOVAs for normalized and raw data both attained a trend level of significance, implying that in group × condition × site interactions the within group effect of condition would predominate (F(42,131) = 1.44/1.46, $p < .06$, Hotellings T²).

The three-way interaction for the raw data (Table 2) showed that the increase was significant at Pz only in the OCD and CON groups ($t = +3.13-4.28$, $p = .009-.0001$); however, in healthy subjects the increase was also detectable at Cz ($t = +2.65$, $p = .014$) and Fz ($t = +1.90$, $p = .07$). The low amplitude in psychotic groups vs high amplitude in comparison groups was confirmed for the OCD vs PH groups (F(3,61) = 3.77, $p = .015$, Scheffe, Figure 3).

For the normalized topographic data a significant three-way interaction did not follow the marked condition by
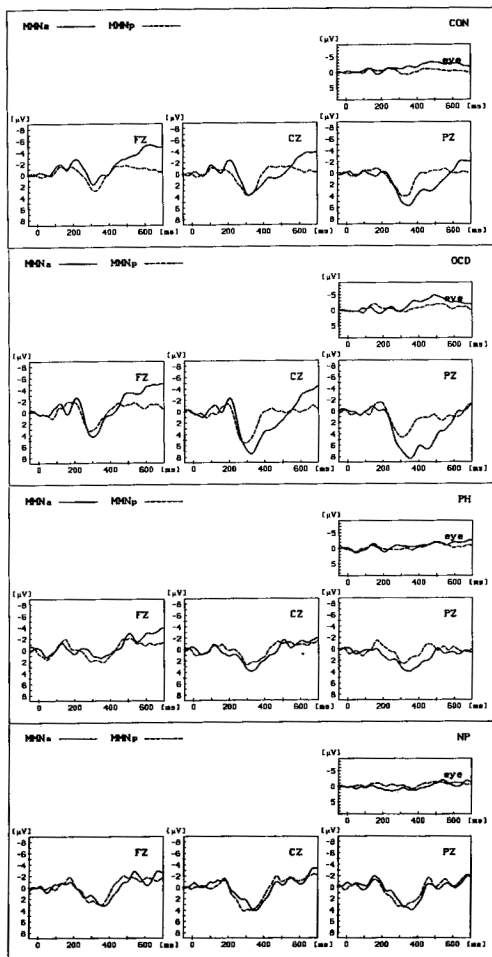
Figure 1. Grand mean 'deviant-minus-standard' difference-waveforms (μV) for four subject groups in four descending panels, respectively, for healthy controls (CON, upper), patients with obsessive-compulsive disorder (OCD), paranoid-hallucinatory psychosis (PH) and non-paranoid psychosis (NP, lower). Records from anterior to posterior sites (Fz Cz, Pz) extend for 700 ms after tone-presentation in the passive (MMNp) and active discrimination condition (MMNa): insets show EOG representations of eye movements.
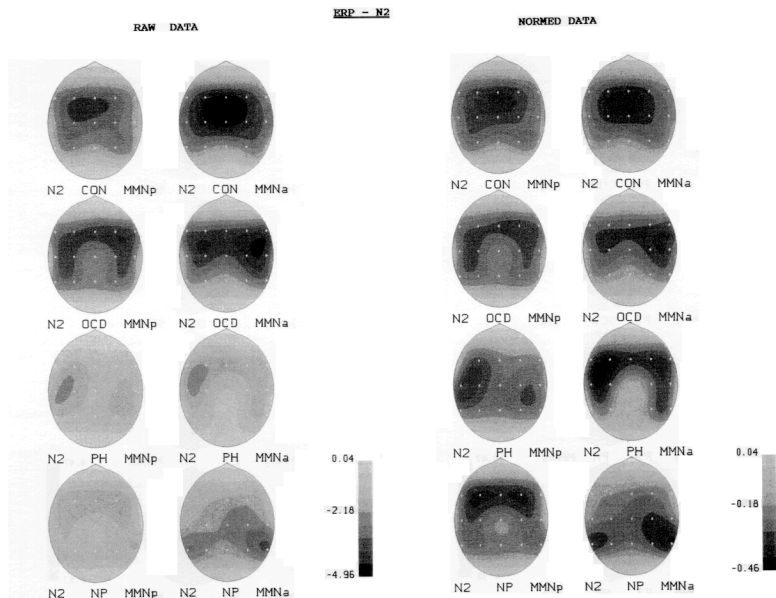
Figure 2. Topographic scalp distribution (nose points up the page) of the amplitude of the N2-like component of the difference-wave (mismatch negativity). Raw data are shown on the *left side* for four subject groups (see Figure 1 legend) in the passive (MMNp) and active conditions (MMNa: scale bar 0–5 μV). Note the reduced values, especially at frontal sites in schizophrenic patients (PH, NP). Vector-normalized data are shown on the *right side* (scale bar adjusted to the range of raw data values). Note the lateralization in patients and temporal peaks in NP patients in the active condition (MMNa).

site interaction (F(14,812) = 31.3, e = .430, corrected $p <$ .01). Posthoc t test comparisons indicated a decreased contribution from lateral frontal and temporal sites with focused attention across groups (F7, F8, T3, T4; $t = -1.64--6.19$, $p = .1-.0001$). The lack of group topographic differences in the normalized data is illustrated in Figure 3.

Across groups there was a significant increase of latency with the onset of focused attention (condition × site, raw data, F(14,812) = 5.6, e = .534, corrected $p <$ .01); however, the group × site interaction was marginal (F(42,131) = 1.6, $p = .03$, Hotellings T^2) and the larger increase in patient groups only attained trend significance in the three-way interaction (Table 2, compare Figure 1).

Precursor-like Components in the Difference-Waveform

Figure 1 shows a negative component in passive and active difference waveforms (MMNp and MMNa) smaller than the succeeding N2-like MMN component and with an earlier N1-like latency (mean 126 ms SD 40 (OCD) to 130 ms SD 30 (PH) at Fz in the passive condition). It was preceded by a P1-like deflection (mean latency 61 ms SD 24 (CON) to 73 ms SD 27 (OCD) at Cz) and succeeded by a small positive deflection with a P2-like latency (mean 150 ms SD 43 (CON) to 196 ms SD 56 (PH) at Cz). There were no significant group or condition effects for these latency measures.
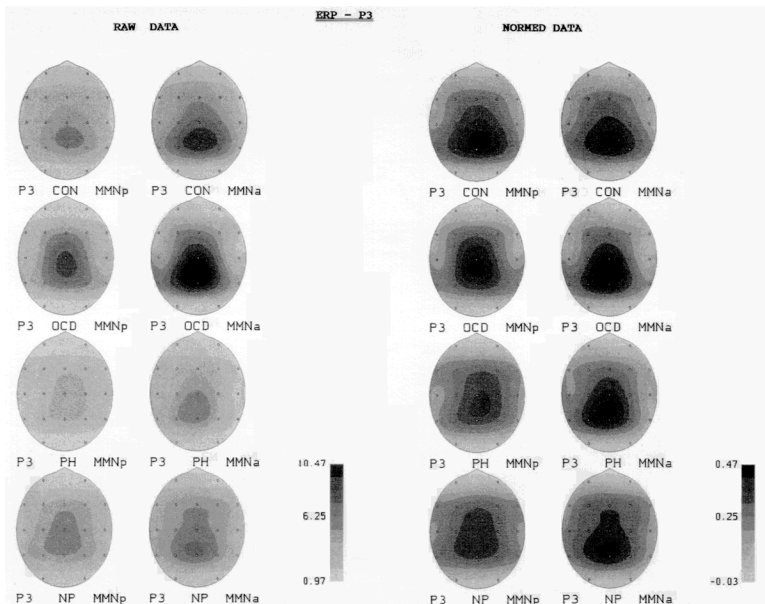
Figure 3. Topographic distribution of the amplitude of the P3-like component of the difference-wave. Raw data are shown (*left*) for four subject groups (see Figure 1 legend) in passive (MMNp) and active conditions (MMNa). Note the increased values in the active condition (MMNa all groups) and the low values in schizophrenic patients (PH, NP). Vector-normalized data are shown on the *right*. Note the similar centroparietal distribution of activity between groups.

For the P1-like component significant condition × site interactions for both raw and normalized data (F(14,812) = 6.6/6.0, e = .212/.405, corrected $p < .01$) showed that, independent of subject group, there was generally a trend for an increase at lateral frontal and for a decrease at posterolateral temporal sites in the active condition ($t = \pm 2.41$, $p = .019$).

The three-way interactions for normalized data (Table 2) confirmed the bilateral temporal decrease in both schizophrenic groups ($t = -3.4$, $p < .006$), and particularly in the NP with respect to comparison groups (F(3,61) = 7.3/8.1, $p = .0003–.0001$, Scheffe for PH and NP at T5, NP at T6). This should be viewed in the context that P1 peaks had frontocentral maxima in the psychotic and centroparietal loci in the comparison groups (Figure 4).

Further, the absence of a conventionally significant overall group by site effect (Hotellings T^2 circa 1%) serves to emphasize the role of condition in producing a differential three-way interaction.

For the N1-like component significant condition × site interactions for both raw and normalized data (F(14,812) = 3.6/3.2, e = .466/.501, corrected $p < .01$) implied a possible increase in (frontocentral) negativity across groups in the active condition, but this could not be confirmed posthoc. There were no significant group interactions (e.g., Table 2). Topographic maps (Figure 5) show all groups with a more or less frontal distribution and the NP group with an additional minor left temporal peak.

The condition × site interaction for the P2-like component was significant for raw data (F(14,812) = 2.3, $p <$
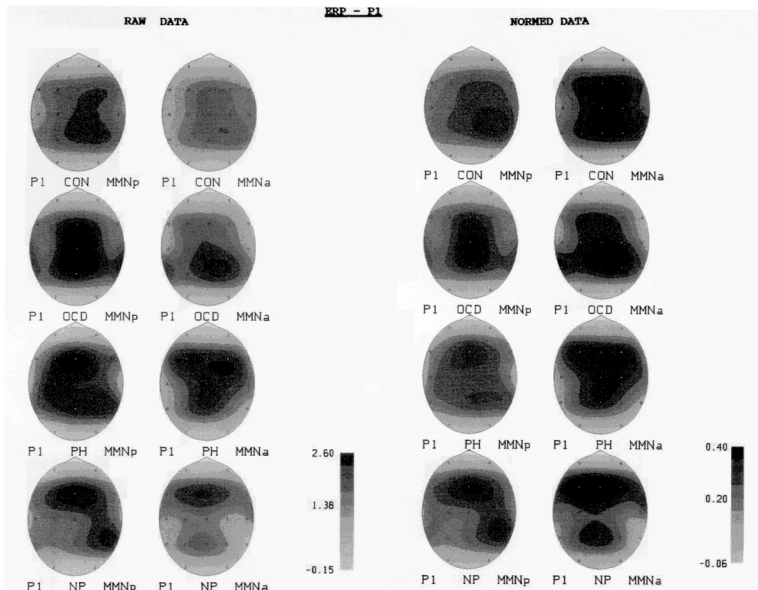
Figure 4. Topographic distribution of the amplitude of the P1-like component of the difference-wave. Raw data (*left*) are shown for four subject groups (see Figure 1 legend) in passive (MMNp) and active conditions (MMNa). Vector-normalized data are shown on the *right*. Note the frontocentral vs centroparietal loci in schizophrenic vs comparison groups and the bilateral temporal decrease in the active condition (especially NP).

.05), but Hotellings and averaged tests conflicted on the normalized data. The group by site interaction was not significant. There were isolated but not systematic significant decreases of positivity over temporal sites in some patient groups.

Three-way interactions including group (Table 2) showed a trend for patients, particularly the PH group, to show more positivity at Fz in the passive (raw data) and active condition (normed data; both $F(3,61) = 5.0/6.5$, $p = .004–.0007$, Scheffe). The topographic maps (not shown) illustrated more of a frontal spread of positivity in patient groups from the usual posterior maximum. The result is merely a trend, but is strongly consistent with the MMN results described above.

Discussion

Main Effects

An attenuated MMN amplitude was confirmed for schizophrenic patients. This was exaggerated as a function of the increased MMN in comparison with (not schizophrenic) subjects associated with the focusing of attention required in the discrimination condition. While the topography of MMN in patients showed signs of lateralization in the passive condition, a posterolateral locus in nonparanoids was unexpectedly restricted to the active condition. Although the earlier N1-like deflection tended to increase in the attention condition in all groups against expectations,
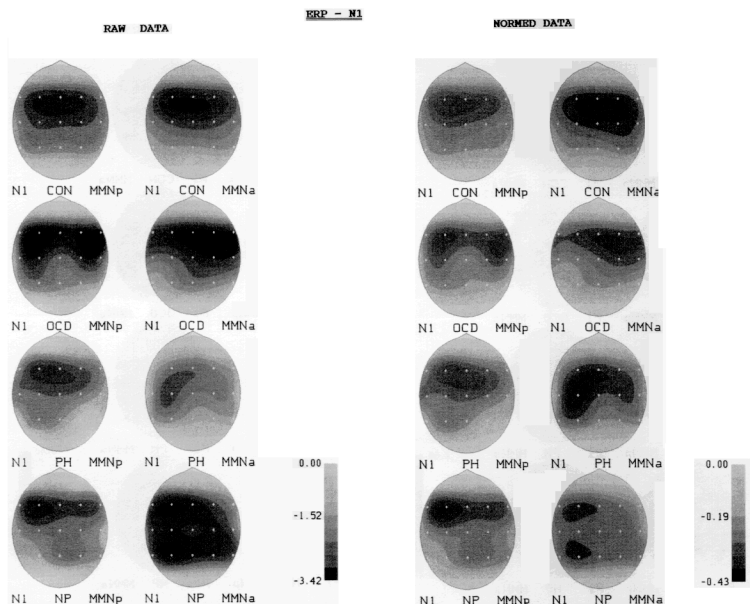
Figure 5. Topographic distribution of the amplitude of the N1-like component of the difference-wave. Raw data are shown (*left*) for four subject groups (see Figure 1 legend) in passive (MMNp) and active conditions (MMNa). Note the trend for frontal values to increase in the active condition (but not for the PH group). Vector-normalized data are shown on the *right*. Note the broadly similar distribution of activity between groups and conditions but also the start of a lateral temporal representation in the NP group, better seen in the N2-like component (Figure 2).

there were no statistically confirmed group differences as with the later N2-like MMN component.

The subsequent P3-like positive deflection in schizophrenic patients did not increase significantly between diffuse and focused attention conditions as in control and OCD groups. But while smaller in both schizophrenic groups in passive and active conditions, it did not show topographic differences between groups.

The early P1-like deflection did not reflect changes seen in later positive deflections but did partially mirror later MMN changes (e.g., frontal increase and temporal decrease of positivity in schizophrenic patients). The focused attention condition induced few effects on P1-like topography except for a general decrease of involvement of

lateral sites; however, the P2-like deflection extended more frontally in all three patient groups than in controls (again mirroring MMN), but this was independent of the condition (unlike MMN).

Effect of Condition

In Figure 3 it may be seen that while schizophrenic groups showed reduced MMN in both diffuse and focused attention conditions, the effect was larger in the active condition as the increase shown by control and OCD groups did not occur. This has practical and theoretical importance.

The practical importance is that reports of no MMN reduction in schizophrenics may reflect a) the selection of

subjects with relatively intact automatic information processing and/or b) that the subjects were *not* actively attending to something else,—a condition that from the present results appears to enhance the MMN difference.

A common method for obtaining MMN is to offer a book to read while presenting the tones. There is, however, no clear demonstration that subjects are actively attending to the book. Negative findings (e.g., O'Donnell et al 1994) may result from obtaining records from patients that were not attending to or interested in anything at the time. The point is emphasized by these authors in their report of a "N1b" difference after subtracting ERPs to nontargets in the reading from a counting condition. This argument also applies to negative reports associated with the presentation of an ancillary task. Thus Kathmann et al (1995) did not report whether patients were accurately tracking the visual target presented or that the task was indeed demanding of attention and effort.

In contrast, the discrimination performance of the schizophrenics here clearly shows that attention was focused on the task. By the same token we cannot rule out that their impaired accuracy and their impaired MMN could have a common basis; however, one may also ask if it was the "state" of focused attention that exaggerated a group difference in topography already present in the passive condition but, through the low amplitude, was masked by noise. On the limited data available in this study we are unable to rule this possibility in or out. Perusal of Figure 2 shows that all patients showed some "bilateralization" of MMN away from the midline in the passive condition. A comparison with the "N1-like precursor" in Figure 5 shows further that in NP patients negativity can localize at temporal sites, here on the left. Because of the small amplitudes involved and the integral variability of ERPs between schizophrenic patients (Roemer and Shagass 1990) this issue is unlikely to be resolved in this paradigm. It may be better to use stimulus-locus in measuring MMN as this feature is reported to be more salient with regard to ERP records (Michie et al 1990).

The theoretical importance of the enhanced MMN in an active condition lies with the demonstration that a degree of activation (e.g., here from controlled processing) normally results in increased differential processing of irrelevant stimuli (present results and Oades et al 1995). As reported in the Introduction, controlled processing is frequently impaired in schizophrenics and thus it was to be expected that such an impairment here would exaggerate the normal–psychotic difference in MMN. The question remains whether the effect is attributable to processing negativity associated with the target (Paavilainen et al 1993), active processing of irrelevant stimuli for comparative discrimination purposes, or is a spill-over from

general interest, effort, or activation induced by the discrimination requirement as suggested by Oades et al (1995) and elaborated by Pribram and McGuinness (1993).

In a similar vein to our preferred explanation, O'Donnell et al (1994) have suggested that impairments in early negative components in passive and active conditions in schizophrenia might be attributed to general features of arousal and that the weakness in the difference-wave is restricted to the active condition. Further, in contrast to the proposal of Paavilainen et al (1993), it may be pointed out that measures of processing negativity have generated different results. In our patients there were much weaker group effects on processing negativity Oades et al (1996a) and Ward et al (1991) found that weak processing negativity in psychotic patients correlated with both negative *and* positive symptoms. These latter results show an effect of symptom-severity whereas the current report emphasizes an effect of symptom-type.

Locus in Time

Not all reported difference-waveforms show components other than the MMN before a late positivity, as can be seen in Figure 1, but early and late negative components can be seen in MMN reports (Winsberg et al 1993; O'Donnell et al 1994), in processing negativity (Ward et al 1991), and the negative difference (Woods et al 1993: see also Introduction). The presence of such deflections could reflect methods for selecting sweeps for averaging or the filters used. But as they appear more pronounced in the active condition it is also possible that they reflect the active attentional processes used. These, in turn, would be expected to incur selective inhibitory modulation of information flow as reflected by positive deflections in the waveform (Schupp et al 1994). Indeed a recent report using a passive/active two-tone paradigm found clear N1-like *and* N2-like amplitude reductions in the MMN difference waveform at latencies of about 102 and 210 ms for a diagnostically unspecified group of schizophrenics (Javitt et al 1995c).

Generalizing, the P1-, P2-, and P3-like deflections showed a lack of similarity and have their own specific characteristics, as elaborated elsewhere (Oades et al 1996a). The N1-like peak did not show group differences and change like MMN with condition, although NP patients did show considerable (left) temporal negativity recalling MMN. P1- and P2-like peaks did not resemble the late positive complex, although naturally their size did mirror changes in the negative components at the same loci. It should not be surprising that these peaks show some specific features if the deflections reflect different functions. For example, Kofoed et al (1995) suggested that

a pre-MMN positive component, determined magnetoencephalographically, represents the initiation of stimulus evaluation.

In summary, in the present data the P1-like deflection in schizophrenics was more frontally localized than in OCD and control subjects. The P2-like deflection tended to be larger in schizophrenics and thus extended more frontally from a posterior locus that all groups had in common. The P3-like component was weakly expressed in schizophrenic subjects, but strongly expressed in OCD patients in the active condition.

Notably, the N1-like deflection showed no statistically significant differences between conditions or groups; however, from Figures 1 and 2 it would seem that early negativity was most marked in OCD patients and showed an additional left temporal locus of activity in NP patients. These observations may obtain significance in future studies firstly, because early studies of MMN demonstrated an onset as early as 60 ms poststimulus (review Näätänen 1990), secondly in the principle components analysis of Javitt et al (1995c) the N1-, N2- and P3-like components loaded exclusively with diagnosis onto the first, the most important factor, and thirdly, because increased excitability in the form of a negative shift has been reported from OCD patients (Towey et al 1993; Oades et al 1996a).

An attenuation of the enhancement of N1 in the attended channel was described for schizophrenics by Pritchard (1986). The interesting feature in the present results is that the consequences of this were seen at N2-like latencies: the usual MMN increase in the active condition seen in controls was not noted in schizophrenics; however the opposite, an enhancement, did seem to be occurring in OCD patients: a difference that needs to be confirmed in future studies. Further studies of the processing of irrelevant stimuli with difference-waves in divided attention paradigms may well make use of deflections other than MMN in the waveform to assist in delineating differences of processing strategies between schizophrenics, other patients, and healthy subjects.

It is appropriate to consider briefly the factor of the age of our subjects. The first question is whether the range of subjects' ages spread across an age-span of rapid development could have contributed to the differences recorded. This is unlikely firstly as the subjects were so closely matched, pairwise, for age (see Methods) and secondly we have examined the influence of development in normal subjects (8–22 yr of age) in this paradigm (Oades et al 1996b). Here we showed that while amplitudes can differ in size and locus in children younger than those tested here, latencies were the only MMN measures to change in adolescence (early frontal components were shorter in 14 yr-olds and posterior late components were shorter in 17

yr-olds). This might have contributed to the paucity of group latency differences, but otherwise the youth of our subjects may be considered representative of young adults.

Late Positivity

An updating function, attributed to the tone-elicited P3 (Donchin and Coles 1988) may also be appropriate to the late positivity to be found in the difference wave (Faux et al 1988). It may be elicited by pitch and frequency differences, even if there is no obvious consequence to any tone, as in the passive condition. For healthy subjects these stimulus differences evidently take on more significance in a discrimination situation, even if the attention is focused on another stimulus, for the difference-P3 amplitude increases even after irrelevant stimuli, confirming the report of Oades et al (1995); however, consistent with data reviewed by Pritchard (1986) both PH and NP psychotic patients seemed to remain oblivious to these context-dependent changes.

No topographic differences for the P3-like component in the difference-wave were found. This is consistent with the recent findings by Javitt et al (1995c) but contrasts with single tone elicited P3 components where a variety of lateralized changes between conditions have been noted to distinguish healthy from schizophrenic subjects (Faux et al 1988; McCarley et al 1993; Strik et al 1994; Oades et al 1996a).

Locus in Space

Normalization of the MMN difference-waveform data showed a striking reduction of MMN at frontal sites for NP patients. An apparent increase of negativity at lateral posterotemporal sites in NP was not seen in PH patients. This may have been overlooked in other studies either because this waveform has only been studied in passive conditions, the authors did not look for and analyze temporal site data appropriately (e.g., Javitt et al 1995c), or patient groups were derived from clinical diagnostic traits rather than current symptoms (Oades 1995).

The decrease could implicate hypofrontal function, widely reported in schizophrenic patients with predominantly negative symptoms (e.g., Buchsbaum 1990) and a compensatory processing strategy being allocated to temporal lobes. This assumes dysfunction of a generator in frontal regions (Giard et al 1994), which otherwise has not been widely reported.

Alternatively, if the generator is located only in primary (N1, Scherg et al 1989) or secondary auditory association cortex (N2, O'Donnell et al 1993)—with the dipole oriented on the cortex curvature to record maximum negativity over frontal areas—then this orientation may

have become altered in NP patients, who from their symptomatology may be those who show atrophy in temporal regions (Shenton et al 1992). This issue could be resolved by joint MRI–ERP studies of the type used by McCarley and colleagues.

A third possibility is that the temporal locus for MMN in NP patients is an artifact. The source of the artifact could derive from jaw movements that contribute to the variability commonly found in temporal ERP recordings. Even if such an artifact were contributory, it seems unlikely to be explanatory for the following reasons. The posterior temporal locus was statistically significant on the right, here, but marked bilaterally (Oades 1995, Fig. 4) in the active not the passive condition (Figure 2). Temporal loci for MMN have also been reported in young patients with complex tic or Tourette syndrome but in the passive condition (Oades et al 1996c). It is therefore enigmatic why such artifacts should be found in at least two patient groupings but not in OCD or attention-deficit-hyperactivity patients or normal subjects (young and old) all tested in the same paradigm. Further, it is not evident why the artifact should appear in the one or then in the other condition irrespective of task requirements. Lastly if the latency should be regarded as crucial for the artifact, we would note that the effect may occur more on the left side around 100 ms (Figure 5) but on the right at 200 ms in NP patients (Figure 2). Clearly the present result needs to be replicated, but it is useful to consider what biological bases may be common to the NP patients tested.

It is worth briefly considering the importance of the frontal areas, if not for the source of the MMN, but the source of the influence on auditory cortical MMN. MMN is a form of auditory working memory (see Introduction) and a recent report has shown that frontal working memory-related neural activity in monkeys was sensitive to D1 agents (Williams and Goldman-Rakic 1995). Indeed

the neuronal effect of antagonists was more efficient for nonrelevant stimulus fields than for target fields, which makes the results particularly interesting for MMN generated by nontargets. The authors noted that schizophrenic patients with reduced cortical dopamine activity, possibly as a result of neuroleptic therapy, showed improved working memory performance when given amphetamine: we have found that the NP patients in this study indeed showed reduced dopamine activity, as measured by the excretion of dopamine and homovanillic acid (Oades et al 1994). It would be of interest to see if a challenge with psychostimulants would have a normalizing effect on MMN specific to NP patients apparently not responding to neuroleptic treatment. The feature of neuroleptic nonresponse may be important here. While MMN amplitude was not found to be sensitive to neuroleptic dose either here or elsewhere (Javitt et al 1995c) one could still argue that the presence of an MMN at frontal recording sites in PH patients, albeit small, reflected their neuroleptic responsive state. It could be that differential (mesocortical) dopamine sensitivity of attentional mechanisms in NP and PH patients (Oades et al 1992a) and brought into play by the changeover from passive to active conditions here, is reflected in impaired frontal modulation of temporal lobe mechanisms, as proposed by Frith (1992), and here measured by MMN. This interpretation remains consistent with a potential source of stimulus comparator mechanisms in temporoparietal cortex that receive a large innervation from frontal and cingulate cortices (Oades et al 1996a; Woods et al 1993).

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