Original article

Epileptic Disord 2005; 7 (4): 363-72

A comparative study of mismatch negativity (MMN) in epilepsy and non-epileptic seizures

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Received December 2, 2004; Accepted August 10, 2005

ABSTRACT – This study investigated mismatch negativity (MMN) differences between subjects with non-epileptic seizures (NES), subjects with epilepsy, and healthy controls. Event-related potentials (ERPs) were obtained from 14 patients with NES, 15 patients with epilepsy and 16 healthy control subjects. A conventional MMN procedure was used with a random sequence of 12% deviant tones (922 Hz) and 88% standard tones (1000 Hz). Subjects were instructed to ignore the tones delivered through headphones whilst reading a book. Significant differences in distribution of the mismatch negativity (MMN) in patients with NES compared to controls were obtained (F3, $p \leq 0.019$; Cz, $p \leq 0.044$) and longer MMN duration in patients with epilepsy compared with patients with NES ($p \leq 0.039$) was observed. The change that has been analyzed is one of relative (or scaled) amplitude rather than absolute amplitude. These differences observed at Cz/F3 suggest an increase in emphasis of the MMN in the fronto-central region in patients with NES compared to healthy controls, suggesting that the MMN is generated in a different way in NES compared with controls. This could indicate that one of the normal MMN generator areas does not function normally in NES. Increased absolute amplitude of the MMN has previously been observed in anxiety disorders particularly in post-traumatic stress disorder (PTSD). We discuss similarities between NES and PTSD, suggesting that the increased relative amplitude obtained in this study may be related to mechanisms of generation of NES. The prolonged duration of the MMN in epilepsy could be related to difficulties in processes associated with novelty discrimination (closure of MMN generating mechanism). This information processing dysfunction could be associated with the concentration and memory difficulties that are observed in some patients with epilepsy. This study provides electrophysiological evidence of abnormal processing of auditory stimuli in both clinical conditions when compared to healthy controls, and interictal differences between a group of patients with epilepsy and a group of patients with non-epileptic seizures, as measured by the MMN.

Key words: mismatch negativity, MMN, event-related potential, epilepsy, non-epileptic seizure, seizures

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The term non-epileptic seizures (NES), refers to epileptic seizure-like events without concomitant epileptiform EEG changes and with presumed psychological aetiology. Epilepsy is the main clinical entity to consider when making a differential diagnosis and, despite much clinical study, the differentiation of epileptic seizures from NES can be difficult.

Epilepsy is a condition characterised by recurrent episodes of paroxysmal disturbance of normal brain functioning. In order to make a reliable diagnosis of epilepsy there needs to be evidence that these paroxysms of disturbance involve both disruption of ongoing behaviour and abnormalities of brain electroencephalographic (EEG) activity recognised as epileptiform. However on the one hand, a normal interictal EEG does not exclude epilepsy and on the other hand there are normal EEG variants that may mimic epileptiform activity. Only 30-40% of patients with epilepsy show epileptiform discharges on a single, interictal awake recording (Ajmore and Zivin 1970). A diagnosis of NES is suggested by the absence of EEG changes during seizures. Ictal recordings are much more reliable in distinguishing between epilepsy and NES, but they are difficult to obtain and even in these circumstances, occasionally, the standard EEG 10-20 scalp electrode placement fails to reveal epileptiform activity that is restricted to deep temporal or frontal foci.

With respect to the physical nature of seizures, there is no clinical phenomenon that occurs solely and exclusively in epilepsy. It has been stated that everything that happens in epilepsy can happen in NES and *vice versa* (Wyler *et al.* 1993).

Several studies have investigated changes of auditory event-related potential (ERPs) in patients with epilepsy. Among these, Mervaala *et al.* (1992), who studied patients with treatment-resistant TLE pre- and post-surgery, and Rodin *et al.* (1989), who studied a mixed group of patients with chronic epilepsy, reported significantly longer P3 latencies and smaller amplitudes in patients with epilepsy when compared with healthy controls. In contrast, Drake *et al.* (1986) obtained larger amplitudes and longer latencies for P3 and N2b in patients with complex partial or secondarily generalised seizures compared to healthy controls.

Very little is known about the possible neurophysiological basis of NES. Drake *et al.* (1993), using an auditory oddball paradigm, reported ERP differences between patients with NES and patients with epilepsy. Their results showed P3b latencies significantly longer ($p < 0.05$) in subjects with epilepsy than in patients with NES.

Mismatch negativity (MMN) is an early auditory event-related potential (ERP) elicited when infrequent ("deviant") sounds occur in a sequence of repetitive ("standard") sounds even in the absence of attention to these sounds (Näätänen 1984). It has been proposed (Näätänen *et al.* 1989a) that MMN arises if there is mismatch between the physical features of a deviant stimulus and a neuronal sensory-memory trace produced by repetitive standard stimuli. MMN is considered to reflect the earliest cortical event in the cognitive processing of auditory information (Pfefferbaum *et al.* 1995) being part of auditory preattentive memory also termed "echoic memory" (Cowan *et al.* 1993, Näätänen *et al.* 1989a, Näätänen *et al.* 1989b). MMN is thought to be generated by an automatic, attention-independent, preconscious neural process that contrasts ongoing sensory inputs with a memory trace encoding the physical features of preceding stimuli. MMN is a frontocentral negativity with a maximum amplitude recorded at frontal electrodes. It usually peaks between 100 and 200 msec after deviation onset. In contrast to P3, the generators of the MMN component are well defined: a bilateral supratemporal auditory cortex generator and one in the right frontal region (Giard *et al.* 1990, Sams *et al.* 1991, Näätänen 1992).

Smaller amplitude and/or longer latency MMNs have been observed in several studies of subjects with neurocognitive dysfunctions (Carpenter *et al.* 1988, Harvey *et al.* 1990, Pekkonen *et al.* 1994), brain injuries (Alho *et al.* 1994) and in general in states associated with lower performance level in cognitive or motor tasks (Pietrowsky *et al.* 1990). A review of the changes in MMN in a variety of psychiatric disorders appears in Gene-Cos *et al.* (1999). Abnormalities of auditory information processing as measured by MMN have been associated with Parkinson's disease, prefrontal lesions and autism among others. However, no previous studies have explored the role of MMN in differentiating between NES and epilepsy.

The aim of the present study was to determine electrophysiological differences, as measured by MMN, between epilepsy and NES. Considering that epilepsy, in contrast with NES, has an organic basis and has been associated with cognitive deficits, we hypothesised that patients with epilepsy would have longer MMN latencies and smaller MMN amplitudes than patients with NES or healthy controls, and that NES subjects would have similar ERPs to healthy controls.

Methodology

Subjects

ERP recordings were obtained from NES, epilepsy and age-matched control groups. Details of sample numbers, mean age, and female/male ratio are shown in *table 1*.

The age at onset of the seizures in both conditions was different. For the NES group, 10 patients started having seizures in adulthood, whereas, for the epilepsy group, 5 were diagnosed during childhood and 6 in their teens.

Subjects with NES were recruited from two neuropsychiatric centres (tertiary referral centres) based in two teaching hospitals, and the diagnosis had been established either with videotelemetry or 24 hour-EEG recordings; in all cases EEG had been obtained during a "typical" sei-

Table 1. Comparison of gender and age in different subject groups.

Groups	Number of subjects	Mean age (years)	Female	Male
NES	14	40.8	10	4
Epilepsy	15	41.3	8	7
Controls	16	37.4	9	7

zure. All patients had been followed-up for at least 5 years. During this follow-up period none of the subjects with NES or healthy controls developed epilepsy.

Subjects with epilepsy were recruited from a specialised epilepsy clinic in a teaching hospital, and suffered from treatment refractory epilepsy. Patients had a diagnosis of either complex partial seizures with secondary generalisation (10 patients), or primary generalised seizures (5 patients). Diagnosis was based on a combination of clinical, EEG and structural imaging data. Control subjects were recruited from non-blood-related relatives of the patients participating in the study, non-medical hospital staff (such as technicians or secretaries), and members of the public. At bedside testing, all the subjects had normal hearing and were found to have an IQ within the normal range as measured by the National Adult Reading Test (NART) (Nelson 1982). Handedness was tested using the Annett hand preference questionnaire (Annett 1970). All subjects were right-handed except for an ambidextrous control subject, a left-handed patient with epilepsy and one left-handed and one ambidextrous patient with NES.

Mood disorders were assessed using the Beck Depression Inventory (BDI) (Beck *et al.* 1961) and the Hospital Anxiety and Depression Scale (HAD) (Zigmond and Snaith 1983). In addition, all subjects were interviewed by a psychiatrist (NGC) using a semi-structured psychiatric interview, assessing current and past organic and functional psychiatric disorders.

Subjects with major organic or functional psychiatric disorders were excluded from the study.

Stimuli and procedures

Stimulus delivery and data acquisition were controlled using Psylab equipment (Contact Precision Instruments). Subjects were tested individually during a morning session in a sound-attenuated room. A conventional procedure for eliciting MMN with a frequency difference between the standard and the deviant stimuli was used. The stimuli were tones with an intensity of approximately 70 dB delivered through headphones in random order (except that the first 5 tones were standards and that 2 deviants were never delivered sequentially). The subjects sat in a comfortable chair and were instructed to ignore the tones while reading a book or magazine of their own choice.

The stimuli consisted of pure tones of 40msec duration with a rise/fall time of 5 msec. The standard stimuli were 1000 Hz tones with a probability of 88% and the deviant tones had a frequency of 922 Hz and a probability of occurrence of 12%. Tones were presented at a rate of approximately 2 per second with a constant interstimulus interval (ISI) of 500 msec (measured from the end of one stimulus to the onset of the next stimulus). Two hundred deviant stimuli were presented to each subject in a single block.

Subjects were instructed to read while recording was taking place, and to ignore the tones delivered through the headphones. They were also advised to relax and to avoid movements.

EEG recordings

The EEG was recorded using silver/silver chloride electrodes from midline (Fz, Cz and Pz) and the superior frontal (F4 and F3) sites according to the international 10-20 electrode placement system (Jasper 1958). All electrodes were referred to linked earlobes (Sam *et al.* 1985, Shelley *et al.* 1991, Kathmann *et al.* 1995). EOG recorded between electrodes placed at the outer canthus of the left eye and the glabella, enabled both horizontal and vertical aspects of eye movements to be recorded in a single channel. All electrodes were applied to the scalp using an adhesive (ten20 paste) and interfaced by a conductive medium (NU prep); the impedance between the electrodes and the skin did not exceed 5 KΩ.

The EEG and EOG were recorded continuously at a sampling rate of 500 Hz per channel and with a bandwidth of 0.3 to 100 Hz. Responses to each stimulus were subsequently averaged off-line.

Data analysis

Trials with excessive movement activity or with EOG activity exceeding ±45 μV were excluded from analysis. Responses to the deviant and standard stimuli were averaged separately for each individual. The averaging period was 350 msec, including a 50-msec prestimulus baseline used for amplitude measurements. The final averages for the standard and the deviant stimuli were saved as an ASCII file, to allow for baseline correction, 7-point smoothing of the waveforms, and measurement of various waveform features using software written for the purpose by one of the investigators (RCP, QBASIC).

Analysis of the averaged evoked responses focused on the components in the range 50-300 msec after stimulus onset. The primary analysis was performed by averaging the peak amplitude and latency values for each component across subjects in each group. N1 and P2 were determined

Table 2. Depression and anxiety scores of the three groups.

	BDI	HAD	HADanx
Controls	2	8	6
NES	6.5**	14*	8
Epilepsy	5#	10	7

Statistically significant results: NES *versus* controls: * p = 0.011; ** p = 0.005.
Epilepsy *versus* controls: # p = 0.010.

from the response to the standard stimuli. The latency of the MMN amplitude was initially identified from Fz (except in a few cases when it was more clearly defined at F4 or Cz), and measured at the same latency in the other channels as the average voltage in a 10 msec period either side of the peak (a total of 20 msec window). MMN latency was evaluated as the time of occurrence of the peak measured from stimulus onset. The onset of the MMN was taken from the difference waveform at the point where it crossed the baseline (0 μV) and offset as the time the voltage of the response returned to this baseline. MMN duration was measured as the difference between onset and offset. These initial analyses were performed by two independent researchers (NGC & RCP), one of them blind to the sources of the waveforms. When there was a discrepancy between them, waveforms were measured together with a third person (GB) and a consensus was reached in each case.
Differences in MMN amplitude, latency and duration were analysed using repeated measures ANOVA with between-subject factor GROUP, and within-subject factor SITE. In addition, changes in MMN topography were examined following amplitude scaling using the method described by McCarthy & Wood (1985).

Results

Clinical and demographic findings

Separate analyses were conducted to investigate gender, medication, IQ and mood disturbances. Using one-way ANOVA, across groups there were no significant differences in gender and age *(table 1)*, but significant differences were found between control subjects and clinical groups on IQ and mood scores. All the subjects had an IQ within the normal range, however control subjects had significantly higher IQ scores when compared to the epilepsy group (IQ: controls: 114; epilepsy: 107 (control *versus* epilepsy, d.f. = 25, p = 0.006); NES: 106 (control *versus* NES, d.f. = 13.62, p = 0.06); (NES *versus* epilepsy, d.f. = 23, p = 0.7). This difference in IQ significance was due to the fact that the standard deviation of the controls and epilepsy group were similar (5.63 and 6.60 respectively); whereas in NES, the individual range of IQ within this group was larger (standard deviation: 12.10). Both clinical groups, (NES subjects and subjects with epilepsy) had higher depression scores than controls *(table 2)*.
In relation to medication, none of the control subjects were on medication. In the epilepsy group, 6 patients were on one antiepileptic drug, 6 on two or more antiepileptic drugs and 3 on no medication. In the NES group, 6 patients were on no medication, 4 patients on one antiepileptic drug, 3 on antidepressants and one on painkillers. None of the clinical or demographic data correlated with electrophysiological findings.

Group N1-P2 comparisons

No significant differences between groups were observed for the amplitudes of the N1-P2 complex measured in the response to standard stimuli (means ± standard deviations of N1-P2 complex (μV): controls: -1.85 ± 2.25: NES: -3.37 ± 3.08: epilepsy: -2.56 ± 2.28); (controls *versus* NES: d.f. = 28, p = 0.13), (controls *versus* epilepsy: d.f. = 30, p = 0.38) and, (epilepsy *versus* NES: d.f. = 23.7, p = 0.43).

Group comparisons of MMN amplitude raw data

For those comparisons, we used repeated measures ANOVA (*table 3*): considering the central electrodes (Fz, Cz, Pz), there was a highly significant effect of electrode

Table 3. Raw data: means ± standard deviations of peak amplitudes (μV) of MMN in healthy controls, non-epileptic seizure and epilepsy.

Variables	Electrode	Controls (n = 16)	NES (n = 14)	Epilepsy (n = 15)
MMN peak amplitude (μV)	Fz	-3.71 ± 2.46	-2.29 ± 2.54	-3.16 ± 3.21
	Cz	-3.60 ± 2.97	-1.81 ± 1.98	-2.42 ± 3.45
	Pz	-3.00 ± 2.75	-0.79 ± 1.37	-0.74 ± 2.36
	F4	-3.62 ± 2.53	-2.56 ± 2.71	-2.67 ± 2.37
	F3	-3.22 ± 2.35	-1.96 ± 2.54	-2.99 ± 3.43

Table 4. Normalised data: means ± standard deviations of scaled measures of peak amplitudes of MMN in healthy controls, non-epileptic seizure and epilepsy.

Variables	Electrode	Controls (n = 16)	NES (n = 14)	Epilepsy (n = 15)
MMN scaled measures of peak amplitude (μV)	Fz	-1.10 ± 0.69	-1.51 ± 1.94	-1.66 ± 1.29
	Cz	-1.07 ± 0.84	-1.92 ± 1.30*	-1.37 ± 1.39
	Pz	-0.86 ± 0.79	-1.15 ± 0.58	-0.62 ± 0.98
	F4	-1.07 ± 0.72	-1.45 ± 1.86	-2.03 ± 1.87
	F3	-0.96 ± 0.66	-1.83 ± 1.14**	-1.55 ± 1.42

Peak amplitudes shown are those obtained after scaling with McCarthy and Wood's procedure. Statistically significant results: NES *versus* controls: * p = 0.044; ** p = 0.019.

Table 5. Means ± standard deviations of peak latencies, onset, offset and duration (ms) of MMN in healthy controls, non-epileptic seizure and epilepsy.

Variables MMN (ms)	Electrode	Controls (n = 16)	NES (n = 14)	Epilepsy (n = 15)
Latency	Fz	120.50 ± 21.80	116.14 ± 30.37	122.80 ± 32.62
Onset	Fz	82.12 ± 15.56	73.28 ± 19.87	76.26 ± 23.91
Offset	Fz	162.87 ± 30.66	147.71 ± 34.91	172.00 ± 38.92
Duration	Fz	80.75 ± 33.97	74.42 ± 23.66	95.73 ± 31.14#

Statistically significant result: epilepsy *versus* NES: # p = 0.049.

(d.f. = 1.39; p < 0.0001). There was no significant within-subject effect (d.f. = 2.78; p = 0.305, Greenhouse-Geisser). There was a trend towards significance for interaction between group and electrode (d.f. = 2; p = 0.092) Considering the frontal electrodes (Fz, F4, F3), there was no significant effect of electrode (d.f. = 1.32; p = 0.245); no significant within-subject effect (d.f. = 2.65; p = 0.397, Greenhouse-Geisser), and there was no significant interaction between group and electrode (d.f. = 2; p = 0.414).

Calculation of scaled amplitude measures

Given the highly significant effect of electrodes at Pz (note in *table 3*), in order to allow for effects of distortion between electrodes, we calculated scaled amplitude measures, according to McCarthy & Wood (1985). Group MMN comparisons using scaled amplitude measures: patients with NES when compared by repeated measures ANOVA to healthy controls had larger relative amplitudes at all sites, but these only reached statistical significance at Cz (d.f. = 27; p = 0.044) and F3 (d.f. = 26; p = 0.019). For the epilepsy group, the relative amplitudes were larger at all electrodes except at Pz compared to healthy controls, but did not reach statistical significance; although there was a trend toward significance at F4 (d.f. = 29; p = 0.06) (*table 4*).

Relationship between latency, onset, offset, duration and clinical data

There were no statistically significant differences between groups for onset, offset or peak latencies However, between the two clinical groups, MMN duration differed, with significantly longer duration in patients with epilepsy compared to patients with NES (d.f. = 25.9; p = 0.047) (*table 5*).

Figures 1, 2, 3 and 4 show event-related brain potentials (ERPs) to standard and deviant stimuli and the different waveforms (MMN) in a healthy control, NES and a subject with epilepsy.

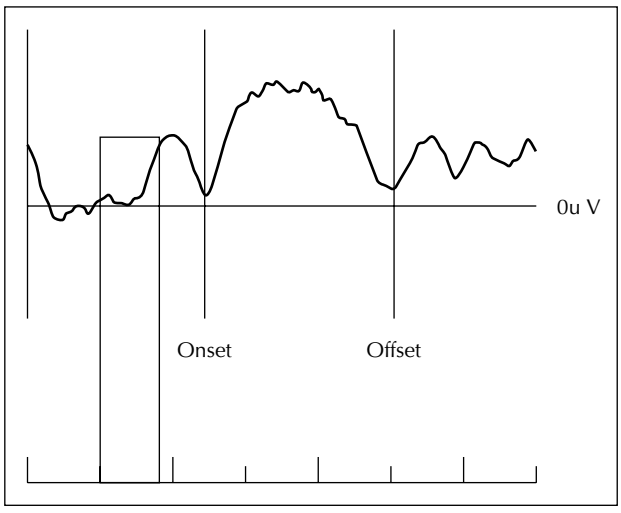

Figure 1. Difference waveform: points between where the MMN crosses or becomes near to zero volts.

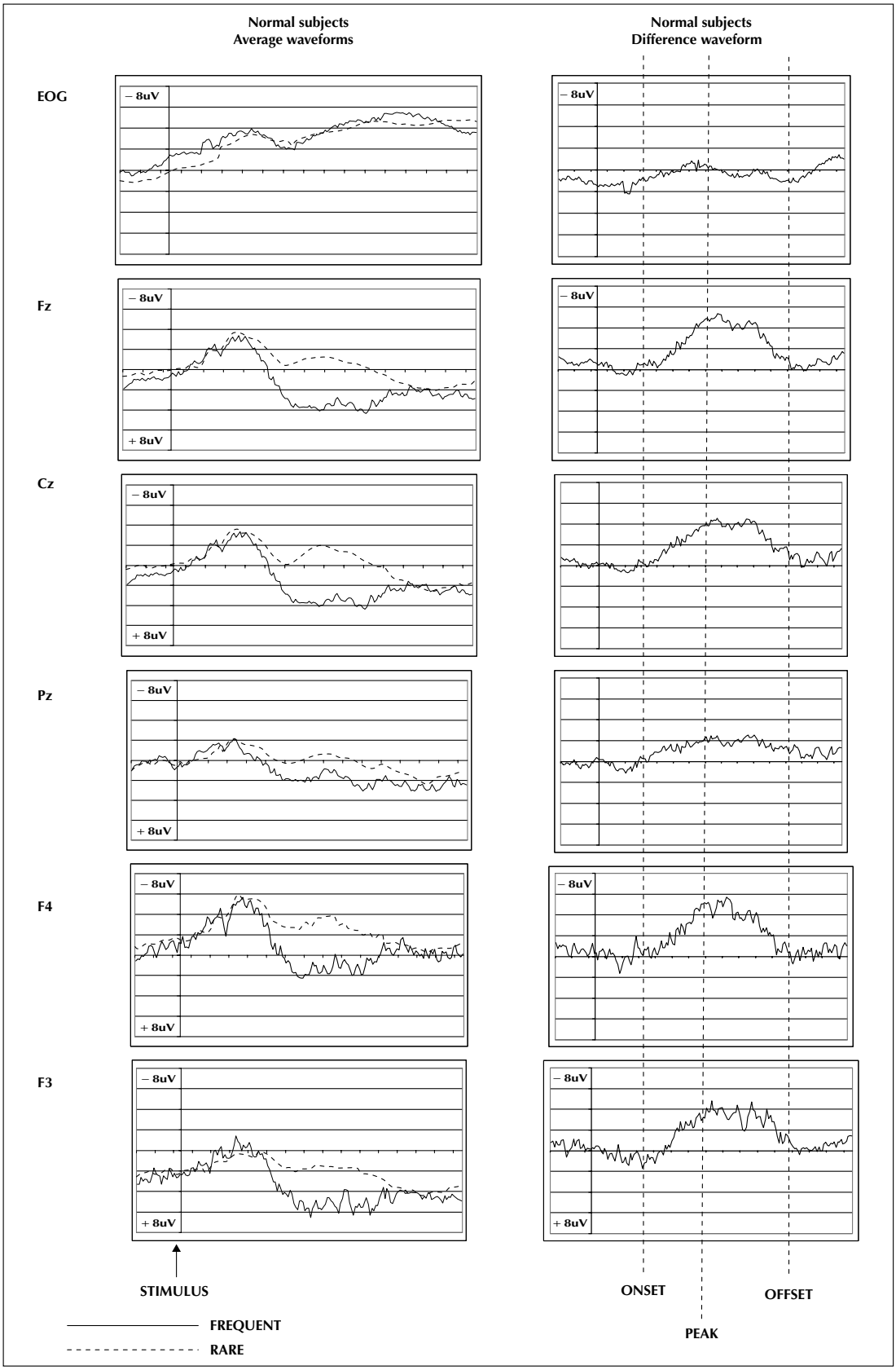

Figure 2. Grand average waveforms and corresponding difference waveforms in control subjects.

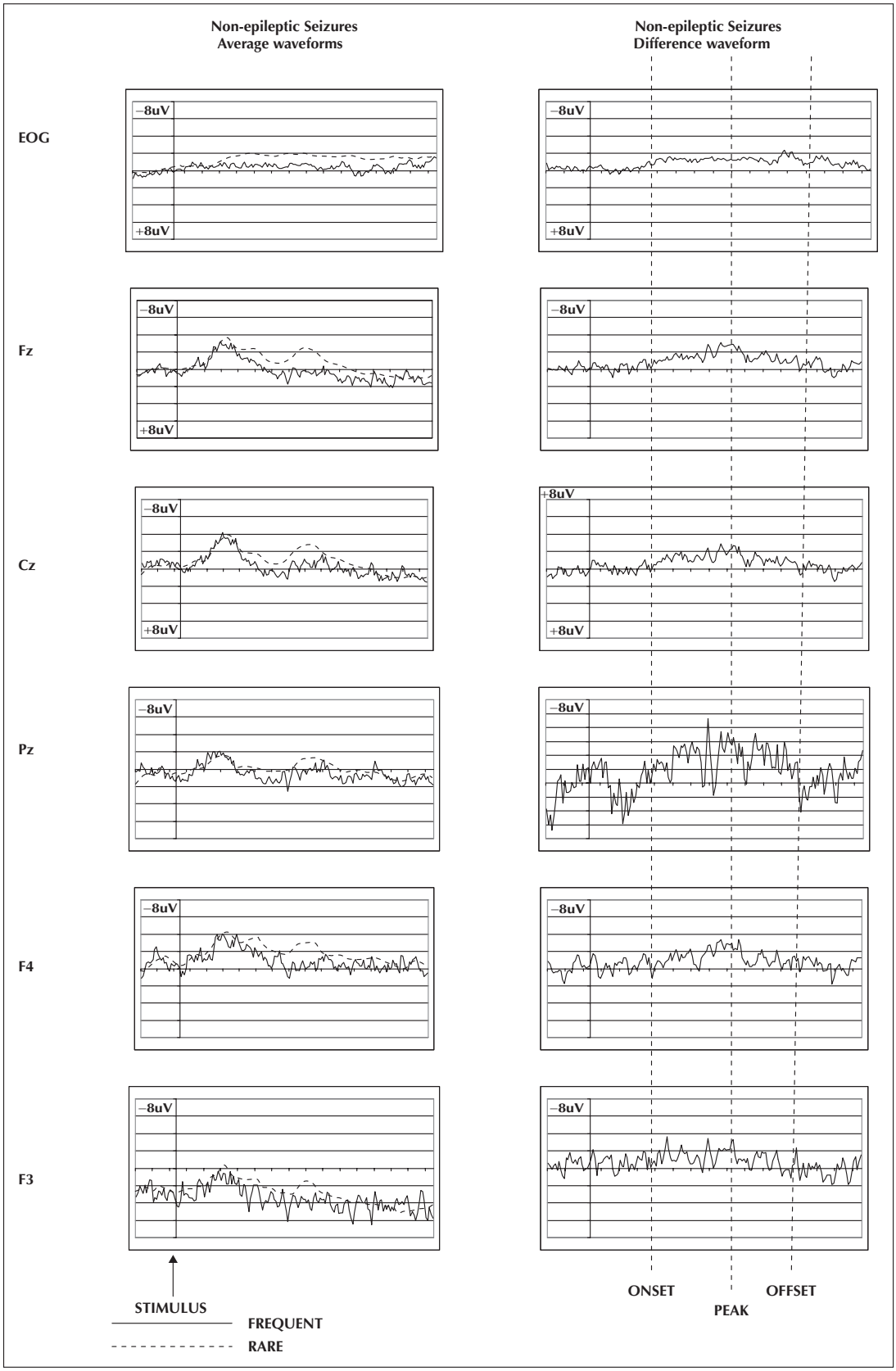

Figure 3. Grand average waveforms and corresponding difference waveforms in subjects with NES.

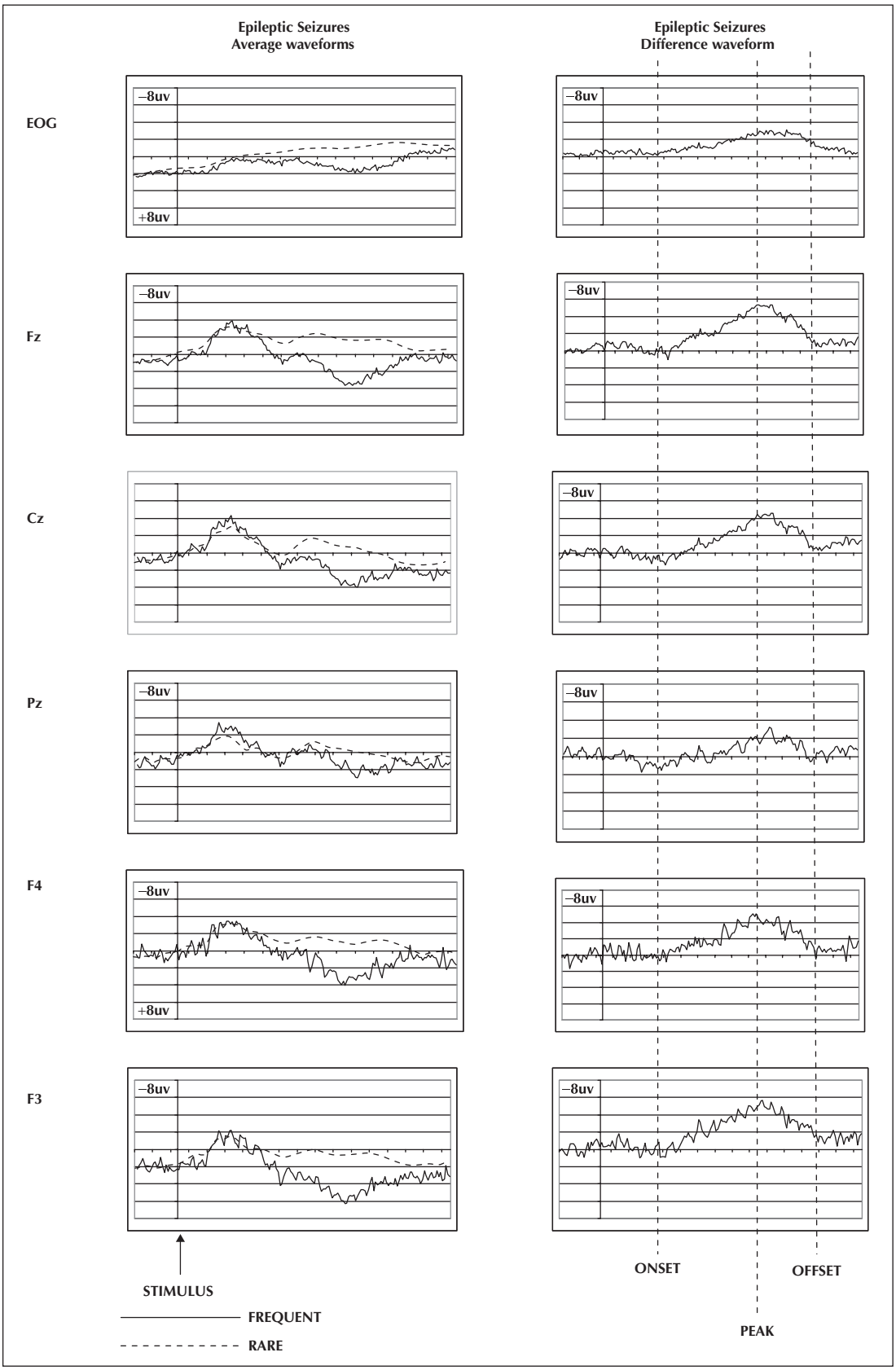

Figure 4. Grand average waveforms and corresponding difference waveforms in subjects with epilepsy.

Discussion

In the present study, MMN differences were found between controls and both patients groups. Both patient groups had larger scaled measures of MMN amplitudes when compared to healthy subjects. However, these differences only reach significance in subjects with NES, who showed significantly larger relative MMN amplitudes in frontocentral electrodes compared to healthy controls. There were no significant differences between the two patients groups except for the MMN duration, which was significantly longer in patients with epilepsy compared to patients with NES.

The fact that between control subjects and patients, no differences were seen in the N1-P2 complex evoked by standard stimuli indicates that the differences between these patients are not related to potential group differences in the analysis of the physical characteristics of stimuli. The increased amplitude at Cz and F3 seen in NES is unlikely to be due to seizure activity, as similar findings would, in that case, have been expected in the group of subjects with epilepsy. The finding is more likely attributable to some other factors linked to the NES phenomenon.

There is evidence to indicate that MMN reflects the beginning of the switching of the attention mechanism or orienting response, to novelty in the auditory environment (Näätänen 1995). As an index of the functional state of the cortex, MMN amplitude is larger for states of higher vigilance or when the level of intrusiveness of the novel stimuli is larger (Lang *et al.* 1995). In non-epileptic seizures, larger MMN may indicate higher vigilance in this patient group.

In this context, it is interesting to note that in a previous study (Pouretemad *et al.* 1998), patients with NES showed a significant reduction in prepulsive inhibition (PPI) when compared to healthy controls. The startle response is usually inhibited when a weak to moderate stimulus is presented at a brief interval before the startle-eliciting stimulus is presented. The degree to which the startle response is inhibited by the prepulse is called PPI, which indicates the amount of sensorimotor gating. The results found by Pouretemad *et al.* (1998) showed a significant reduction in PPI in NES patients, and therefore a disturbance of sensorimotor gating. The relation between abnormal sensorimotor gating and increased MMN amplitude is not clear. However, a possible explanation of our patients' greater response to novelty may be, in part, related to defective sensorimotor gating and subsequent increased intrusiveness of novel stimuli, associated with a state of hypervigilance. MMN is known to be greater for states of higher vigilance (Lang *et al.* 1995). This increase of intrusiveness of novel stimuli could lead to a larger MMN relative amplitude as observed in our study.

In further support of this proposition, increase in startle response with loss of normal inhibitory modulation of the startle response has also been demonstrated in subjects suffering from post-traumatic stress disorder (PTSD) (Ornitz and Pynous 1989). Moreover, increased MMN amplitude has been observed in PTSD. Morgan *et al.* (1999) found larger MMN amplitude in female rape victims when compared to healthy controls, with a significant correlation between the MMN amplitude and the Mississippi PTSD symptoms scale scores. The connection between PTSD and NES in the clinical setting has already been suggested in the literature (Betts and Boden 1992, Cartmill and Betts 1992, Betts 1998).

The MMN changes observed in NES may play a significant role in the clinical picture of this condition. Patients with NES, at times of stress, may become overloaded with irrelevant stimuli, surpassing their coping abilities. Their responses to such a situation may then be externalised as seizure-like activity. Also, the fact that MMN is generated by an automatic, preconscious neural process (Catts *et al.* 1995, Näätänen 1995) would suggest that this disturbance is not consciously created as in the case of malingering.

The main difference observed between the two clinical groups, epilepsy *versus* non-epileptic seizures, was a longer MMN duration in patients with epilepsy. In previous electrophysiology studies, using different experimental procedures, patients with temporal lobe epilepsy had longer P3 and N2 latencies compared to healthy controls (Drake *et al.* 1986, Grippo *et al.* 1994). The prolonged duration of the MMN in epilepsy could well be related to difficulties in processes associated with novelty discrimination. However, in this study MMN latency to peak was within normal range, whereas duration (offset minus onset) was longer, pointing to a difficulty mainly in the closure mechanism of the MMN process. This information processing dysfunction might be related to the concentration and memory difficulties observed particularly in patients who have temporal lobe epilepsy, as patients with epilepsy may spend more time evaluating stimulus novelty and finding the switch of attention from one stimulus to another difficult.

In summary, this study provides electrophysiological evidence of abnormal processing of auditory stimuli in both epilepsy and NES compared with controls, with differences between the two disorders in terms of the nature of the MMN changes. In addition, we have demonstrated, with the MMN, interictal differences between patients with epilepsy and patients with non-epileptic seizures. □

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