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ARCHIVAL REPORT

Are Auditory-Evoked Frequency and Duration Mismatch Negativity Deficits Endophenotypic for Schizophrenia? High-Density Electrical Mapping in Clinically Unaffected First-Degree Relatives and First-Episode and Chronic Schizophrenia

Elena Magno, Sherlyn Yeap, Jogin H. Thakore, Hugh Garavan, Pierfilippo De Sanctis, Daniel C. Javitt, and John J. Foxe

Background: Mismatch negativity (MMN) is a negative-going event-related potential (ERP) component that occurs in response to intermittent changes in constant auditory backgrounds. A consistent finding across a large number of studies has been impaired MMN generation in schizophrenia, which has been interpreted as evidence for fundamental deficits in automatic auditory sensory processing. The aim of this study was to investigate the extent to which dysfunction in MMN generation might represent an endophenotypic marker for schizophrenia.

Methods: We measured MMN to deviants in duration (25 msec, 1000 Hz) and deviants in pitch (50 msec, 1200 Hz) relative to standard tones (50 msec, 1000 Hz) in 45 chronic schizophrenia patients, 25 of their first-degree unaffected biological relatives, 12 first-episode patients, and 27 healthy control subjects.

Results: In line with previous work, MMN amplitudes to duration deviants (but not to pitch deviants) were significantly reduced in patients with chronic schizophrenia compared with control subjects. However, both duration and pitch MMNs were completely unaffected in the first-degree biological relatives and this was also the case for the first-episode patients. Furthermore, length of illness did not predict the extent of MMN deficit.

Conclusions: These findings suggest that the MMN deficit seen in schizophrenia patients is most likely a consequence of the disease and that MMN, at least to basic auditory feature deviants, is at best only weakly endophenotypic for schizophrenia.

Key Words: Endophenotype, event-related potentials, first-degree relatives, first-episode schizophrenia, mismatch negativity, schizophrenia

Schizophrenia is such a devastating disease, in large part because it affects such a widespread realm of brain functions, from higher order cognitive processes such as sustained attention, working memory, and executive functions (1–4) to early and late sensory processes in both the visual (5–9) and the auditory domains (10–12). While plenty of effort has been devoted to understanding the prominent cognitive deficits in schizophrenia, increasingly, more studies have revealed how early sensory dysfunction may also be a valuable predictor of the development of the disease. Among the latter, impairments of early auditory processing, such as the reduction of auditory mismatch negativity (MMN) amplitude in patients with schizophrenia, have attracted particular interest in the literature (for a comprehensive review, see 13). The MMN is an auditory event-related potential (ERP) typically elicited by infrequent deviant events presented in a stream of repetitive events, even in the absence of attention (14), and thus it constitutes an excellent and objective measure of the integrity, or breakdown, of auditory sensory networks. It is easy to measure, requiring no explicit task or attention from the subject, and is so robust that it can even be elicited in coma patients (15).

A central issue in present day research efforts centers on establishing good endophenotypic measures for the development of debilitating mental disorders such as schizophrenia. There is accumulating evidence in the literature that inheritance of some of the genetic liability patterns of schizophrenia is enhanced among unaffected family members of schizophrenia patients, as indicated by mild disruptions of executive functioning, verbal and visual memory, auditory attention, and verbal ability, similar to those found in patients (16–19). Side by side with neuropsychological testing and genetic investigations, event-related potentials represent a simple and effective tool for investigating the neurophysiological processes underlying cognitive and sensory dysfunction in schizophrenia. A number of studies of the P50 and P300 potentials have certainly suggested that auditory dysfunction may be endophenotypic for schizophrenia (20–27). For example, a recent study on electrophysiological measures of auditory processing, as measured in monozygotic twin pairs (20), has shown that impairment in P50 suppression and P300 amplitude and latency are genetically

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transmitted. Additionally, a recent study on early visual processing has shown impaired P1 generation not only in medicated patients with schizophrenia but most strikingly in their clinically unaffected first-degree relatives (28). The decreased P1 wave was found in the absence of any age, gender, or medication effects, strongly suggesting that it is associated with genetic risk for schizophrenia. The P1 deficit appears to be a very promising candidate as an endophenotypic marker for the disorder, and recent work has begun to uncover specific gene variants responsible for this deficit (29).

It is less clear if the MMN can also be used to identify genetic liability to schizophrenia, since only two relatively small family studies have reported reduced MMN in first-degree relatives of schizophrenic patients (30,31), while another much larger study found no differences (32). Nonetheless, given the ubiquity of MMN deficit findings in chronic schizophrenia patients, the MMN has been repeatedly predicted to be a useful candidate endophenotype for schizophrenia (20,33).

The advantage of studying first-degree biological relatives lies in the fact that this population has not developed the disease and yet is more likely to carry the genetic risk for it, and unaffected relatives are not medicated, therefore eliminating the risk of confounding results with the effects of drugs. In the current study, we investigated whether the MMN deficit nearly ubiquitously identified in chronic schizophrenia is also observed in unaffected first-degree biological relatives, to evaluate whether this ERP component represents a promising endophenotypic marker for schizophrenia.

A second goal of this study, which involved a large cohort of chronic schizophrenia patients, was to assess the extent to which MMN deficits are linked to the progression of the disease or whether the deficit is established early in the disease and remains relatively stable thereafter. While recent-onset patients (within 18 months of diagnosis) seem to be predisposed to show an MMN impairment, first-episode schizophrenia patients (within 6 months from first admission) do not appear to show the same deficit (13), suggesting that MMN impairment may occur at a later stage of the disorder. To this end, we also assessed the possible effects of length of illness and of medication status on the degree of degeneration of this ERP component.

Methods and Materials

Participants

The chronic patient group was comprised of 45 individuals (14 female patients; aged 19–63; mean ± SD age = 42.80 ± 12.65 years) with a diagnosis of schizophrenia as defined by DSM-IV criteria (1 patient also had concurrent epilepsy). Length of illness, defined as the time since first hospitalization or presentation to the services, ranged from 1 year to 35 years for this group. Eight were inpatients, and 37 were outpatients. All but 1 of the chronic patients were on antipsychotic medication (23 on atypical, 15 on typical, and 6 on a combination of both) with a mean chlorpromazine equivalent dose of 429.22 mg/day (range 50–1200 mg/day). One chronic patient had ceased taking her medications 3 months prior to testing and was medication-free at the time of testing. Symptom ratings were analyzed using the Brief Psychiatric Rating Scale (BPRS) (34) (mean ± SD score = 37.69 ± 9.98) and the Scale for the Assessment of Negative Symptoms (SANS) (35) (mean ± SD score = 37.39 ± 26.37). Twelve additional first-episode patients, unrelated to the chronic patients, also served in this experiment (3 female patients; aged 17–37 years; mean ± SD age = 24.25 ± 6.17 years). None had any concurrent medical condition. First episode was defined as those patients within 3 months from first diagnosis (i.e., at time of first hospitalization or presentation to the services). Ten of these first-episode patients were inpatients, and two were outpatients. Only one first-episode patient was medicated at time of testing with 300 mg/day of chlorpromazine; all others were drug-naïve. The first-episode patients' mean SANS score was 46.92 ± 11.83, and their mean BPRS score was 38.83 ± 23.66. All patients were free of other medical conditions or substance abuse. Patients were recruited from the St. Vincent's Hospital Catchment Area in Fairview, Dublin, Ireland.

Twenty-four first-degree biological family members (14 female subjects) were also recruited, according to a criterion of a maximum of three unaffected first-degree relatives for each patient (19 families total; 5 first-degree relatives from 4 family members were related to first-episode patients). These were aged 18 to 64 (mean ± SD age = 35.7 ± 15 years). The relatives' group consisted of the parents (n = 7), the siblings (n = 12), or the children (n = 5) of affected individuals meeting DSM-IV criteria for schizophrenia. The control group was comprised of 27 subjects with no family history of psychiatric or neurological disorder (14 female subjects), aged 19 to 64 (mean ± SD age = 38.0 ± 12.9 years). Relatives and control subjects were free of any psychiatric illness or symptoms by self-report using criteria from the Structured Clinical Interview for DSM-III-R–Non-Patient Edition (SCID-NP) (36), and all reported no history of alcohol or substance abuse. None was on any psychotropic medication at the time of testing. Healthy control subjects and first-degree relatives received a modest remuneration of € 40 for their time.

Handedness was determined by the Edinburgh Handedness Inventory (37); six chronic patients, two first-episode patients, five relatives, and five control subjects were left-handed. All subjects reported no hearing impairment and normal or corrected-to-normal vision. The ethics committee at St. Vincent's Hospital approved all procedures and all participants signed a written informed consent after the details of the study were fully explained to them and before participating in the study.

Stimuli and Task

The task comprised one experimental block of 30 minutes duration. A rest was given after the first 15 minutes, and additional rests were given if required by the participants. In total, subjects were presented with approximately 3000 auditory stimuli, of which 2400 (80%) were standard tones of 1000 Hz presented at 50 msec, 300 deviant tones (10%) of 1000 Hz at 25 msec (dev-dur), and 300 deviant tones (10%) of 1200 Hz at 50 msec (dev-hz). The stimulus onset asynchrony was 500 msec.

Stimuli were presented binaurally through headphones (Sennheiser-HD600), while participants were asked to ignore the sounds and watched a black and white Charlie Chaplin movie with no sound.

Data Acquisition

Continuous electroencephalogram (EEG) was acquired through the ActiveTwo Biosemi electrode system from 72 scalp electrodes, digitized at 512 Hz with an open passband from DC to 150 Hz. For analysis and display purposes, data were subsequently filtered with a 0-phase-shift 45 Hz low-pass filter (24 dB/octave) after acquisition. No high-pass filter was applied. With the Biosemi system, every electrode or combination of electrodes can be assigned as the "reference," and this is done purely in software after acquisition. Biosemi replaces the "ground" electrodes used in conventional systems with two

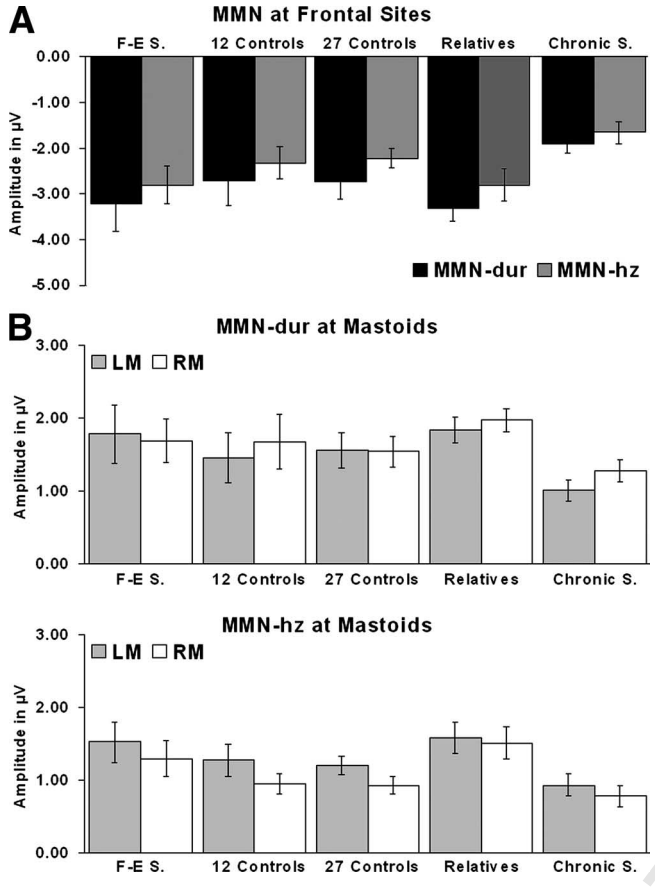

Figure 1. (A) Average amplitudes for the duration and frequency mismatch negativity at seven frontocentral electrode sites. Groups on the x axis are chronic schizophrenia (Chronic S.) patients, first-episode patients (F-E S.), first-degree healthy biological relatives, and healthy control subjects (including a subgroup of 12 age-matched to F-E S.). **(B)** MMN amplitudes at the left (LM) and right (RM) mastoids are plotted illustrating the characteristic polarity inversion of the MMN (i.e., positive values). For illustration purposes, the mastoids data shown were computed from average-referenced data. Amplitudes are in microvolts (μV). Error bars represent standard error of the mean (SEM). Chronic S., chronic schizophrenia patients; F-E S., first-episode schizophrenia patients; LM, left mastoid; MMN, mismatch negativity; MMN-dur, mismatch negativity duration; MMN-hz, mismatch negativity frequency; RM, right mastoid; SEM, standard error of the mean.

separate electrodes: common mode sense (CMS) active electrode and driven right leg (DRL) passive electrode. These two electrodes form a feedback loop, which drives the average potential of the subject (the common mode voltage) as close as possible to the analog-to-digital converter (ADC) reference voltage in the AQ: 4 AQ: 5 AD-box (the ADC reference can be considered as the amplifier "zero"). For a detailed description of the referencing and grounding conventions used by the Biosemi active electrode system, the interested reader is referred to the following website: http://www.biosemi.com/faq/cms&drl.htm. All data were re-referenced to the left mastoid after acquisition, for analysis.

Event-Related Potential Analysis

Data were analyzed using BESA Version 5.1.6 (Brain Electric AQ: 6 Source Analysis) software (www.besa.de). All electrode channels were subjected to an artifact criterion of ±120 μV to reject trials AQ: 7 with excessive electromyograph (EMG) or other artifacts. Blinks and large eye movements were rejected before averaging. Epochs of 200 msec prestimulus to 500 msec poststimulus were analyzed and baseline-corrected relative to the interval −100 to 0 msec. Only the deviants and the standard stimuli that were immediately preceded by standard stimuli were used for averaging. That is, the first standard stimulus following a deviant was excluded from all analyses. The average trial numbers accepted for the standard, dev-dur, and dev-hz, respectively, were for the relatives 1526 ± 214, 254 ± 36, 255 ± 32; for the chronic patients 1507 ± 218, 260 ± 54, 260 ± 60; for the first-episode patients 1525 ± 373, 252 ± 62, 253 ± 64; and for the control group 1521 ± 204, 252 ± 34, 254 ± 33.

We investigated the possibility of reduction of both MMN types (duration and pitch) in clinically unaffected first-degree biological relatives, as well as the integrity of these components in early-stage schizophrenia. Mismatch negativity was defined as the difference waveform obtained by subtracting the standard tone ERPs from the deviant tone ERPs. For each group and for each MMN type, an average MMN amplitude measure was obtained by averaging individual MMN amplitudes over a set of seven frontocentral electrodes (i.e., AFz, Fz, FCz, F1, FC1, F2, and FC2) (Figure 1). Both duration and pitch MMN amplitudes were F1 maximal in the 140 to 180 msec interval (Table 1). T1

The mean amplitude measures from the four groups were submitted to a linear mixed model (LMM) with one fixed factor of group, one random factor of family membership (accounting for the fact that some of our sample of first-degree relatives were related with the patients and with each other), and two covariates (age and gender). In two separate models, mismatch negativity duration (MMN-dur) and mismatch negativity frequency (MMN-hz) mean amplitudes were used as the dependent variable. AQ: 8

Age was used as a covariate, as it differed across groups: chronic patients were older than relatives [$t(38) = 7.15$, $p < .0001$] and first-episode patients [$t(67) = 2.08$, $p < .05$], while first-episode patients were also younger than control subjects [$t(37) = 4.51$, $p < .0001$] and first-degree relatives [$t(33) = 3.24$, $p < .005$]. As covariance for age could potentially remove the effects of chronicity, a secondary analysis using repeated measures analyses of variance (ANOVAs) with group as between-subjects factor, gender as covariate, and the duration and frequency MMN mean amplitudes as within-subject factors, was also performed to compare MMN amplitudes across an aged-matched control subgroup and first-episode patients, aged-matched control and chronic patients group, and aged-matched control and relatives group. For the first-episode patients contrast, the control subgroup consisted of 12 control subjects (6 female subjects) aged 19 to 31 (mean = 26.3 ± 3.9 years). For relatives and chronic patients, the original control group was adequately aged-matched.

Table 1. Mean Amplitude Measures of Frequency and Duration in All Groups and Subgroups Using a Left Mastoid Reference

	MMN-dur (SD)	MMN-hz (SD)
Group		
Control subjects (27)	−2.74 μV (1.98)	−2.22 μV (1.10)
Chronic patients (45)	−1.91 μV (1.35)	−1.66 μV (1.61)
First-degree relatives (24)	−3.33 μV (1.28)	−2.81 μV (1.70)
First-episode patients (12)	−3.21 μV (2.12)	−2.80 μV (1.40)
Subgroup		
Control subjects (12)	−2.71 μV (1.91)	−2.33 μV (1.19)

Mean is calculated as the average of seven frontocentral electrodes. Standard deviations (SD) are in parenthesis. μV is microvolts.

MMN-dur, mismatch negativity duration; MMN-hz, mismatch negativity frequency.

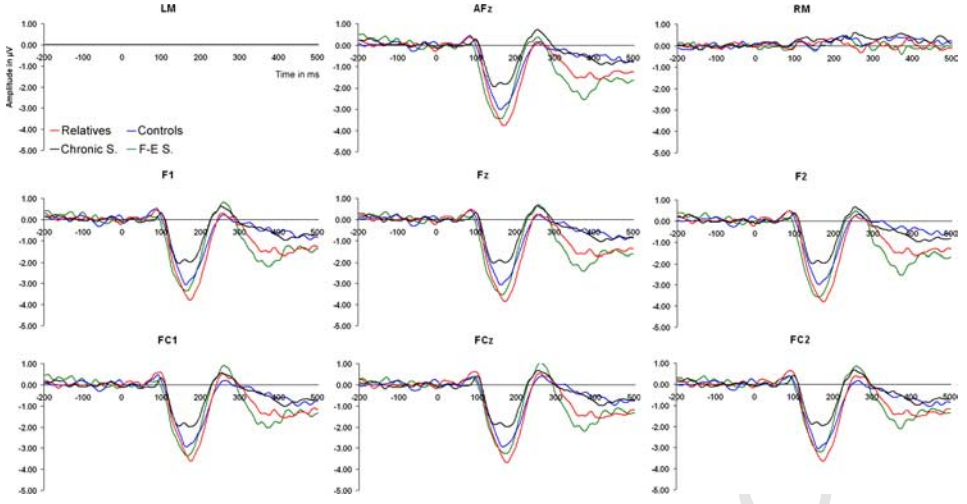

Figure 2. Overview of duration MMN waveforms in all four groups. Data shown at seven representative frontal electrode sites were referenced to the LM. Time is in milliseconds (msec). Amplitudes are in microvolts (μV). Chronic S., chronic schizophrenia patients; F-E S., first-episode schizophrenia patients; LM, left mastoid; MMN, mismatch negativity.

For all analyses, uncorrected pairwise comparison tests (least significant difference [LSD]) were used for significant group effects. All statistical analyses were reported with a significance level of $p < .05$.

Results

F2-3 Figures 2 and 3 show a similar MMN pattern across groups for the first few tens of milliseconds, with changes across group more prominent after 140 msec for both frequency and duration MMN.

The LMM used to compare each mismatch negativity type across the four groups revealed a significant effect of group, both for MMN-dur [$F(3,97) = 4.66$, $p < .005$] and for MMN-hz [$F(3,91) = 4.01$, $p < .01$]. The effect reflected the reduced amplitude of the MMN-dur in the chronic patients (Figure 2) relative to the control group and the other groups. The MMN-hz was reduced in chronic patients (Figure 3) but only compared with the first-degree relatives and to the first-episode patients, but the random effect of familial membership was also significant ($p < .005$) for the MMN-hz, suggesting that this component may vary by familiarity association between patients and first-degree relatives.

The subsidiary ANOVAs comparing MMN amplitudes in the first-episode patients and the subgroup of 12 age-matched control subjects did not show any significant effects, further confirming that MMN was unimpaired in this sample of first-episode patients. The same result was obtained in the contrast between first-degree relatives and control subjects, although the amplitude of the duration MMN was more pronounced than that of the frequency MMN [$F(1,48) = 4.75$, $p < .05$]. A group effect was found in the ANOVA used to compare control subjects and chronic patients, which confirmed that MMN was impaired in the patients [$F(1,69) = 4.36$, $p < .05$]. As for the previous contrast,

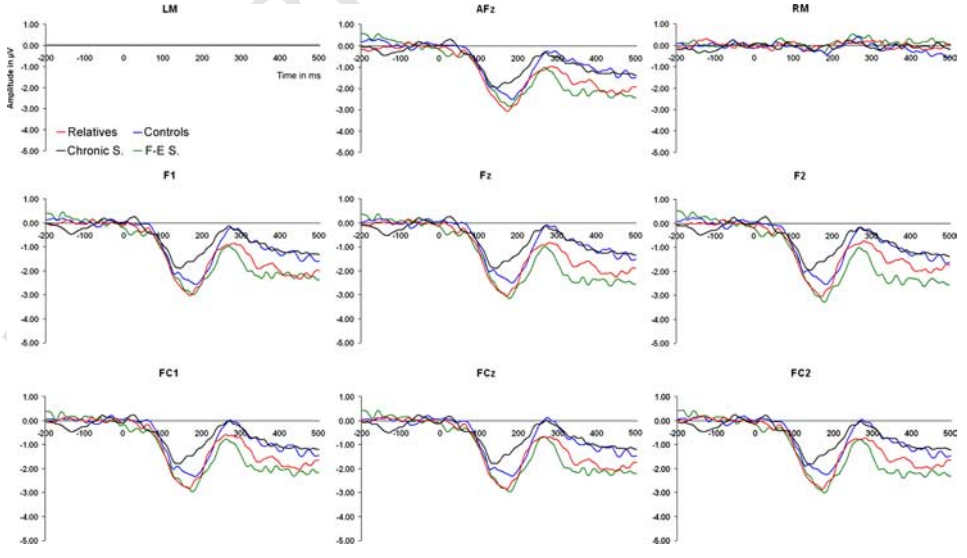

Figure 3. Overview of frequency MMN waveforms in all four groups. Data shown at seven representative frontal electrode sites were referenced to the LM. Time is in milliseconds (msec). Amplitudes are in microvolts (μV). Chronic S., chronic schizophrenia patients; F-E S., first-episode schizophrenia patients; LM, left mastoid; MMN, mismatch negativity.

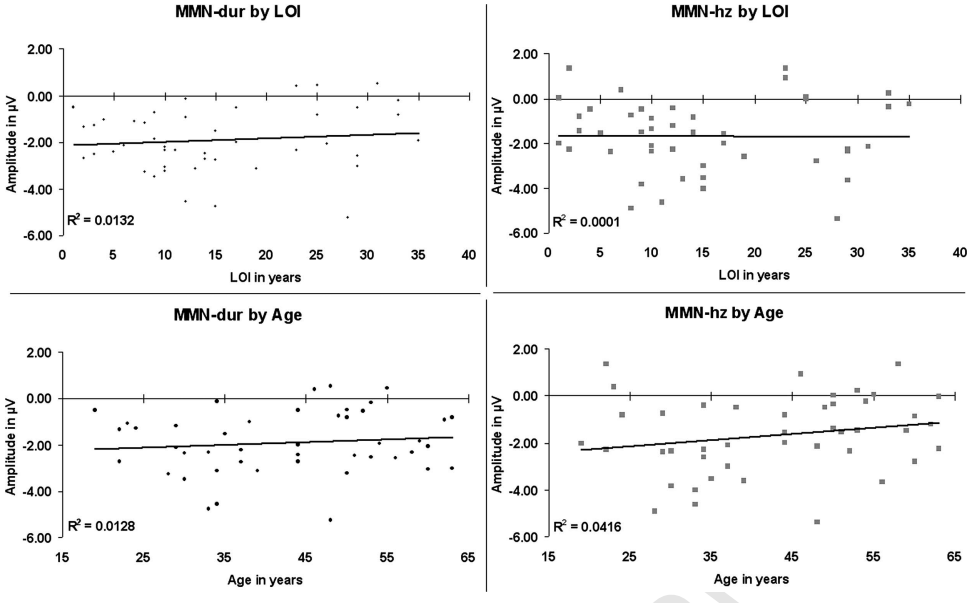

Figure 4. Scatterplots of duration and frequency mismatch negativity amplitude in relation to length of illness and age for the chronic patients group. Amplitudes are in microvolts (μV). LOI, length of illness; MMN-dur, mismatch negativity duration; MMN-hz, mismatch negativity frequency.

MMN-dur was more pronounced than MMN-hz [$F(1,69) = 5.89$, $p < .025$]. Overall, these pairwise contrasts confirmed that MMN amplitude did not differ across the nonchronic populations (Figure 1).

Finally, within-group correlations using amplitudes from MMN-dur and MMN-hz, age, gender, length of illness, and medication (the latter for the chronic group alone) only showed significant positive correlations between MMN-hz and MMN-dur (chronic patients: $r = .60$; control subjects: $r = .58$; relatives: $r = .60$; $p < .01$), clearly suggesting that these have a similar pattern. Interestingly, neither age nor length of illness significantly correlated with MMN amplitudes (max $r = .20$, $p = .18$), as shown in Figure 4. The dosage of antipsychotic also did not significantly correlate with MMN deficit (max $r = .15$, $p = .33$).

Discussion

Recent ERP research has focused increasingly on the identification of possible indices of disposition to schizophrenia (16,18,28). Among the deficits under the lens, the auditory mismatch negativity has generated particularly vigorous research interest, given its generally robust impairment in patients with the disease. Here, we investigated the possibility that the widely reported MMN deficit might also be evident in unaffected first-degree biological relatives of patients showing MMN deficits, which would constitute strong evidence that the deficit is genetically linked rather than a function of the disease process itself. Our results, however, are not consonant with this thesis, as MMN was wholly unaffected in the present population of first-degree relatives. As such, we must conclude that MMN deficits, at least when evoked by very basic feature deviants (pitch and duration), do not represent an optimal endophenotype for schizophrenia. In support of this conclusion, similar negative results were reported by Bramon *et al.* (32) for duration MMNs in a large sample of first-degree relatives ($n = 37$). On the other hand, two other groups have reported evidence for MMN deficits in first-degree relatives. One study reported significant deficits in the frequency MMN, although the number of subjects was relatively small, with just 15 relatives and 16 control subjects participating, and these subjects were not matched for age (30). It is also worth pointing out that the schizophrenia probands in the Jessen *et al.* (30) study, of which there were only 11, showed no difference in MMN when compared with the control subjects, raising questions as to how an MMN deficit in relatives could be considered genetically linked when their ill brethren failed to show the deficit. To our knowledge, only one report to date has shown a significantly reduced duration MMN in first-degree relatives (31). In that study, duration MMNs were studied in 17 relatives, compared with 21 control subjects and 22 chronic patients. Mismatch negativity amplitudes in the relatives were significantly reduced relative to the control subjects and were not significantly different to those of the patients. In a more recent study by the same group, however, duration MMN was not found to be significantly different between first-degree relatives and control subjects in a much larger sample (53 relatives versus 44 control subjects), although the authors do report a trend at an alpha level of .085 (38). Taken together, the results from these studies would appear to be largely consistent in showing that the MMN is, at best, only very weakly endophenotypic.

Results from first-episode patients are also consistent in pointing to a lack of endophenotypy for the MMN. Both Umbricht *et al.* (39) and Salisbury *et al.* (40,41) have reported normal MMN amplitudes in first-episode patients. Here, in our small first-episode sample ($n = 12$), we also find no evidence of a deficit in either the frequency or duration MMN. The consistency of these results across studies must strongly suggest that the duration MMN deficit we did find in the chronic patients is likely tied to the progression of the disease rather than genetic risk factors, as has been previously suggested (39,40). On the other hand, Javitt *et al.* (42) found that MMN generation was impoverished in schizophrenia patients within just 1.5 years of their first episode, so the development of the deficit appears to occur relatively rapidly after the first psychotic episode. An obvious question is whether the MMN deficit worsens over time as the illness progresses or if the deficit establishes itself early in the disease and is constant thereafter. Our results are consistent with the latter position, as we found no significant correlation be-

tween length of illness and MMN amplitude, suggesting that those who were ill longest were similarly impaired to those who had been ill for a relatively shorter period. As such, the data suggest that the MMN deficit in schizophrenia is largely a consequence of the disease but does not appear to worsen substantially during its progression. Confirmation of this proposition will, however, require a longitudinal study. One such study by Salisbury *et al.* (41) has suggested that MMN impairment may index progressive volume reductions in Heschl gyrus, as left Heschl's gyrus reduction correlated with MMN reduction in patients in the early years after first hospitalization, despite the fact that their MMN were of normal amplitude at this time. It is worth reiterating that our first-episode patients were all within 3 months of their first admission, although it is quite possible that some may have had a protracted period between the onset of psychosis and their initial hospitalization. Furthermore, dosage of neuroleptic medication in the chronic patient group did not significantly correlate with MMN deficit, consistent with Michie (43) and with the idea that MMN appears insensitive to standard pharmacological treatment in schizophrenia.

The lack of MMN deficits in our present population of first-degree relatives is also noteworthy because using almost exactly the same cohort of relatives, we have previously shown a robust visual P1 deficit (28). This is an important point because of an inherent risk of selection bias in studies of first-degree relatives. That is, it is entirely plausible that it is the healthier members of a given patient's family that are more likely to remain engaged with the patient over the long term and, hence, are more likely to volunteer for disease-related research. Thus, it could be argued that more robust effects might be seen if an unbiased first-degree group could be sampled. However, the fact that this group has previously shown a strong deficit in their visual evoked potential (VEP), one that appears to be strongly endophenotypic, argues against a selection bias account here. It is also important to point out that even weakly endophenotypic markers for schizophrenia may still prove very useful as elements of a battery of metrics for risk assessment. That is, compilation of a set of measures, some with high sensitivity but low specificity and others with high specificity but low sensitivity, may prove to be an excellent multivariate strategy for assessing risk, a strategy that has already been applied with some success by Price *et al.* (38). It was also noted by a reviewer of this article that the finding of a significant effect of family membership for MMN-hz could well suggest that a deficit in this component may indeed run in schizophrenia families but that it is manifest in only a subset of these families. If so, this might explain some of the inconsistencies in the literature and may point toward a potential subtyping strategy.

It is perhaps curious that chronic patients did not show an MMN deficit relative to control subjects for the pitch deviant but only for the duration deviant, although their pitch MMN was significantly smaller than that of both of the other groups (relatives and first-episode patients). The implication is that duration processing may be significantly more impaired in schizophrenia than pitch processing, a pattern that has also been noted in previous studies (42; see 43 for a comprehensive treatment). Michie *et al.* (31) have suggested that the relatively greater deficit for duration MMN may derive from the fact that duration processing involves more complex neural computations than simple pitch processing. If this thesis is accurate, then one fertile area for future investigation will be in the use of so-called pattern MMNs (44-47). In such studies, MMN can be obtained in healthy control subjects where to identify what is constant across stimuli requires generation of an abstract rule on a preattentive basis. That is, sounds are preattentively grouped and treated as constituting a constancy, not on the basis of their absolute values but in terms of a constant relationship among the sounds. If the more robust deficit in duration MMN relative to frequency MMN is indeed a function of more complex processing, then measures of MMN to abstract patterns, which would certainly involve far more complex processing, would be much more likely to tax the MMN system. The weak findings regarding endophenotypy for duration MMN might well be amplified using such an approach. Of course, the use of a more complex task to elicit the MMN will also likely invoke different underlying physiological mechanisms to those of the basic MMN, which might, in turn, be further removed from specific susceptibility genes than a simple pitch or duration MMN.

Conclusions

The present study confirms previous findings in the literature of a deficient duration MMN in patients with chronic schizophrenia. Moreover, the current results offer evidence in support of the notion that MMN alone is not a strong endophenotypic marker for schizophrenia, since it is wholly unimpaired in first-degree relatives. Rather, the deficit in this component appears to arise as a consequence of the illness rather than representing a premorbid symptom of it, a contention also supported by the lack of MMN deficits in first-episode patients. The data suggest that visual sensory processing deficits may provide more fertile ground for the development of diagnostic measures than the far more studied auditory system, although efforts to combine multiple endophenotypic markers across sensory modalities may represent the best strategy for future development.

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AQ1— Please provide name and location of manufacturer.

AQ2— Please provide name and location of manufacturer.

AQ3— Please spell out DC.

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AQ7— Is EMG spelled out correctly?

AQ8— Are MMN-dur and MMN-hz spelled out correctly?