What has MMN revealed about the auditory system in schizophrenia?

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Abstract

Evidence that deficits in early auditory processing occur in schizophrenia was first provided by an ERP study demonstrating that mismatch negativity (MMN) to duration increments is reduced in medicated patients. Our subsequent research, which is reviewed in this paper, demonstrates that duration MMN reduction cannot be attributed to neuroleptic medication, and is specific to schizophrenia. It is not dependent upon the nature of the task used to distract attention away from the auditory modality. Most importantly, a reduced duration MMN in schizophrenia is a replicable result, having been observed in multiple independently-selected groups of patients from two separate laboratories. It also occurs in unaffected first-degree relatives of patients, suggesting that it may be a vulnerability marker of the disorder. The most intriguing questions however, relate to what underpins the reduced MMN to duration increments in schizophrenia and therefore, what it reveals about the nature of the auditory system deficit in this disorder. Three hypotheses are considered here: a pervasive problem in auditory sensory memory; a specific impairment in duration processing; or an abnormality within the window of temporal integration, coincident with the early phase of auditory sensory memory. Our data so far offer preliminary support for the third hypothesis only, although the possibility of a more broadly defined deficit in temporal processing restricted to brief or rapidly-presented auditory stimuli is canvassed. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Mismatch negativity (MMN); Schizophrenia; Auditory sensory memory; Duration processing; Temporal window of integration

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1. Introduction

Schizophrenia is a debilitating disorder affecting approximately 0.5% of the Australian population (Jablensky et al., 1999), a figure that is comparable with the outcome of epidemiological studies in many other populations (Jablensky et al., 1992). It is associated with increased morbidity and mortality, substantial socio-economic costs to the individual and society and marked impairment in social functioning. Schizophrenia is characterised by a range of signs and symptoms which are often categorised as falling into two classes: positive symptoms such as hallucinations, delusions, thought disorder and bizarre behaviour and negative symptoms which include flat affect, alogia, avolition and anhedonia (Crow, 1980).

There has been increasing recognition in recent years that in addition to the behavioural signs and experiential symptoms of the disorder, patients with schizophrenia also exhibit cognitive impairments in a number of domains: attention; memory and executive functions. Furthermore, these cognitive impairments are proving to be a fundamental feature of the psychopathology of schizophrenia and in this respect, as important in characterising the disorder as the range of clinical signs and symptoms. It is also becoming increasingly evident that neurocognitive deficits have considerable impact on the daily lives of patients by restricting their functional capacity and contributing in a major way to their social disability. It has been argued that these deficits are more strongly predictive of functional outcome than psychotic symptoms and in many instances, negative symptoms as well (Green, 1996). However, this assertion is somewhat controversial with a number of influential studies demonstrating a relationship between functional outcome and symptoms but not cognitive deficits (Norman et al., 1999). Conventional neuroleptics do not usually have a major impact on neurocognitive deficits despite pronounced effects on psychotic symptoms. While atypical antipsychotics are more effective in ameliorating cognitive impairments, residual impairments remain (Keefe et al., 1999).

The goal of the research reviewed in this paper is to investigate the brain mechanisms that underpin at least some of the cognitive deficits exhibited by patients with schizophrenia in order to obtain a better understanding of the pathophysiology of the disorder. Currently, assessments of cognitive deficits play no role in the choice of therapeutic options for patients. It is foreseeable that further advances in treatment of this debilitating disorder may be achieved with a shift from treatments targeting symptoms to treatments targeting the underlying pathophysiology. The research to be reviewed began in the late 1980s in Sydney as part of a joint research program carried out by the Biological Schizophrenia Research Team (BSRT) based at Prince of Wales Hospital, Sydney. This research utilised electrophysiological measures of brain function, namely, brain event-related potentials (ERPs), to investigate early auditory processing in schizophrenia. The particular ERP that has been the focus of continuing research over the ensuing years and the subject of this rather selective review is the mismatch negativity (MMN), first reported by Näätänen et al. (1978).

MMN is a negative component of the event-related potential (ERP) which is elicited by any discriminable change (Näätänen and Tiitinen, 1998) in a repetitive background of auditory stimulation (Winkler et al., 1996). It is typically recorded from sequences of auditory stimuli in which low probability deviant sounds are interspersed amongst frequent standard sounds while the subject’s attention is directed elsewhere, by requiring them to read a book (Sams et al., 1985), carry out a visual task (Alho, 1992) or watch a video of choice (Kraus et al., 1996). MMN has been reported for deviants on a variety of auditory dimensions: frequency (Sams et al., 1985), intensity (Näätänen et al., 1978), duration (Näätänen et al., 1989), spatial location (Paavilainen et al., 1989) and more complex stimulus features, such as temporal information (Tervaniemi et al., 1994), phonemes (Aaltonen et al., 1987) and spectrotemporal patterns (Schroger

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1 The chief investigators of the Biological Schizophrenia Research Team were Neil McConaghy, Stanley Catts, Philip Ward, Sally Andrews and Pat Michie.
et al., 1992). As MMN does not rely on attention to or detection of the deviant stimuli, it has been characterised as an automatic or pre-attentive brain response (although there is some debate about the extent of the attention-independence of MMN (Alain et al., 1994; Näätänen et al., 1993b; Woldorff et al., 1991). Theorising about the functional role of MMN in auditory cognition has emphasised processes that encode a representation of previous stimuli in auditory sensory memory (Näätänen, 1990; Näätänen et al., 1993a) and in particular in the so-called ‘long’ sensory store (Cowan, 1988) which persists for approximately 10 s.

Recognition that schizophrenia is associated with a deficit in early auditory processing first emerged from evidence based on the mismatch negativity (Shelley et al., 1991). In this study, MMN to duration deviants was recorded in eleven medicated patients with a DSM-III-R diagnosis of schizophrenia and eleven age and sex-matched controls. MMN to both duration increments and

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**Fig. 1.** Grand average MMN difference waveforms at the Fz site obtained by subtracting the ERP to standard stimuli short or long from the ERP to deviant stimuli long and short, respectively. MMNs to long duration diviations (duration increments) for patients (thin trace) and age and sex-matched controls (thick trace) are shown in the left column, MMN to short duration diviations (duration decrements) in the right column. Data on medicated patients with a diagnosis of schizophrenia are shown in the top row, on unmedicated schizophrenia patients in the middle row and bipolar patients in the bottom row. Negativity is plotted up. (Adapted from Catts et al., Brain potential evidence for an auditory sensory memory deficit in schizophrenia, 152, 213–219, 1995. Copyright 1995, the American Psychiatric Association. Reprinted with permission).
duration decrements was recorded in separate runs using two tone durations of 50 ms and 100 ms. For each condition, the stimulus onset asynchrony was 510 ms, the probability of the deviant duration was 10% and all tones were 633 Hz, 80 dB SPL with a 10-ms rise and fall. Participants’ attention was directed away from the sound stimuli by asking them to carry out a simple visual discrimination task. MMN to duration increments (50 ms standard, 100 ms deviant) was significantly smaller in patients than in controls, whereas MMN to duration decrements, although clearly showing a similar trend, did not differ significantly in the two groups (see top section of Fig. 1). This was the first published report showing that MMN was reduced in schizophrenia and consistent with the prevailing view of MMN at the time, was interpreted as reflecting an impairment in early pre-attentive auditory processing in schizophrenia (Shelley et al., 1991). Such a deficit was seen as also potentially underlying previously observed deficits in controlled attention, such as those indexed by processing negativity and P3 amplitude reductions in patients (Michie et al., 1990; Ward et al., 1991) in complex selective attention tasks.

The subsequent research reviewed here is grouped into three sections which address three separate questions about duration MMN in schizophrenia:

- How robust is the reduction? Is it affected by medication, is it specific to schizophrenia and does it occur in at-risk individuals?
- Under what circumstances does it occur? Is the reduction affected by the nature of the distractor task?
- What does it reflect: a generalised deficit in sensory memory, a deficit in temporal processing (e.g. duration) or some other factor?

2. Robustness of the duration MMN reduction in schizophrenia

A second study conducted by the BSRT (Catts et al., 1995) explored whether the reduction in duration MMN was due to the medicated status of the patients in the first study (Shelley et al., 1991) by assessing a group of neuroleptic-free patients and in addition, examined the specificity of the finding by including patients with a bipolar affective disorder. There were eleven unmedicated patients with a DSM-III-R diagnosis of schizophrenia and eleven patients with a bipolar affective disorder, all of whom, except one, were medicated. As the bipolar group of patients were older and included more females than the schizophrenia group, separate age and sex-matched control groups were recruited for each patient group. In all other respects, the design in terms of stimulus characteristics was identical to the Shelley et al. (1991) study. The outcome of this study was that the unmedicated patients showed virtually the same degree of MMN reduction to a duration increment as the medicated patients (see middle row of Fig. 1) whereas the bipolar patients (bottom row of Fig. 1) showed no evidence of a MMN reduction to either duration deviant relative to their matched controls. Therefore, the evidence indicates that MMN reduction to a duration increment in schizophrenia cannot be attributed to neuroleptic medication and is not a consequence of having a serious psychiatric condition, although the question of specificity to schizophrenia must await assessment of patients with other disorders. Furthermore, it seems that the duration increment condition discriminates better between patients with schizophrenia and healthy controls than the duration decrement condition despite the fact that the short and long duration stimuli in the two conditions were identical (50 ms vs. 100 ms). The reasons for this pattern are unclear, although inspection of Fig. 1 suggests that duration decrements produce a smaller MMN in healthy controls and therefore, the insensitivity of this condition may simply be due to floor effects.

A current popular strategy in investigations of neurocognitive impairments in schizophrenia is to study populations at genetic risk for schizophrenia, namely first degree relatives of patients with a schizophrenia diagnosis (Michie et al., 2000b). The major goal of this research has been to find evidence of neurocognitive deficits in unaffected
first degree relatives which may be markers of vulnerability or predisposition to the disorder. An additional benefit is that if deficits are found in first degree relatives that parallel those found in patients, they cannot be attributed to the effects of medication and illness. This strategy has been adopted in a large family study currently underway at the Centre for Clinical Research in Neuropsychiatry at Graylands Hospital in Perth. A range of neurocognitive and electrophysiological measures are obtained from patients and their first degree relatives and from a group of healthy control individuals. MMN to duration increments are measured as part of the protocol, using stimulus characteristics identical to the Shelley et al. (1991) study.

Preliminary data from 16 medicated patients with a diagnosis in the schizophrenia spectrum (DSM-III-R diagnosis of either schizophrenia or schizo-affective disorder), 15 unaffected first-degree relatives of patients with diagnoses in the schizophrenia spectrum and 20 healthy controls, demonstrated that unaffected first degree relatives also exhibit a reduced MMN to duration increments.

Fig. 2. Grand average MMN waveforms at the midline Fz, Cz and Pz sites to duration increments. On the left, a comparison of first degree relatives of patients (thin trace) with a diagnosis in the schizophrenia spectrum and healthy controls (thick trace), in the middle, a comparison of patients (thin trace) and controls (thick trace) and on the right, a comparison of first degree relatives and patients.
increments (Michie et al., in preparation). In Fig. 2, MMN reduction in first degree relatives is substantial (left column) and almost as marked as the reduction in patients (middle column). In fact, there is little difference in MMN amplitude between patients and first degree relatives at frontal and central midline sites (right column). However, some caution must be exercised in interpreting these data since the three samples are not well matched on age and sex, a consequence of the procedure for recruiting patients and family members into the study, which was based on consecutive admissions to a large psychiatric facility. Furthermore, recruitment into the project was determined not only by whether the patient was willing to participate in the project but also their first degree relatives. There is an imbalance in the sex and age of the three groups: the patients were predominantly male (15 males, 1 female) with a mean age of 32 years (range 20–53 years). There were approximately equal numbers of males and females in the first degree relative group (7 males, 8 females) and they were older, with a mean age of 44 years (range 21–67 years) due to the inclusion of some parents in addition to siblings. The healthy controls were primarily males (14 males, 6 females) and were younger than the relatives, with a mean age of 33 years (range 18–52). Analysis of covariance was used to determine whether the differences evident in Fig. 2 were robust after adjusting for sex and age between the three groups. Using mean amplitude over the interval from 135–205 ms as the measure of MMN amplitude, controls had a significantly larger MMN than patients after adjusting for age and relatives after adjusting for sex and age. Consistently, age did not correlate with MMN amplitude in any group. Therefore, the outcome suggests that MMN to a duration increment is reduced not only in patients but also in first degree relatives, suggesting the MMN may well be a vulnerability marker of schizophrenia. The finding clearly needs replication in samples matched on relevant variables.

In terms of the first major question about duration MMN addressed in this review, namely, how robust is the finding of duration MMN reduction in schizophrenia, the evidence presented in this section is that it is a very replicable finding: it has been observed in independently selected samples, in both medicated and unmedicated patients with a diagnosis of schizophrenia or in the schizophrenia spectrum; and in unaffected first degree relatives. In contrast, it was not seen in a group of patients with a bipolar affective disorder.

3. The effect of distractor task on MMN reduction in schizophrenia

While there is some controversy still about whether MMN is or is not affected by attention, concerns about whether the MMN amplitude difference between patients and controls can be attributed to different attentional strategies have been raised (Alain et al., 1998; Kasai et al., 1999; Oades et al., 1997). Over the last ten years, we have used a variety of distractor tasks from a simple visual discrimination task (Catts et al., 1995; Shelley et al., 1991), to watching a nature video (Michie et al., 2000a), watching an action video in order to answer prespecified questions (Todd et al., 2000, see Fig. 5) or carrying out a complex auditory selective attention task (Michie et al., in preparation). The outcome is the same no matter what sort of distractor task was employed: patients generate a reduced MMN to duration increments in comparison with healthy controls.

MMN data derived from the complex auditory selective attention task experiment are shown in Fig. 3. The task was based on the multidimensional auditory selective attention task first reported by Hansen and Hillyard (1983) and used to study the nature of selective attention deficits in patients with schizophrenia (Michie et al., 1990; Ward et al., 1991). Twenty unmedicated patients and twenty age- and sex-matched healthy controls listened to rapidly presented tone pips (SOA between 200–500 ms) presented at random to the left and right ear. Half the tone pips in each ear were of high pitch and the remainder of low pitch. Subjects were instructed to pay attention to a particular combination of ear and pitch (e.g.
high pitched tones in the left ear) and press a button when they detected an infrequently occurring target tone \((P = 0.07)\) of longer duration (100 vs. 50 ms). All of the behavioural evidence suggested that while patients found this to be a very demanding task, they found it difficult for the same reasons as controls, since the distribution of their errors was virtually identical in the two groups (Michie et al., 1990).

MMN to duration deviants in the sequence of tone pips sharing neither ear of delivery nor pitch attributes with the attended source (e.g. low pitched tones in the right ear when the attended source was high pitched tones in the left ear) were extracted by subtracting the ERPs to standard tones of 50 ms from ERPs to deviants of 100 ms duration. MMN at frontal and central midline and lateral sites is shown in Fig. 3. Inspection of this figure demonstrates that duration MMN was reduced in patients relative to age and sex matched controls. What is also evident is that the morphology of MMN is virtually identical in these data to the previous figures derived from simpler visual distractor tasks. In all instances, duration MMN shows two peaks, one at approximately 120 ms and a second at approximately 200 ms. These two peaks are most clearly visible in patient data. In control data, the earlier peak is often only evident as a notch on the negative going portion of the MMN waveform. Further research is needed to determine the contributions of exogenous components, such as N1 and P2, to these two peaks. The only difference between the data in Fig. 3 and the previous two figures is the smaller peak amplitude of duration MMN in the complex auditory selective attention task that may
be due to faster overall delivery rate (greater density of auditory stimuli) or the irregular delivery rate.

4. What does MMN reduction in schizophrenia tell us about the nature of the auditory system deficit in schizophrenia?

We have investigated three hypotheses about the nature of the deficit in auditory system functioning reflected in the reduction of duration MMN in schizophrenia. The first is that the reduction in duration MMN is part of a pervasive problem in auditory sensory memory functioning in schizophrenia, the second is that patients have particular difficulties in processing the temporal features of stimuli and the third is that the reduced duration MMN is due to an abnormal window of temporal integration. While the evidence supporting or refuting each of these hypotheses is still being accrued, the balance of evidence currently supports the third hypothesis, although a broadly-defined temporal processing deficit might ultimately provide a better account of the problem.

As noted earlier, recent theorising about MMN has drawn attention to the reliance of MMN generation on the integrity of auditory sensory memory (Naätänen, 1990, 1992) and in particular on the so-called ‘long’ sensory store (Cowan, 1988) which persists for approximately 10 s. Therefore, demonstrations of MMN reduction in schizophrenia have been interpreted as reflecting an overall impairment of auditory or ‘echoic’ sensory memory (Catts et al., 1995; Javitt et al., 1995, 1993, 1998). If it is the case that reduced MMN is a reflection of a generalised impairment of auditory–sensory memory functioning, the implications of such a deficit for the patient’s perceptual experience are profound. Cowan (1984, 1988) has summarised various studies suggesting that there are two phases of auditory–sensory memory with very different properties: a brief literal sensory store or window of temporal integration lasting 200–300 ms and a longer-lasting phase of more perceptually resolved information which is preserved for up to 10 or 20 s. Cowan (1995a, 1995b) argues for two fundamental uses of sensory memory, to which both phases may contribute. The first is temporary storage of sensory information. He notes that environmental stimuli, particularly auditory stimuli, are transitory in nature. It is therefore, essential for the nervous system to retain enough of the original sensory information for a short period of time in order for information to be extracted and decisions made about where attention should be directed. The second function is to support the persistence of information arising from one stimulus to the next in order to allow integration of stimuli across time and to prevent perceptual fragmentation. Therefore, on the basis of Cowan’s model, a generalised impairment in auditory sensory memory should give rise to very substantial perceptual and attentional disturbances.

In order to investigate whether the reduction in duration MMN is part of a more pervasive problem in auditory–sensory memory in schizophrenia, we examined whether those patients who show a reduced duration MMN also exhibit reduced MMN to other attributes, such as frequency (Michie et al., 2000a). While the original demonstration of a reduced duration MMN by Shelley et al. (1991) was subsequently replicated for both duration (Catts et al., 1995; Kasai et al., 1999; Lembreghts and Timsit-Berthier, 1993) and frequency MMN (Alain et al., 1998; Hirayasu et al., 1998; Javitt et al., 1993, 1995; Kreitschmann-Andermahr et al., 1999; Oades et al., 1996, 1997; Shelley et al., 1999; Umbricht et al., 1998), there are two studies where a reduction in frequency MMN in patients with schizophrenia was not found (Kathmann et al., 1995; O’Donnell et al., 1994). However, there was a feature common to these two studies which distinguished them from most earlier investigations in which a reduction of frequency MMN in patients with schizophrenia was observed. They used substantially larger frequency differences between standards and deviants (1000 vs. 1500 Hz for O’Donnell et al., 1994; 600 vs. 1000 Hz for Kathmann et al., 1995) than those studies that reported reduced frequency MMN (e.g. 1000 Hz and 1024 Hz for Javitt et al., 1993, 1995). There is one exception to this pattern: Oades and his colleagues (Oades et al., 1996, 1997) employed
a large frequency difference (800 vs. 2000 Hz) and consistently found that MMN is reduced in patients, but even in this instance, Oades et al. (1997) notes that when MMN was measured around the N1 latency range, which is roughly equivalent to the range used by O’Donnell et al. (1994), Kathmann et al. (1995), patients did not differ significantly from controls. MMN measured around the N2 latency range, however, was significantly reduced in patients, particularly in an active listening paradigm. Therefore, the lack of an early latency MMN reduction in these three studies could be a reflection of the fact that the reduced frequency MMN in schizophrenia, particularly in passive listening conditions, is a rather subtle effect that is only evident for relatively small deviant differences. In order to investigate this possibility as opposed to the proposal that there is a general deficit in the generation of MMN, MMN amplitudes to both small and large frequency deviants as well as a duration increment deviant were compared (Michie et al., 2000a).

MMN data from fourteen medicated patients and seventeen healthy control volunteers of similar age and sex distribution were available from three deviant conditions where the standard was a 633 Hz, 85 dB SPL tone of 50 ms, with an SOA of 510 ms in each case: a duration deviant condition of 100 ms; a small frequency deviant condition of 700 Hz (11% difference in frequency); and a large frequency deviant condition of 1000 Hz.

![MMN waveforms](Fig_4.png)  
Fig. 4. Grand average MMN waveforms at the midline Fz and Cz sites from patients (thin trace) and age and sex-matched controls to deviants that were duration increments (100 ms deviant, 50 ms standard) in the left column, or small frequency deviants (700 Hz deviant, 633 Hz standard) in the middle column or large frequency deviants (1000 Hz deviant, 633 Hz standard) in the right column (Reprinted from Clinical Neurophysiology, 111, Michie, Budd, Todd, Rock, Wichmann, Box, & Jablensky, Duration and frequency mismatch negativity in schizophrenia. 1054–1065. Copyright (2000) with permission from Elsevier Science).
(60% difference in frequency). Only duration MMN was significantly reduced in patients relative to controls (see Fig. 4), although there was a trend for MMN amplitude to be smaller to the large frequency deviant as well. In patients, duration MMN amplitude was unrelated to either large frequency MMN amplitude \( r = 0.12 \) or small frequency MMN amplitude \( r = 0.33 \) but, in controls, was highly correlated with large and small frequency MMN \( r = 0.62 \) and 0.57, suggesting that duration MMN is relatively independent of frequency MMN in patients. As the available evidence suggests that the supratemporal generators of duration and frequency MMN have distinct locations Frodl-Bauch et al., 1997; Giard et al., 1995, an anatomical basis for such a dissociation between duration and frequency MMN in patients exists.

It can be seen that the results did not provide strong support for the notion that there is a generalised impairment in auditory–sensory memory in schizophrenia. Although there was a trend for large frequency MMN to be reduced in patients, large frequency MMN in patients was remarkable because of its substantial magnitude (4 /pi 114 V). Clearly patients’ auditory systems are capable of generating a robust mismatch response to some deviant sounds, such as frequency, but at the same time generating a minimal response to sounds that are deviant in duration. This result is suggestive of a specific deficit in processing the temporal properties of sound rather than a more pervasive problem in sensory memory. However, it should be noted that some aspects of these findings conflict with data from Javitt’s group (Javitt et al., 1998) showing that the degree of frequency MMN attenuation in schizophrenia is largest under conditions in which MMN is normally largest. On the basis of Javitt’s findings, one would have expected MMN attenuation to be substantial for the large frequency conditions. A review of the recent frequency MMN literature in schizophrenia by Michie et al. (2000a) revealed that short SOAs of < 300 ms are more likely to produce reduced frequency MMNs in patients than long SOAs, suggesting a differential deficit in frequency processing with rapid delivery rates. It turns out that there is evidence of separate networks in auditory cortex underpinning rapid and slow temporal processing of non-speech sounds (Griffiths et al., 1997), so once again, an anatomical basis for such a differential deficit in patients for fast as opposed to a slow delivery rate, does exist.

Since there was not strong evidence that a pervasive deficit in sensory memory underpins the reduction in duration MMN, we then examined the second hypothesis outlined previously, namely, that patients have particular difficulties in processing the temporal features of stimuli and in particular duration. Previous research by Rammsayer (1990) has shown that patients exhibit temporal discrimination deficits in psychophysical tasks using similar intervals to those used in duration MMN studies to date. Rammsayer’s task was designed to determine the smallest increment in a 50-ms silent interval (demarcated by clicks) that participants could reliably detect on 70.7% of the trials. Patients with schizophrenia required significantly longer intervals to perform equivalently to controls. However, Rammsayer’s task required judgements about the duration of empty intervals, whereas duration MMN is derived from differences in the duration of filled intervals. In order to determine whether patients who have a reduced MMN also show deficits in temporal discrimination, duration discrimination thresholds and MMN to a duration increment were investigated (Todd et al., 2000) in 21 medicated patients and 25 healthy controls matched on age, sex and NART (National Adult Reading Test; Nelson and Willison, 1991), the latter providing an estimate of premorbid IQ. Two psychophysical measures of temporal discrimination thresholds were obtained. The first task measured the smallest increment in a 50-ms tone (i.e. a filled interval task) that the participant could detect on 70.7% of trials. The second task determined the smallest gap in milliseconds that could be detected in a 150-ms white noise burst. This gap estimate is thought to represent the limit of temporal resolution in the auditory system (Snell et al., 1994). Duration MMN was measured using identical stimulus parameters to the duration increment condition of Shelley et al. (1991).

Todd et al. (2000) found that MMN amplitude
to a duration increment was significantly reduced in this group of patients (see Fig. 5) even though the duration increment (100 vs. 50 ms) used to generate MMN was well above the duration discrimination threshold (see Fig. 6) for every patient tested. There were some patients ($N = 3$) who had very prolonged filled interval duration discrimination thresholds (Fig. 6), however, overall there were no significant differences between the patients and controls in behavioural estimates of duration discrimination. These outliers in terms of duration discrimination thresholds had MMN amplitudes that were indistinguishable from other patients and certainly could not explain the overall reduction in the patient MMN amplitude. This finding was surprising given that accumulating evidence supports a common underlying representation of stimulus properties subserving both the MMN comparison process and behavioural discrimination (Schröger, 1997). There was also no evidence that estimates of gap detection thresholds were prolonged in patients (although there was one outlier) suggesting that in general, the temporal resolution of the auditory system is unaffected in schizophrenia. There remains the possibility that there are a subset of patients who do have difficulties in temporal extent judgements (the outliers on the psychophysical tasks) and that a larger or different sample of patients might reveal more substantial numbers with this prob-

![Grand average MMN waveforms at all scalp sites from patients (thin trace) and age, sex and NART-matched controls (thick trace) to duration increments. Scalp sites are re-referenced to mastoids. Mastoids are referenced to nose and show the expected phase reversal of MMN. (Reprinted from Psychiatry Research, 96, Todd, Michie, Budd, Rock & Jablensky, Auditory sensory memory in schizophrenia: Inadequate trace formation? 99–115, Copyright (2000), with permission from Elsevier Science).](image-url)
lem. However, the data suggest that reduced duration MMN is observed in patients who do not show significant duration discrimination impairments and are not strongly supportive of the proposal that reduced duration MMN in patients can be attributed to a problem in processing temporal features as measured here.

This leaves the third and possibly most interesting suggestion. The duration increment deviants, that have been employed in all of the studies reviewed so far, will not only be perceived as longer in duration than the standards but will also be perceived as louder. This is because of the phenomenon of temporal summation or integration of acoustic energy that occurs over the first 200 ms of a sound, sometimes referred to as the window of temporal integration (Näätänen, 1992). This period also coincides with Cowan’s early phase of auditory sensory memory (Cowan, 1984). Psychophysical studies show that because of this temporal summation effect, a 100-ms tone will sound approximately 3 dB louder than a 50-ms tone. Therefore, 100-ms deviants interspersed between 50-ms standards are in fact double deviants: they are longer and louder. Hence, reduced duration MMN in patients could be due to a problem in this early window of temporal integration. This possibility has been tested in two ways: by investigating the N1 component of the auditory ERP to tones separated by short SOAs (Todd et al., 2000) and by measuring duration MMNs to stimuli that fall outside this window of temporal integration (Johnston et al., in preparation).

The N1 component of auditory ERPs, in addition to being responsive to transient changes in auditory stimulation, is exquisitely sensitive to the temporal properties of stimulus presentation. It has been well known for some time that N1 increases in amplitude in an exponential fashion for SOAs between 500 ms and 10 s (Näätänen and Picton, 1987), a time course that is similar to the second phase of auditory sensory memory distinguished by Cowan (Lu et al., 1992). What is not so well known is that for SOAs shorter than 500 ms, N1 increases again. That is, when two stimuli are separated by SOAs < 300 ms, N1 to the second tone is enhanced (Loveless et al.,

![Image](image_url)

**Fig. 6.** Distribution of 70.7% thresholds for patients and controls for duration discrimination thresholds (Δd) relative to a base of 50 ms and a gap threshold (Δg) for detecting a gap in a 150-ms noise burst. X: mean thresholds. †: outliers (more than 2 standard deviants above the mean). (Reprinted from Psychiatry Research, 96, Todd, Michie, Budd, Rock & Jablensky, Auditory sensory memory in schizophrenia: Inadequate trace formation? 99–115, Copyright (2000), with permission from Elsevier Science).
enhancement is maximal for SOAs of approximately 100 ms and declines to a minimum by 400 ms. Budd and Michie (1994) proposed that the N1 enhancements at brief interstimulus intervals reflect a process of temporal integration of auditory–sensory information over a time period that coincides with the earlier phase of auditory–sensory memory distinguished by Cowan. Budd (2000) has provided further evidence strengthening the link between the window of temporal integration and N1 activity that is enhanced at SOAs < 300 ms.

In addition to exploring the issue of whether duration MMN in patients is due to impairments in processing the temporal features of sounds, Todd et al. (2000) examined the pattern of N1 amplitudes over a range of SOAs in the same group of patients. The procedures were identical to Budd and Michie (1994): 4000 binaural tones (1 kHz, 70 dB SPL, 50 ms duration with 10 ms rise and fall time) were presented at random SOAs between 50 and 1050 ms. ERPs were created based on the SOA between the current stimulus and the preceding stimulus resulting in 10 subaverages, each based on 100 ms wide SOA window, namely, 50–150, 150–250, 250–350 ms, etc., up to 950–1050 ms, which were then corrected for response overlap (particularly at the shorter SOA ranges) using a level 1 ADJAR procedure (Woldorff, 1993). Todd et al. (2000) found that while patients showed facilitation of N1 at short SOAs, their pattern differed from controls in showing a slower rate of change over the range from 50 to 250 ms (see Fig. 7), particularly at the Cz site. These results are consistent

Fig. 7. Left: plot of the N1/SOA function at Fz and Cz sites for patients (broken line) and controls (solid line). Shaded regions depict the region corresponding to the early phase of auditory sensory memory. Error bars: ± S.E. Right: N1 responses at Fz and Cz sites for the 50–150 ms SOA and 150–250 ms SOA range for patients (thin line) and controls (thick line). (Reprinted from Psychiatry Research, 96, Todd, Michie, Budd, Rock & Jablensky, Auditory sensory memory in schizophrenia: Inadequate trace formation? 99–115, Copyright (2000), with permission from Elsevier Science).
with problems in the window of temporal integration occurring over the early phase of auditory–sensory memory. Furthermore, the amplitude of N1 at the shortest SOA interval (50–150 ms) was highly correlated with MMN amplitude to duration increments in controls, however, this was not the case in patients, consistent with an interpretation that temporal summation of acoustic energy measured by N1 facilitation at 50–150 ms SOA did not contribute to the amplitude of duration MMN in patients. These results are consistent with the third proposal outlined at the beginning of this section, namely, that reduced duration MMN in patients is due to abnormalities occurring within the window of temporal integration.

Further support for this third proposition is evident from very preliminary data collected by Johnston et al. in our laboratory, in which MMN to duration increments was compared in patients and controls for tone durations outside the window of temporal integration. Two MMN paradigms were employed: a long-duration condition in which standard tones were 300 ms and deviant tones were 550 ms; and a short-duration condition which was identical to all of the duration increment paradigms described previously, that is, standard and deviants of 50 and 100 ms, respectively. The choice of duration values for the long condition stimuli was based on pilot data from healthy controls demonstrating that the duration increment discrimination threshold was on the average 25 ms for a 300-ms tone and 5 ms for a 50-ms tone. An attempt was made to match the deviant–standard differences in the two conditions in terms of discriminability. A comparison of patients ($N = 17$) with age, sex and NART-matched controls ($N = 14$) demonstrated that for mastoid re-referenced data, there is no difference between patients and controls in the MMNs generated to duration deviants in the long condition despite the fact that the same group of patients show the expected reduction in duration MMN in the short condition. These preliminary results indicated that reduced duration MMN is restricted to short duration stimuli, that is, to stimulus durations that are likely to reflect processes occurring over the initial early phase of auditory–sensory memory and specifically, those processes related to temporal integration of energy.

5. Summary and conclusions

One of the distinct advantages of using MMN to investigate clinical conditions is the undemanding nature of the paradigm, as its elicitation is not dependent upon the active attention of the participants. This fact no doubt explains its popularity in clinical applications. However, despite the deceptively simple paradigm, MMN has the capacity to reveal important and sometimes fairly subtle features of auditory system functioning. Furthermore, there is now an extensive normative data base on the characteristics of the MMN response at many levels: the variety of stimulus attributes generating an MMN and what these data reveal about the auditory system, the anatomical location of the generators and the functional role of MMN related processes in auditory cognition (see Näätänen and Tiitinen, 1998 for a review). Hence, MMN investigations have been very important for elucidating developmental changes in auditory system functioning: for instance, in infants (Cheour et al., 2000) and with aging (Karayanidis et al., 1995) and processes that are disturbed in clinical conditions, such as in children with learning problems (Kraus et al., 1996) and adults with dyslexia (Kujala et al., 2000), children with cleft palates (Cheour et al., 1998) and patients with Alzheimer’s disease (Pekkonen et al., 1995).

What has MMN revealed about the auditory system in schizophrenia? The observation that MMN to duration deviants is reduced in patients who meet the diagnostic criteria for schizophrenia, reported by the BSRT (Shelley et al., 1991), was the first evidence that there may be early auditory processing deficits in these patients, deficits that had previously gone unrecognised. The goal of the research reviewed in the last section of this paper and of our current research, is to use MMN in combination with behavioural and other electrophysiological measures to clarify the nature of the auditory system deficit in schizophrenia. However, first it was necessary to determine whether the initial observation of re-
duced duration MMN in medicated patients could be attributed to neuroleptic medication, whether it was specific to schizophrenia, could it be replicated in other independently selected groups of patients, was it dependent upon the nature of the distractor task and whether it also occurred in unaffected first degree relatives of patients with a schizophrenia spectrum diagnosis. All of the evidence presented here in relation to these issues and collected in two independent laboratories (one based in Sydney and one in Perth), is positive, although further research is needed, particularly on the specificity question and the robustness of findings in relatives.

The most intriguing questions, however, relate to what underpins the reduced MMN to duration increments in schizophrenia and therefore, the nature of the auditory system deficit in this disorder. The first possibility, of a general problem in auditory–sensory memory, seemed the most likely at the outset, given the extensive data from Javitt’s group showing reduced MMN to frequency deviants in schizophrenia (Javitt et al., 1993, 1995, 1998; Shelley et al., 1999). This possibility did not receive strong endorsement from our data. Although MMN to large frequency deviants was marginally reduced, it is clear that in comparison, the neural processes producing duration MMN are very severely affected in schizophrenia. Reasons for the apparent inconsistency between the results from Javitt’s group and our data are discussed in some detail in Michie et al. (2000a). Javitt and his colleagues have shown that there are two important variables that determine whether patients show a significantly reduced frequency MMN, namely, deviant probability and degree of deviance. However, these variables alone cannot account for the pattern of significant and non-significant findings in the growing literature on frequency MMN in schizophrenia. As noted earlier, a review of the evidence suggests that short SOAs (<300 ms) should be added to the list of variables that are important for the elicitation of reduced frequency MMN in patients and could explain the difference between Michie et al. and Javitt’s findings. If it turns out to be the case that frequency MMN dysfunction in schizophrenia is more readily demonstrated at short SOAs of <300–400 ms, it could be very informative about the nature of the neural processes that are compromised in schizophrenia.

Neither was there strong support from our data that duration MMN reduction is indicative of a problem with temporal processing in schizophrenia given that only a small subset of patients showed evidence of difficulties in making explicit judgements about the temporal extent of stimuli. There was stronger, but still preliminary, support for what may be abnormalities within the window of temporal integration, coincident with the early phase of auditory–sensory memory. Ultimately, however, it may turn out that the deficit is in temporal processing defined in a broader sense but limited to effects occurring over brief time intervals, including transitory changes in frequency and other features, regularity of the timing of stimulus delivery and temporal integration effects that operate over intervals of <300 ms.

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