Mismatch Negativity: Different Water in the Same River

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Key Words

Mismatch negativity (MMN) · Memory · Perception

Abstract

The mismatch negativity (MMN) is a frontal negative deflection in the human event-related potential that typically occurs when a repeating auditory stimulus changes in some manner. The MMN can be elicited by many kinds of stimulus change, varying from simple changes in a single stimulus feature to abstract changes in the relationship between stimuli. The main intracerebral sources for the MMN are located in the auditory cortices of the temporal lobe. Since it occurs whether or not stimuli are being attended, the MMN represents an automatic cerebral process for detecting change. The MMN is clinically helpful in terms of demonstrating disordered sensory processing or disordered memory in groups of patients. Improvements in the techniques for measuring the MMN and in the paradigms for eliciting it will be needed before the MMN can become clinically useful as an objective measurement of such disorders in individual patients.

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Introduction

One cannot step twice into the same river, for the water into which you first stepped has flowed on.
Heraclitus, LI

This paper is a selective review of some recent literature on the mismatch negativity (MMN). Since the MMN is associated with stimulus changes, the epigraphs for the paper's sections are from Heraclitus, an early Greek philosopher who thought deeply about change. (The quotations are from a translation by a modern poet [Davenport, 1995] and the references are to the numbered fragments presented in an annotated literal translation [Kahn, 1979].) The first quotation describes the paradox that what we consider the same is actually always changing. The human brain determines from its experience some things that it can consider relatively constant or invariant. It then either accepts these constants and lives with the variance that they do not completely explain or it remakes a different set of constants to explain the variance more effectively. After an introductory section that discusses these basic ideas, the paper considers some physiological and psychological aspects of the MMN and then looks at how the MMN might be useful clinically.

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Phenomenology of the MMN

Wisdom is whole: the knowledge of how things are plotted in their courses by all other things. Heraclitus, LIV

The MMN is a frontal negative wave occurring in the event-related potential (ERP) evoked by a stimulus that differs from preceding stimuli. In general the stimuli are presented in repeating trains and the stimulus that differs (the deviant) is less probable than the other stimuli (the standards). Essential to understanding the role of the MMN in human information processing is some knowledge about how it is evoked, how it is measured and how it relates to other ERP waves that precede, overlap and follow it. The section concludes with a categorization of the different kinds of invariance that underlie the MMN.

Basic Parameters of the MMN

The classic paradigm for recording the MMN involves presenting a regular train of auditory 'standard' stimuli in which occasional 'deviant' stimuli differ from the others in terms of some physical attribute such as frequency. These stimuli are presented to subjects who are awake but attending to something other than the auditory stimuli. The ERPs recorded in such a paradigm are illustrated in the bottom half of figure 1. The standard stimuli typically evoke an N_1-P_2 complex, but if the stimuli are presented at a rapid rate this response to the standard stimuli is quite small (less than a microvolt in the figure). The response to the deviant stimulus contains two negative waves, which are most clearly seen if the standard response is subtracted from the deviant response as is shown in the bottom ERP waveform of figure 1. The difference waveform shows a negative wave at the same latency as the N_1 (indicated by the filled arrowhead) and a later negative wave called the MMN (indicated by the open arrowhead). The first wave is probably the result of the enhanced N_1 in the deviant response (since the interval between the deviants is much longer than the interval between the standards and the response is therefore less refractory). The relative sizes of these two waves depend on parameters such as the difference between the standard and deviant stimuli and the intervals between the stimuli.

The latency of the MMN is determined by the time at which the deviant stimulus can be distinguished from the standard stimulus. In terms of sensory discriminations that are more or less difficult, the timing may index the accumulation of evidence that a particular stimulus is not the same as the preceding stimuli. In terms of stimuli that differ in duration, the latency of the MMN is determined by the time at which the shorter stimulus (either the standard or the deviant) ends. Recording the MMN to stimuli with different durations is a powerful tool because it allows the experimenter to manipulate the latency at which the MMN occurs (by changing the durations of the standard and/or the deviant stimuli) without significantly changing other aspects of the processing.

When interpreting the latency of the MMN, it is important to disentangle the difficulty of discrimination from the timing of the discrimination process in the processing of the stimuli. If one wishes to determine which type of discrimination occurs earlier in the auditory system, it is essential to measure MMN latencies when the difficulties of discrimination are equivalent. When this is done, the MMN evoked by an earlier than usual stimulus occurs earlier (from the point in time that the deviance occurs, i.e. the onset of the deviant stimulus) than the MMNs evoked by differences in intensity, location and frequency, all of which have equivalent latencies [Deouell and Bentin, 1998]. However, the latency for the MMN evoked by stimuli that differ in terms of periodicity pitch is longer than the MMN evoked by an equivalent pitch change in pure tones [Winkler et al., 1997], suggesting that the cerebral process for determining pitch takes longer for periodic stimuli than for pure tones (even though the stimuli may not be much different in terms of perceptual discriminability). Furthermore, as the interstimulus interval (ISI) gets longer, the latency of the MMN may increase, suggesting that the memory of the standard is perhaps less precise at longer intervals and the recognition of the deviant therefore more difficult [Schröger and Winkler, 1995].

The amplitude of the MMN in general increases with increasing differences between the standard and deviant stimuli. This relationship is generally monotonic but it may show some ceiling effects, as the difference becomes large. Some of the changes in amplitude may relate to the superposition of two or more different types of MMN waves [Schröger, 1995; Takegata et al., 1999].

The auditory MMN is recorded with maximum negative amplitude over the frontocentral regions of the scalp. In general, it is more anteriorly distributed over the scalp than the auditory N_1. Both the N_1 and the MMN usually show polarity inversions when recorded from locations below the Sylvian fissure. The MMN thus differs from the N_{2b} which is often superimposed upon the MMN in the
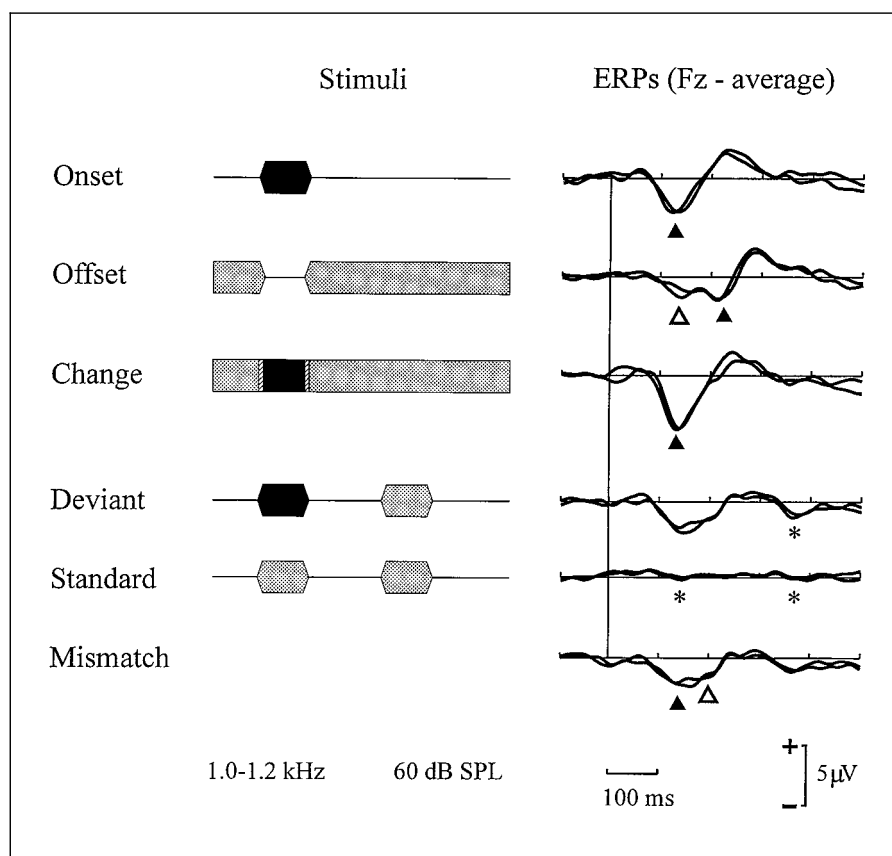
Fig. 1. ERPs recorded with different kinds of stimulus change. On the left of the figure are shown different situations wherein the stimuli change. The right side of the figure shows the potentials evoked at the mid-frontal electrode by these changes. The first line shows a situation wherein a brief (100 ms) tone occurs once every second with an intensity of 60 dB SPL. The onset of the stimulus evokes a response that includes an N_1 component indicated by the upgoing filled arrowhead. The second line of the figure illustrates a situation wherein a continuing tone goes off briefly for 100 ms. The offset of the stimulus evokes a small N_1 wave as indicated by the unfilled arrowhead. A second N_1 wave (indicated by the filled arrowhead) is subsequently evoked by the re-onset of the continuing stimulus. The second N_1 is larger than the N_1 response to the offset despite the fact that it only follows the preceding offset response by 100 ms. The third line illustrates a situation wherein the continuous tone changes in frequency for a brief period. The changes in frequency occurred smoothly over the same 10 ms as the rise and fall times of the stimuli. This evokes a response at the onset of the change as indicated by the filled arrowhead. The fourth set of data illustrates the situation wherein a repeat-ing stimulus changes its frequency. Stimuli were presented at a rate of 4/s and occasionally one of the stimuli changed frequency between 1000 and 1200 Hz. The three ERP waveforms plotted on the right show the responses to the stimuli when a deviant occurred, when a standard occurred and the difference between these waveforms ('mismatch'). The N_1 response to the standard stimuli (asterisks) is very small because of the rapid stimulus rate (it is enhanced when the standard follows a deviant). The difference waveform shows that the stimulus change evokes a broad negative wave that probably contains two components. The first (indicated by the filled arrowhead) proba-bly represents a change in the N_1 response, whereas the second (un-filled arrowhead) represents an additional MMN. The smaller ver-sion of this response (in both the deviant and the difference wave-forms) occurring after the second stimulus probably represents some mismatch processing of the standard stimulus following a deviant. For this figure the responses were averaged across 4 subjects. The two replications occurred in conditions wherein either the 1000-Hz or the 1200-Hz stimulus was the deviant.

parasagittal regions of the scalp but which does not invert in polarity below the Sylvian fissure when using a nose reference [Sams et al., 1984, 1990; Alain and Woods, 1997].

Concepts of Change

The main determinant of the MMN is that the stimu-lus has changed from the previous stimuli. However, since the characteristic paradigm used to elicit the MMN

involves discrete stimuli, two changes occur at the time of the deviant stimulus. The first change is the onset of the stimulus from the background which is usually quiet. This change occurs for the standard stimuli as well and is associated with an N_1 response. The second change is the change in some feature of the deviant stimulus from a preceding stimulus. This change occurs by itself if the stimulus is continuously on and just momentarily changes. For example, a continuous tone may occasionally change its frequency (and then revert back to the standard frequency). This change is also associated with an N_1 response (third waveform in fig. 1). Lavikainen et al. [1995] found two sources for the magnetic N_1 response to such a change in frequency and suggested that these represented the normal N_1 and an MMN, with the MMN occurring earlier than it would have if the frequency change had been part of a separate deviant stimulus. This idea is appealing, but it is also possible that the two components are part of the normal N_1 response. The two-component analysis was not carried out for the typical N_1 to stimulus onset and other evidence suggests that this also has multiple sources that vary in the amount they contribute at different latencies [Näätänen and Picton, 1987; Woods, 1995; Gutschalk et al., 1998; Picton et al., 1999]. The N_1 response to a change in a particular stimulus attribute is often larger than the MMN response to a change between two separate stimuli differing on that attribute. This phenomenon has recently been highlighted by Martin and Boothroyd [1999] in a study evaluating the ERPs evoked by an acoustic change.

In general, the onset of any change in an auditory stimulus is associated with an N_1 wave. (This is not true if the duration of a stimulus increases, when there is no onset response to the change but only the absence of an offset.) The offset of a stimulus (second waveform in fig. 1) elicits a smaller N_1 response than the onset, given equal on-off duty cycles. For brief stimuli (less than several hundred milliseconds) the N_1 response to the offset is either unrecognizable or impossible to distinguish from the offset of the sustained potential. In the data shown in figure 1, when a continuous tone is briefly turned off (second line), the N_1 to the offset (open arrowhead) is smaller than to the subsequent onset (filled arrowhead) despite the differences in the timing of the on and off periods.

It is only when a stimulus differs from one that occurred previously but not adjacently in time that one obtains a distinct MMN in addition to the N_1 (lower three waveforms of fig. 1). Therefore, Näätänen and Picton [1987] suggested that there may be two types of change: a level change (e.g. from silence to sound, from sound to silence or from one frequency to another, thus encom-

passing all the changes discussed in the preceding paragraphs) associated with the N_1 response, and a stimulus change associated with the MMN. The idea of a stimulus change requires parsing the incoming information into discrete stimuli. In terms of perception, the two kinds of change detection may be analogous to sensory analysis and object recognition.

Relations between the MMN and Other ERP Waves

The MMN can be distinguished from earlier difference waveforms on several dimensions. The most important earlier waveform is the N_1 wave, which often increases in amplitude with a change in the stimulus and therefore shows up in the deviant-standard difference waveform (fig. 1). The differentiation depends upon five main findings, although these basic findings are not without some controversy (and we shall return to them in later sections of the paper). First, a MMN occurs whatever the direction of the deviance from a standard intensity, whereas the N_1 wave gets smaller with decreasing intensity of the stimulus regardless of the difference in intensity between the deviant and the standard [Näätänen, 1992]. Furthermore, the N_1 difference is not apparent when the dimension of the deviance involves duration (for stimuli longer than about 30 ms) or pattern. Second, the N_1 responses tend to be more susceptible to changing the ISI than the MMN. The N_1 wave decreases in amplitude when the interval between the stimuli decreases whereas the MMN does not [Mäntysalo and Näätänen, 1987; Czigler et al., 1992] unless the intervals between the deviants also become very short. Third, the MMN is more specific to changes in stimulus attributes than the N_1 wave. When the differences between the standard and deviant are large in the classic paradigm using frequency deviants, the deviant stimulus evokes both a larger N_1 and an additional MMN, but when the deviant is very close to the standard, a significant MMN occurs with little if any change in the N_1 [Sams et al., 1985; Scherg et al., 1989]. However, some evidence suggests that the refractoriness of the N_1 may be much more specific under particular circumstances [Näätänen et al., 1988]. Fourth, as the difference between the standard and deviant is changed the latency of the MMN changes, but the latency of N_1 or the N_1 difference does not. (Since latency cannot play an informative role in perception without an independent assessment of when the stimulus occurred, one is tempted to speculate about collaboration between the N_1 and MMN processes, with the the N_1 providing a latency marker. It is also possible that

different neurons generate the MMN at different latencies.) Fifth, the intracerebral origins of the two processes appear to be quite distinct both magnetically [Sams et al., 1991b] and electrically [Scherg et al., 1989].

The exact roles played by the N_1 and the MMN in perception are not clear. The relationships between these waves and perception were investigated in a complex study using stimuli that differed in periodicity pitch [Winkler et al., 1997]. It was found that the N_1 response was significantly affected by the pitch regardless of the duration of these stimuli, but that the MMN only occurred if the duration of the stimuli was sufficient for the pitches to be perceptually distinguishable. The results show some clear differences between the N_1 and the MMN. However, their conclusion that 'the N_1 generating mechanisms are not part of the sequence of brain events directly underlying perception' seems unwarranted. The MMN occurred later than the N_1 and closer to the time when a particular perceptual response would be made. The earlier N_1 response could indicate the processing of information that was irrelevant to the perceptual distinction set up by the MMN paradigm. The fact that it was not relevant to the MMN distinction, however, does not mean that it would not have been perceptible in different contexts.

The MMN is also distinguished from later difference waveforms that occur in the ERPs such as the N_2 wave and the P_{300} wave. This distinction is predominantly based upon the fact that the MMN is relatively unaffected by either the relevance of the stimulus to any task that the subject is performing or the amount of attention that the subject is paying to the stimuli [Näätänen et al., 1978]. When attention is paid to the stimuli, an N_2 wave is often superimposed on the MMN. In earlier days the two waves were called N_{2a} and N_{2b} [Näätänen et al., 1982]. One way in which they tend to be clearly distinguished is by the scalp topography. When using a nose reference the automatic MMN often reverses its polarity as the active electrode descends below the level of the Sylvian fissure to become a positive wave at the mastoid, whereas the attention-dependent N_{2b} does not [Sams et al., 1990].

The N_{400} that occurs in response to unpredicted words shares some characteristics with the MMN. Most particularly, the N_{400} is evoked by stimuli that are not predicted on the basis of the preceding stimuli. Words that occasionally repeat in a list of other words show a positive displacement in the ERPs relative to their first presentation [for a review, see Rugg and Doyle, 1994]. This repetition effect can be observed even when the repetition of the words is irrelevant to the subject's task, though it does not occur unless attention is paid to the words themselves [McCarthy and Nobre, 1993; Otten et al., 1993]. The repetition effect might represent some extra processing accorded repeated words, but it can just as easily be interpreted in terms of the absence of some N_{400}-like process in the response to unrepeated words [Rugg et al., 1988]. From this perspective, the positive deflection would represent, at least in part, an attenuation of the N_{400} elicited by unrepeated (or unprimed) words. The N_{400} may be similar to the MMN in the sense that both are associated with a mismatch between what the system is primed to process and what is actually presented. However, the level of processing at which these mismatches occur differs. The auditory N_{400} may itself be preceded by an earlier negative wave that indexes the phonological rather than semantic unexpectedness of the stimulus [Connolly et al., 1995]. It is unclear what relationship this bears to the MMN recorded to a deviant phoneme in a more classic MMN paradigm [Maiste et al., 1995; Näätänen et al., 1997]. Nevertheless, the results indicate that mismatch processes occur at multiple levels during the processing of sensory information. What we call the MMN differs from later mismatch processes by being automatic.

Modality

The MMN has been extensively described in the auditory modality. Whether or not it occurs in other sensory modalities remains unclear [recently reviewed by Näätänen and Alho, 1995]. The question of whether the MMN or an analogue thereof occurs in modalities other than the auditory modality is crucial to our understanding of what the MMN represents. Does it only occur during the processing of auditory information? If so, why is the auditory system special? Is it common to all sensory processing? If so, why is it difficult to record outside the auditory system?

It is possible that modality-specific differences in sensory memory or the nature of sensory analysis may make the MMN difficult to record in non-auditory modalities. It is also possible that attention may work differently in the different sensory modalities. Visual stimuli may need attention to be processed to a level sufficient to support the differentiation of standards from deviants, whereas auditory stimuli may be automatically processed to a higher level. The auditory system lacks the powerful attentional controls exercised by where the gaze is directed and whether the eyelids are open or not.

Another explanation for the difficulty in detecting an MMN in other modalities might be the complexity of the generators in these modalities. The auditory cortices are mainly arrayed on the supratemporal plane and auditory processing in these cortices will be associated with dipoles that tend to point frontocentrally regardless of their location on the supratemporal plane. Mismatch processes in the somatosensory system may have overlapping radial and tangential dipoles and may derive from both SI and SII cortical areas, much like the simple sensory responses. In the visual system, the number of different cortical areas, the specificity of processing in each of these areas, and the great variety in the orientations of the dipoles generated in these areas could explain the lack of a clear MMN. Even the exogenous visual evoked potentials (often called P_1, N_1, and P_2) vary much more in their scalp distribution with differences in the stimuli and the way in which they are processed than do the auditory evoked potentials. The choice of reference electrode in the visual system is problematic, since the ears and mastoids can pick up potentials from the temporo-occipital regions.

Despite these complexities, there is some recent evidence for ERP differences between non-auditory standards and deviants that might represent mismatch processing. In the somatosensory system, the extra negative deflection that occurs in the 100- to 200-ms range when a vibratory stimulus occasionally shifts from one finger to another may represent a mismatch process [Kekoni et al., 1997], although it is difficult to distinguish this from an enhancement of the usual N_{140} response. Tales et al. [1998] used a visual paradigm wherein double bars occasionally replaced single bars above and below an attended foveal stimulus. Both types of peripheral stimuli were irrelevant to the task and outside of the focus of attention on the foveal field (although still clearly visible). The deviant visual stimuli elicited a temporo-occipital negative wave (recorded using a frontal reference) in the latency range of 250–400 ms that might represent the visual analogue of the auditory MMN. This was later than the posterior N_2 wave that occurred when the foveal target was detected. A recent study has suggested that an olfactory MMN might be evoked when a deviant odor occurs in a regular train of unattended odors [Krauel et al., 1999].

Standards and Deviants

Crucial to any understanding of the MMN is some idea of what constitutes 'standard' and 'deviant'. Two processes underlie the brain's distinction between standards and deviants: parsing the incoming information into units and categorizing these units in terms of their probability of occurrence. The units may vary with the type of information being received and with the sensory abilities of the receiver. Although the deviant is most typically a deviant stimulus, it may also be a deviant feature or, when defined by multiple stimuli, a deviant event. However it is defined, the variant is less probable than the standard.

In order for the MMN system to recognize that a deviant is different from the standard there must be a memory of the standard. Näätänen [1992] considered the relevant memory to be sensory memory. However, two levels of representation seem to be involved: representations of the recent acoustic past and representations of regularities or invariances extracted from what is available in sensory memory [Schröger, 1997; Ritter et al., 1998; Winkler et al., in press]. Sensory memory provides the raw data from which invariant aspects of the stimuli are extracted. The extraction of the rules governing the stimuli might occur in sensory memory or in some other system with access to the information in sensory memory. A minimum of two stimuli must be presented in order for the system to establish a representation of invariance for frequency [Winkler et al., 1996a]. The minimum number of stimuli required for the system to establish other kinds of invariances remains to be determined. Once a representation of invariance has been established, a stimulus that violates that representation can elicit an MMN. Five kinds of invariance can be considered: simple, complex, hypercomplex, patterned or abstract.

Simple Invariance

This involves a situation wherein the standard stimuli are all identical in every possible way (frequency, intensity, duration, location, etc.). Infrequent deviant stimuli that differ in any discriminable manner from the standard stimuli elicit an MMN, indicating that representations of invariance for all the acoustic parameters are established. The classic example is a simple oddball paradigm, such as was used in the discovery of the MMN [Näätänen et al., 1978]. Although the standards may be simple, they can also be complicated in structure. For example, they may be phonemic stimuli composed of different formants [Näätänen et al., 1997]. What is crucial is that all standards are identical.

Complex Invariance

This occurs in circumstances where none of the stimuli available in sensory memory at any given moment are

identical, but some features of these stimuli are identical. An example is a paradigm presenting tones of many different frequencies and intensities such that no two tones within the span of sensory memory have the same combination of frequency and intensity. There are, therefore, no standard stimuli as such. However, if a tone deviates with respect to a feature that is otherwise constant, such as duration, it elicits an MMN [Gomes et al., 1995]. The MMN system finds what feature is constant in the changing standard stimuli and establishes a representation for this invariance.

Hypercomplex Invariance

In this situation, a combination of multiple stimulus features defines what is invariant. The standard stimuli may come in several forms each defined by a particular set of stimulus features, and the deviant stimulus is the rare occurrence of a stimulus combining features from different standard stimuli. The fact that the deviant stimuli that elicit the MMN do not differ from representations of invariance based on any one feature differentiates hypercomplex invariance from simple and complex invariance. An example involves standard stimuli characterized by one of three different intensity-frequency combinations [Gomes et al., 1997]. The deviant has the frequency of one of the standard stimuli and the intensity of another standard stimulus, but this particular combination of features is specific to the improbable deviant stimulus. Similar results were obtained by Sussman et al. [1998a] who used location and frequency as the stimulus features and by Takegata et al. [1999] who used intensity and frequency.

Pattern Invariance

This involves relationships between different stimuli. An example is a brief tone that regularly alternates between two frequencies as it repeats. A deviant stimulus is the occasional repetition of the previous frequency rather than the standard alternation to the other frequency [Nordby et al., 1988b; Alain et al., 1994]. In this situation the pattern of alternation is what is invariant and the disruption of this pattern elicits the MMN. Pattern invariance can involve a sequence of as many as 8 tones [Näätänen et al., 1993b] and can involve changes in intensity as well as changes in frequency [Schröger et al., 1996]. Another type of pattern deviance involves the timing of the standard stimuli with the deviant stimuli identical to the standard stimulus but occurring after a shorter than usual ISI [Ford and Hillyard, 1981; Nordby et al., 1988a]. Here the regular interval between the stimuli is what is invariant. Pattern deviance may thus involve either the sequence or the timing of stimuli.

Abstract Invariance

This occurs when what is invariant across stimuli cannot be determined on the basis of the absolute physical attributes of stimuli. Saarinen et al. [1992] used pairs of stimuli that had a particular relationship (e.g., the second tone was higher in frequency than the first tone), but the actual attributes of the pairs randomly varied among five different levels. A pair of tones that had a different relationship (e.g., decreased in frequency from the first to the second tone) elicited the MMN. In this case, what was invariant had to be based on an abstract rule. Paavilainen et al. [1995] extended this finding to a situation where one rule applied to pairs of tones delivered to one ear (e.g., they went up in frequency) and another rule applied to pairs of tones delivered to the other ear (they went down in frequency). In a further extension of this finding, Paavilainen et al. [1998] varied the absolute frequencies of the tone pairs among ten levels and randomly varied the ear to which the first tone of a given pair was delivered. Another example of an abstract rule associated with the MMN occurs when the perceived pitch of the standard stimuli regularly decreases and deviance occurs whenever the pitch increases or remains the same [Tervaniemi et al., 1994a]. The deviance is the absence of a decrease in the perceived pitch from one stimulus to the next, regardless of the pitch of the particular deviant stimulus.

The differentiation between the different representations of invariance is not always clear-cut. A complicated stimulus event may be characterized by a particular pattern of tones [Winkler and Schröger, 1995]. The invariance in this pattern may yield a simple invariance if the stimulus event is considered as a single stimulus and a pattern invariance if the tones comprising the stimulus event are considered separately. The difference would likely depend on the rapidity at which the successive parts are presented. The type of invariance might also vary with the context in which it occurs. A simple acoustic change such as frequency may be interpreted as a deviance from a multi-stimulus pattern (rather than just a deviance in frequency) if it occurs together with other changes in a patterned sequence of stimuli [Alain et al., 1998a]. Pattern and abstract invariances are clearly related, with pattern invariance depending on the specific features (such as their frequencies, intensities or durations) of the stimuli that make up that particular pattern, and abstract invariance depending on the relationship between stimulus features independently of their specific values.

The types of representations of invariance differ in terms of the logic that defines what is invariant. For simple invariance, the logic involves the identity of all the acoustic features of the standards and the inequality of the deviant stimulus. For complex invariance, a disjunctive process is used: some of the stimulus features may be invariant while others are not. For hypercomplex invariance, the logic involves conjunction: the multiple standard stimuli each combine features in a unique way. For pattern invariance, the logic requires the inference of constant regularities involving more than one stimulus. For abstract invariance, the logic requires the inference of a relationship between stimuli (or between stimulus features) independently of the specific stimuli or features. Although logical terms often describe conscious mental processes, the MMN processes do not require conscious cognition and, indeed, may provide some insight into logical processes that occur automatically in the human brain.

The distinction between the different kinds of invariance is important from more than a theoretical point of view. The different kinds of invariance need to be represented in different neuronal circuits. These processes can work quite independently, as shown by Takegata et al. [1999] who found that a stimulus that differed from the standard in terms of both a simple feature (location) as well as a conjunction of features (frequency and intensity), elicited an MMN that was equal to the sum of the MMNs evoked separately by feature or feature conjunction deviants. The neuronal mechanisms for the different types of invariance may occur in different regions of the brain and may show different effects of attention or arousal. Thus, Alain et al. [1999] have shown that the pattern MMN has a different scalp distribution from the frequency MMN, and Alain and Woods [1997] have shown that the pattern MMN is susceptible to attentional modulation whereas the intensity MMN is not.

Representations of invariance may be based on single features or gestalt-like combinations of features [Gomes et al., 1997]. At times the brain may combine different variations of the standard (e.g., slightly different levels of intensity) or 'substandards' into one general representation of invariance typified by the average of the various substandards [Winkler et al., 1990]. In other situations, the memory of the different standard stimuli might be maintained separately. Thus, Winkler et al. [1992] showed that two representations of invariance along one stimulus dimension (in this case, two levels of frequency) can be maintained simultaneously, and Winkler et al. [1996b] showed that a single deviant stimulus could

evoke two MMNs when it had a duration that differed from two different standard durations. There might be some trade-off between making multiple memories for different standard stimuli (or features) and combining stimuli together into an overall gestalt-like standard. There may also be no limit to the number of kind of representations of invariance that may be maintained simultaneously. By way of illustration, Gomes et al. [1995] varied intensity and frequency. Since the stimuli were delivered in such a way that two identical stimuli could not be present in sensory memory at the same time (an average of 72 trials elapsed between presentations of two tones that had the same combination of intensity and frequency), it was only possible for regularities of separate features to be extracted. In this case, stimulus duration was kept constant, and a change in stimulus duration elicited the MMN. Thus, a representation of the invariance of stimulus duration was developed. However, there is no reason to believe that changes in any of the other features that were constant across tones (rise time, perceived location, etc.) would not have elicited MMNs as well.

The actual process whereby the brain establishes some representation of invariance has not been extensively investigated. Some recent studies have looked at the MMN as the brain learns to discriminate standard and deviant stimuli [Näätänen et al., 1993b; Kraus et al., 1995; Tremblay et al., 1998]. Repetition is clearly essential and the more probable the occurrence of a particular stimulus, feature or pattern among others, the more likely will it be included in the representation of what is invariant [Ritter et al., 1995]. Attention may not be necessary but it likely facilitates the process of standardization. Other recent studies have looked at how extensive past experience with language [Näätänen et al., 1997; Cheour et al., 1998; Winkler et al., 1999] or with music [Koelsch et al., 1999] can affect the sensitivity of the MMN in present paradigms. We know much about the kinds of invariances the MMN system detects. The mechanisms whereby the brain determines what is invariant are yet to be discovered.

Physiological Approaches to the MMN

Nature loves to hide. Heraclitus, X

We do not yet understand what the MMN represents in terms of physiological processes. Exactly how a model of a standard stimulus is made by the brain and how this might be compared to incoming sensory information is
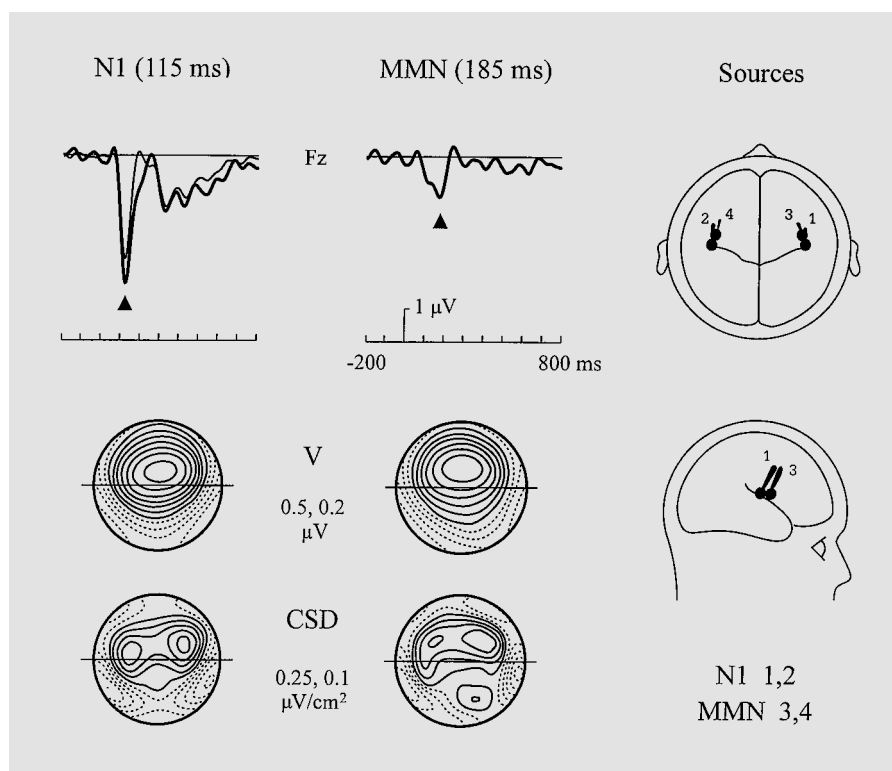
Fig. 2. Source analysis of the N_1 and MMN waves. These results derived from data obtained by Otten et al. [in press]. The stimuli occurred at a rate of 1/1.5 s. Deviant stimuli occurred with a probability of 25%. Data were obtained from 12 subjects and combined over conditions wherein the subject performed either an easy or a difficult visual attention task. The grand mean waveforms at Fz are plotted in the upper left. Below these data are shown maps (of both the voltage and the current source density) for the N_1 wave to the standard stimulus and for the MMN wave obtained in the difference waveform. The maps are plotted using an azimuthal equidistance projection with the outside limit of the map representing a level near the mastoids. The MMN has its maximum amplitude slightly anterior to that of the N_1 response. Both measurements show a clear polarity inversion below the Sylvian fissure that is most evident in the current source density (CSD) plots. On the right of the figure are shown the results of source analysis using Brain Electric Source Analysis. The sources were constrained to fit the waveforms at the latencies of the N_1 peak in the standard waveform and the MMN in the difference waveform. The analysis was constrained to have only two dipoles and for these to be symmetrically located between the hemispheres. The source dipoles for the MMN are slightly anterior to those for the N_1 response.

not known. Certain experimental approaches have worked in the past to increase our understanding of the physiological bases of the scalp-recorded potentials and these have also been pursued for the MMN.

Scalp Topography and Source Analysis

A very important approach to understanding the brain processes underlying different ERP waves is to determine their intracerebral sources. There are small but consistent differences between the scalp distribution of the N_1 wave and the MMN wave. In particular the MMN wave is usually more frontal in its distribution. Source analyses of the two waves show that they may both derive from focal intracerebral currents on the supratemporal plane, with the generator for the MMN being slightly anterior to the generator for the N_1 wave (fig. 2). These results, which have consistently been found for both electrical [Scherg et al., 1989] and magnetic recordings [Hari et al., 1984; Sams et al., 1991b; Tiitinen et al., 1993], clearly indicate that the generators are different. However, a caveat is that there may be significant overlap between the two generators. Some of the neurons responding during the N_1 may also be responding during the MMN. For example, the N_1 may be generated in a large area of the supratemporal plane with an equivalent dipole at the centre of the widespread activation, and the MMN may be generated in

small areas of the auditory cortex specific to processing the particular auditory attribute that characterizes the deviant.

An additional frontal generator for the MMN has been suggested on the basis of scalp current source densities [Giard et al., 1990]. This may represent some frontal response to the information processed in the temporal lobes or activity in some parallel system that monitors attentional processes. This component likely represents activity that is stimulus independent in terms of cognitive processing. (The term 'stimulus independent' is used instead of 'non-specific' since the latter often carries connotations of the epiphenomenal, and since the activity may be quite specific in terms of response processing.)

The scalp topography of the MMN can be different for different kinds of MMN. Giard et al. [1995] compared the scalp distribution of the MMN elicited by rare deviant sounds differing from the standard in intensity, frequency or duration. They found that the scalp topography varied as a function of the type of deviant and proposed that different MMNs derive from different neural generators. Frodl-Bauch et al. [1997] found that equivalent dipole sources underlying the frequency MMN were significantly more anterior than the sources underlying the duration MMN. Alho et al. [1996] found that the magnetic mismatch response evoked by a change in tonal frequency showed a different intracerebral source from a similar change in one element of a combination of musical notes (a chord). This suggests that the processing of the deviance is specific to the type of standard stimulus (a tone or a chord) rather than to the actual physical change (a frequency deviance). Näätänen et al. [1997] found a larger magnetic mismatch response in the left hemisphere compared to the right for phonemic stimuli. Tervaniemi et al. [1999a] found that the source strengths for the magnetic mismatch responses differed in their interhemispheric symmetry when the mismatch involved phonemes or musical chords. The source strengths were not different in the left hemisphere, but the source for the chord mismatch was much larger than the source for the phoneme mismatch in the right hemisphere. The source locations differed in both hemispheres between chords and phonemes. Alain et al. [1999] found that the electrical MMN in response to a frequency deviant was more frontal than the MMN in response to a pattern deviance.

These results indicate that the source underlying different MMNs may differ. However, although specific MMN generators may exist for detecting deviances of different kinds, it is also possible that the same set of generators may contribute to each of the different scalp-recorded MMNs but that the relative contribution of each generator may vary. For example, the generators may include a process specific to detecting deviance and another process, such as calling attention to the change in the stimulus environment regardless of the type of change. The two generators may have different scalp topographies, as may for example occur if a sensory MMN is generated in the temporal lobe and a stimulus-independent MMN is generated in the frontal lobe. The different scalp distributions may then reflect different degrees of activation of sensory and stimulus-independent generators. For example, the activation of the stimulus-independent generator may depend upon such things as the size of the mismatch. If this is so, it is essential to compare scalp topographies across the different types of deviance after adjusting for the discriminability of the deviant stimuli. Deouell and Bentin [1998] closely controlled for discrimination difficulty and were unable to find any significant difference in scalp topography among MMNs related to changes in pitch, intensity, interval and location. These negative results, however, may have been caused by the difficulty in distinguishing subtle differences in scalp distribution when the measured signals are small relative to the noise levels. Paavilainen et al. [1991] found similar scalp topographies among frequency, intensity and duration MMNs (with a right-sided predominance for all types) but noted that the polarity inversion at the mastoid was less prominent for the intensity MMN than for the others, indicating some differences in the source configurations underlying the different MMNs.

Using a principal-component analysis of the topographies, Alain et al. [1999] were able to demonstrate that no common signal space could account for the MMNs evoked by frequency deviance and pattern deviance. This result indicates that the two kinds of MMN do not arise in the same set of generators with varying relative strengths. The neuronal circuitry underlying deviance detection thus varies as a function of the type of deviance. Since Tiitinen et al. [1993] found that sources of the magnetic response to a frequency mismatch were tonotopically organized in a manner similar to the N_{1m} response, it appears that the neurons underlying a particular type of deviance detection also vary with the actual deviant stimulus, i.e. that the mismatch response is specific to the deviant stimulus and not just the amount of deviance. We therefore suggest that the scalp-recorded MMN is generated by neurons in the temporal lobe that specifically react to the stimulus change and by other neurons (probably frontal) that are stimulus independent. We further suggest that the groups of neurons in the temporal lobe

responsible for generating the MMN differ for different dimensions of deviance, and that different neurons within these groups are activated by different deviant stimuli (or features) along these dimensions.

Lesions

The evaluation of deviance-detection responses in patients with focal cerebral lesions adds another dimension to our knowledge of processes underlying the MMN. Woods et al. [1993] found that the MMN was not affected by temporoparietal lesions that affected the N_1 wave, indicating that the MMN was probably generated in regions of the temporal lobe anterior to the N_1. Alain et al. [1998c] examined the effect of unilateral damage to the prefrontal cortex, temporoparietal cortex, and hippocampus on the MMN. These results indicate that lesions to the temporal lobes significantly attenuate the MMN to stimuli presented in the ear contralateral to the lesion. The MMN in these lesioned patients is far more lateralized than the N_1 response. The MMN may therefore reflect a level of processing that occurs after auditory objects have been placed in contralateral space.

Focal frontal lobe lesions attenuate the MMN to stimuli in either ear (contralateral or ipsilateral to the lesion) [Alho et al., 1994b; Alain et al., 1998c]. The frontal lobe is therefore somehow involved in the mismatch process, either by participating in the network underlying the memory system or by facilitating the memory processing. In the latter case, the frontal lobe might act to set up the sensory system to respond to deviance in certain ways and with certain thresholds.
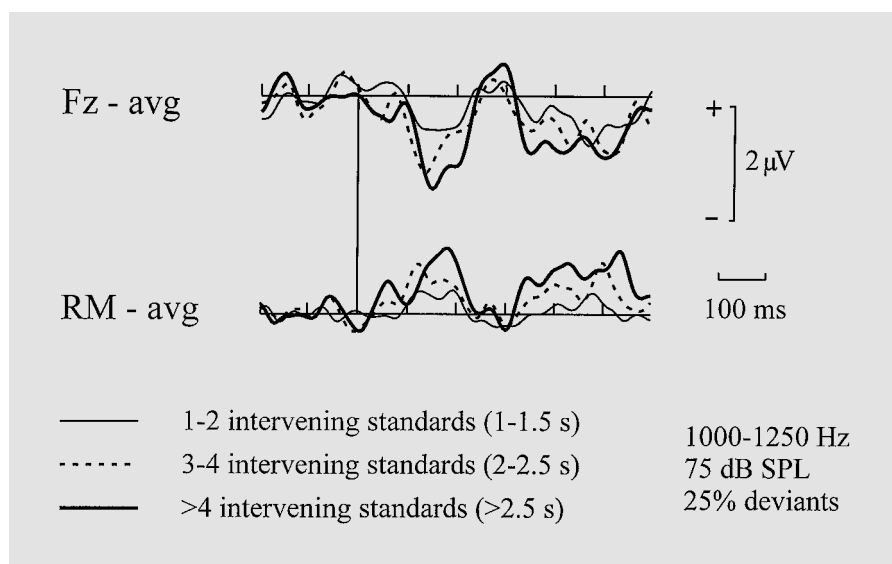
Intervals between Stimuli

A physiological response becomes smaller when the ISI becomes shorter. The usual interpretation of this phenomenon is in terms of refractory periods. However, other mechanisms are possible. The response may represent the re-activation of neurons that normally respond to the stimulus. If these neurons maintain their response for a period of time, they need only be brought back to the firing level needed to represent a stimulus. This 're-activation' hypothesis depends upon the fact that the sensory evoked potentials mainly occur at the onset of a stimulus, when there is synchronized activity in a population of neurons, and do not occur during a continued response to the stimulus (other than small sustained baseline shifts)

because the neuronal firing pattern becomes desynchronized. However, this hypothetical re-activation would be metabolically costly in terms of sustaining activity in the responsive neurons. It is more efficient to code the memory for the previous stimulus in terms of subliminal changes in the excitability of the neurons. Mathematical modelling of the responses of cortical neurons indicates that it is possible to maintain such changes of excitability for several seconds [May, 1999].

Changing the ISI is a powerful way to dissociate the MMN and the N_1 response. The shorter the interval from the preceding stimulus, the smaller the N_1 wave, as distinguished from the MMN which changes little. Some reports have suggested that MMN increases with decreasing ISI [Sams et al., 1993]. Most reports, however, have found that the MMN is not significantly increased by decreasing ISIs, although its relative resistance to decreasing intervals still makes it quite different from the N_1 [Näätänen et al., 1987; Böttcher-Gandor and Ullsperger, 1992; Czigler et al., 1992; Schröger and Winkler, 1995].

Unfortunately, the desired distinction is probably not as clear as it seems initially. Five different parameters may determine the responses in these experiments: the interval between the standard stimuli, the interval between the deviant and the preceding standard, the probability that a deviant stimulus will occur on any particular trial, the interval between the deviant stimuli, and the number of standard stimuli intervening between the deviants. Manipulating one of these variables can indirectly affect the others. For example, the less probable a deviant stimulus, the longer the average interval between deviant stimuli and the larger the number of intervening standard stimuli. The most common experimental manipulation of changing the general ISI (both standard-standard and standard-deviant) will change both the time between the last standard and the deviant and the time between the preceding deviant and the present deviant. Javitt et al. [1998] looked at the MMN recorded under multiple ISIs and deviant probabilities. The MMN was significantly larger the more improbable the deviant stimulus and was not significantly affected by the ISI. The MMN showed some increase with increasing interdeviant interval, but this was not significant on statistical testing. Sams et al. [1983] looked at the MMN in terms of the sequence of preceding stimuli and found that the MMN was larger if the deviant stimulus was preceded by a greater number of standard stimuli. These data contain an additional complexity in that the standard stimulus following a deviant stimulus can evoke an MMN.

Fig. 3. Effects of interdeviant interval on the MMN. These responses represent deviant-standard difference waveforms obtained during a study of the effects of attention on the mismatch on the MMN [Otten et al., in press]. The stimuli occurred at a rate of 2/s, and deviant stimuli occurred with a probability of 25%. Deviant stimuli were separately analysed on the basis of how many standards intervened between the preceding deviant stimulus and the one evoking the response. The greater the number of these stimuli, i.e. the greater the interval between the deviants, the larger the MMN response recorded with a latency between 150 and 200 ms. The MMN was recorded as a negative wave at Fz or a positive wave at the right mastoid (RM).

The MMN may be determined by two temporal factors. First is the interval between the deviant stimulus and the preceding standard stimulus. Näätänen [1992] has suggested that a smaller MMN occurs when this interval is longer. However, it is not clear exactly how long the interval can be before the MMN no longer occurs or how the MMN amplitude varies with increasing interval. For example, the amplitude may maintain itself at a fairly constant level and then after a period of time the MMN may no longer occur [Ritter et al., 1998]. Second is the interval between one deviant stimulus and the preceding deviant stimulus. This relationship may be very similar to that of the N_1 wave in response to repeating stimuli that do not change, with a longer interdeviant interval causing a larger MMN. In experiments comparing measurements across blocks, the interdeviant interval is confounded with the probability of the deviant stimulus. Within-block comparisons can partially disentangle the two parameters (at least as regards the global probability of the deviant stimulus). Figure 3 presents some data from an experiment that was primarily designed to look at the effects of attention and ISI on the MMN (which we shall discuss more fully later in this paper). If we maintain a constant probability for the deviant stimulus and look at the MMN separately for different intervals between the deviants, the MMN is indeed larger when the interval between deviants increases.

These results might also be explained by the number of standard stimuli intervening between the deviant stimuli. It is possible that the memory strength is increased by

repetition of the standard stimuli and that the deviant stimulus thus evokes a larger MMN because of the stronger standard memory. Imada et al. [1993] looked at the temporal determinants of the magnetic mismatch response using paradigms which independently manipulated the intervals between the deviant stimulus and the immediately preceding standard stimulus, and the interval between the deviant stimuli. They found that the magnetic mismatch response increased significantly with increasing interdeviant interval and showed a slight (but insignificant) decrease with increasing interval from the preceding standard stimulus. They also used a complex paradigm which maintained a constant interdeviant interval and a constant interval between the deviant and the preceding standard while varying the number of intervening standard stimuli. There was no significant change in the amplitude of the mismatch response.

Physiological Mechanisms of the MMN

Although this paper cannot extensively review the studies of the MMN in animals, three aspects are worth noting in relation to the physiological mechanisms that underlie the MMN. First, an MMN-like wave can be recorded in many different regions of the auditory system [Csépe et al., 1989; Kraus et al., 1994]. It thus seems to represent a widespread neuronal mechanism. Second, the MMN appears to involve the same regions of cortex as normally respond to afferent input [Csépe et al., 1987;

Javitt et al., 1992]. Third, the MMN is attenuated by blockade of the NMDA (N-methyl-*d*-aspartate) receptors [Javitt et al., 1996].

Näätänen [1992, p. 139f] pointed out that the MMN might occur through two possible mechanisms: through the activation of non-refractory cells by 'fresh' afferents or by a comparison of incoming activity to a memory representation of the standard stimulus. The fresh afferent explanation depends upon the specificity of a neuron's response to stimuli with different characteristics. For example, many auditory neurons respond best at one frequency and respond less as the frequency of the stimulus moves away from this characteristic frequency. A standard stimulus of a particular frequency activates those neurons that have this frequency within their receptive field and makes these neurons temporarily refractory to further stimulation. If a further standard stimulus occurs during this refractory period, the total response of the neurons is smaller than to the first standard stimulus. However, if a deviant stimulus with a different frequency occurs during this refractory period, it may activate neurons that are not refractory because they did not respond to the standard stimulus (since their receptive fields include the deviant frequency but not the standard frequency). The ensemble response is therefore larger than that to the standard. This explanation was initially used by Butler [1968] to account for the effects of changing the frequency of an auditory stimulus on the N_1-P_2 response. The response to the deviant increases as the difference between the deviant and the standard stimulus increases (and the number of neurons responding to both stimuli decreases).

Several aspects of the MMN suggest that it is not mediated by fresh afferents. First, the MMN does not occur in the response to the first standard stimulus when nothing would be refractory. Second, the MMN can occur at a latency much longer than the response to the standard stimulus. Third, the latency of the MMN varies inversely with the size of the difference between deviant and standard, whereas this is not true of refractory effects on the N_1 (where amplitude changes with little if any effect on latency). Fourth, the MMN can be evoked if some part of the standard stimulus is omitted, thereby decreasing the total number of afferents rather than activating fresh afferents [Winkler and Näätänen, 1994; Nordby et al., 1994]. These and other reasons suggest that the MMN reflects the activity of a set of neurons separate from those responding to afferent activation. One possibility is that the MMN indicates the output of a process that compares the incoming activity to a stored representation of the standard stimulus [Näätänen and Alho, 1995; Alho, 1995; Winkler and Näätänen, 1994].

However, the MMN might occur without the need for a direct comparison between the deviant stimulus and the memory of the standard stimuli. Näätänen [1984; recently reviewed in Näätänen and Alho, 1997] suggested that the repetition of the standard stimuli might act not only to inhibit a further response to these stimuli but also to disinhibit other neurons with receptive fields more specific than those that respond to the standard stimulus. These neurons could then respond if and when stimuli different from the standard stimuli occur. If they are normally in a state of tonic inhibition, these neurons would only become responsive once they have been disinhibited by one or more standard stimuli. This proposal does not require any comparison process. The duration of the memory would then be determined by the peristence of the disinhibition. Javitt et al. [1996] suggested that this disinhibition might involve unblocking NMDA receptors in cortical neurons, since NMDA antagonists block the generation of the MMN in primate auditory cortex. A problem with this proposal is that inhibition (and thus disinhibition) is usually greater for neurons closer (both topographically and in terms of their frequency responsiveness) to those that initially respond to the standard stimulus, whereas the MMN is larger with greater deviance. This can be modelled in the circuitry, but the mechanisms are more complicated than simple disinhibition.

May et al. [1999] have recently proposed a neuronal model of MMN generation that involves three processes: recurrent excitation, adaptation (local inhibition) and lateral (non-local) inhibition. The model has been worked out mathematically using parameters obtained from studies of neurons in mammalian cerebral cortex. The model nicely explains both the amplitude and the latency of the MMN evoked by frequency deviants [Tiitinen et al., 1994]. The model does not involve a comparison process, and does not require a set of neurons distinct from those responding to afferent input. Its virtues are its simplicity and its derivation from known parameters of cortical neurons. Differences between the receptive fields (tuning curves) of different neuronal populations might explain the differences in the source analyses for the N_1 response to the standard (generated by all responding cells) and the MMN response to the frequency deviant (generated by those cells that have frequency-specific fields). Similar neuronal modelling can also provide relatively simple explanations for such phenomena as the MMN to a deviant stimulus that is identical to the standard but occurs at an earlier time than expected [May, 1999]. Mod-

elling the processes that underlie higher-order invariances (pattern and abstract) would be more complex, but nevertheless essential to our understanding how the MMN system works.

Psychological Aspects of the MMN

In searching out the truth be ready for the unexpected, for it is difficult to find and puzzling when you find it. Heraclitus, VII

The paper now turns to how the MMN is affected by internal rather than external information. The human brain builds models of the world, but these models are unable to predict everything. The MMN system indexes one of these models. In any modelling system, when the unexpected occurs, it must be either dismissed as irrelevant or incorporated into the model. The key to a better model is often a minor discrepancy in the present model.

Memory

One important aspect of the MMN is its relationship to memory. The MMN occurs if the deviant stimulus differs from some memory of the previous standard stimuli. The MMN differs from the simple activation of a non-refractory set of neurons since it only occurs if standard stimuli have previously occurred, i.e., a memory must have been initiated before a deviance from that memory can be detected [Cowan et al., 1993]. A stimulus presented by itself or after a long interval evokes a large N_1 response but does not evoke any definite MMN. Memory involves information processed at one time having an effect on information processed at a later time. Three different periods of time must be considered when evaluating the MMN in terms of memory. These times determine the establishment and persistence of the memory for the invariance.

First, the information necessary for defining the separate stimuli must be integrated over a brief period of time. Estimates of this period suggest that it is probably in the range of 150–300 ms. Tervaniemi et al. [1994b] showed that the omission of the second of two tones in a pair elicited an MMN if the interval between the tones was 140 ms or less (total duration of the pair was 260 ms or less) but not when the paired tones were separated by a longer interval. It is likely that at the longer intervals the tones were perceived as separate rather than paired. Similar estimates of the interval have come from stimulus omissions in continuous trains of stimuli [Yabe et al.,

1997]. Repeating two deviant stimuli in a row at different stimulus intervals gives two MMNs if the interval is longer than about 200 ms but only one MMN if the interval is shorter [Winkler et al., 1998; Sussman et al., 1999a]. This stimulus integration time will probably vary with the type of stimulus information being integrated.

Second, there must be a time during which the sensory data are available for regularities in the incoming information to be detected. This period of time pertains to the duration of sensory memory. In an extensive review of the literature, Cowan [1984] concluded that auditory sensory memory lasts somewhere between 10 and 20 s. Regularities recognizable within this period of time can then be encoded as representations of invariance. For non-pattern deviance the MMN system must distinguish the different stimuli, estimate their relative probabilities and categorize them as standard and deviant. Clearly the system must process at least 3 stimuli – 2 standards and 1 deviant – before it can determine that one of the stimuli is a repeating standard and the other a less probable deviant. Winkler et al. [1996a] found that an MMN to a change in frequency requires at least 2 standard stimuli. Once a particular invariance has been learned, a single standard stimulus can re-establish it at a later time [Cowan et al., 1993; Winkler et al., 1996a].

In order for the MMN system to recognize a repeating pattern of stimuli, it must process at least 2 examples of the standard pattern within the period of sensory memory. The time over which a pattern can be recognized as invariant by the MMN system was clearly indicated in a study wherein stimuli were presented in a regular sequence with the deviant stimuli separated by exactly 4 standard stimuli [Sussman et al., 1998b]. When the stimuli occurred with an ISI of 1.3 s [Scherg et al., 1989], a clear MMN occurred with the deviant stimulus even though its occurrence was completely predictable and not deviant in terms of the repeating 5-stimulus pattern. Two examples of the pattern, however, would have taken 13 s, and this would have been at the limits of sensory memory. If the ISI was decreased to 100 ms, no clear MMN occurred, indicating that the system that generates the MMN had been able to recognize the pattern and therefore did not consider the fifth element of the pattern as deviant. The distinctness of the pattern also plays a role, perhaps because the clarity of information maintained in sensory memory decays with time. In studies wherein 2 stimuli alternate, a deviant repetition elicits a larger MMN when the ISIs are shorter and when the alternating stimuli are more different [Alain et al., 1994]. When the standard and deviant stimuli are close together, the MMN system may

not detect the pattern [Ritter et al., 1992]. The integration of stimuli into a pattern therefore depends on the distinctness of the stimuli as well as the duration of the pattern.

Third, once it has been established, the representation of the invariance must last for a period of time without further reinforcement. There are no definite data concerning this period which might be perhaps 10 or even 20 s, i.e., similar to the duration of sensory memory. This estimate derives from studies that increase the standard-deviant interval until the deviant no longer elicits an MMN [Mäntysalo and Näätänen, 1987; Sams et al., 1993]. Unfortunately this is difficult since one has to decide when the measured MMN reaches zero (and this is not statistically very powerful).

The MMN system is based on two levels of representation: representation of recent stimuli in sensory memory and representation of invariances extracted from this memory. This raises the question of where in the flow of information processing the representations of invariance are stored. Schröger [1997] considered representations of invariance to be stored in the long store of auditory memory. Ritter et al. [1998] argued that the MMN system both extracts and maintains the representations of invariance. Whereas these questions have not been resolved, the view that the MMN operates on the basis of two levels of representation impacts on attempts to use the MMN to determine the duration of sensory memory. If the two levels of representation do not have the same duration, the current practice of lengthening the interval between the standards and the deviants until the MMN is no longer elicited yields ambiguous results, since the interval may exceed the duration of sensory memory or the duration of the relevant representation of invariance.

Object Perception

Auditory perception involves the grouping of incoming auditory information into auditory objects located in space [Bregman, 1990]. Since auditory objects persist over time, these objects can also be considered as streams of auditory information. The MMN appears to operate after auditory objects have been perceptually put together.

An experiment may illustrate this point. Ritter et al. [in press] presented tones in both ears. One combination of intensity, frequency, and duration for tones in the left ear alternated with another combination of these features for tones in the right ear. The idea was to have multiple features go together in each ear, in other words, to create the impression of two objects, one on the left and one on the right. The standard duration was 100 ms in the left ear and 300 ms in the right ear. Occasional deviant stimuli with a duration of 200 ms occurred in each ear (with the intensity and frequency appropriate to that ear). If the system were only tracking features, as in Gomes et al. [1995], then 2 MMNs should be elicited with latencies differing by 100 ms – one mismatching the 100-ms standard and initiated at 100 ms and one mismatching the 300-ms standard and initiated at 200 ms. Instead, only 1 MMN was elicited by deviants delivered to a given ear, with a latency appropriate for the standard duration of the tones presented to that ear. There was no MMN at the latency appropriate for detecting a difference from the immediately preceding tone (in the opposite ear). Thus, it appears that the MMN system was tracking (or maintaining a memory for) two separate objects.

Sams et al. [1991a] studied the effect of visual information on the processing of auditory speech stimuli. All of the speech stimuli were the syllable /pa/. Most of the stimuli were presented together with a video of a speaker articulating the same syllable. However, 16% of the stimuli were presented together with a visual /ka/ and the subjects heard these as /ta/ in keeping with the illusion called the 'McGurk effect' [McGurk and MacDonald, 1976]. These discordant stimuli (auditorily identical to the others) evoked a clear MMN, with a source in the temporal auditory cortex. The putting together of the visual and auditory information (or, more exactly, the effect of the visual information on the auditory processing) occurs prior to the MMN system.

Näätänen and Winkler [1999] have reviewed the MMN literature in the light of current ideas about auditory perception. They propose two distinct stages of auditory information processing. The first stage is the analysis of the separate features of the sound. The second stage is the binding together of these features into perceptible auditory objects or representations. They suggest that the auditory N_1 occurs after the first stage of processing and the MMN occurs after the second.

Attention

Many experiments recording the MMN do not clearly define what the subject is doing when the stimuli are being presented. Often the subject is reading. However, sometimes the subject is just described as 'passively' listening to the stimuli. This approach to the MMN would be reasonable if the MMN were independent of whether the stimuli are attended or not.

The initial description of the MMN proposed that it occurred automatically, regardless of whether or not subjects pay attention to the deviating stimulus [Näätänen et al., 1978]. Subsequent studies confirmed that MMN amplitude to large changes in a simple feature such as tonal frequency was insensitive to whether or not the stimuli are being attended [Alho et al., 1992, 1994a; Näätänen et al., 1993a; Woods et al., 1992]. However, as the definition of the deviating stimulus becomes more precise in terms of a simple deviant or more complex in terms of pattern, the MMN becomes more susceptible to attention. Smaller MMN amplitudes for ignored stimuli have been found for small changes in frequency [Alho et al., 1992; Woods et al., 1992], intensity [Näätänen et al., 1993a; Woldorff et al., 1991], duration [Alain et al., 1994] and pattern [Alain and Woods, 1997]. These effects of attention might be caused in part by the superposition of an attention-dependent N_{2b} component upon the MMN. However, Woldorff et al. [1998] have recently provided a clear demonstration that the attention-dependent magnetic MMN elicited by intensity changes had its source in the auditory cortex.

The circumstance that attention can affect the MMN does not necessarily mean that the MMN system itself is directly controlled by attention. As Woldorff et al. [1991] suggested, the processing of unattended tones in their experiment might have been attenuated prior to reaching the MMN system. In support of this possibility, Woldorff et al. [1987] found an attention effect (a reduction of activity associated with unattended tones) at a latency of around 20 ms in the experiment that showed the attentionally sensitive MMN. Attention might therefore not have had any direct effect on the MMN system but only on its inputs.
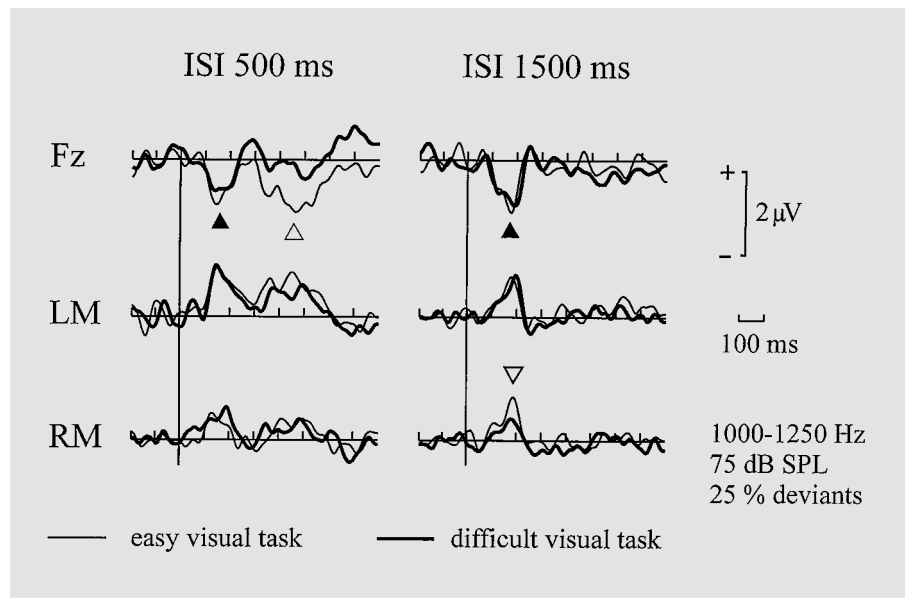
The studies described so far in this section used attention within the auditory modality to address the automaticity of the MMN. The MMN is most often recorded when the subject pays attention in the visual modality (e.g., reads) and ignores the auditory stimuli. Alho et al. [1992, 1994a] found no effect of visual processing load on MMN amplitude to either small- or large-frequency deviants, and Kathman et al. [1999] found no effect of visual attention on the MMN to duration or frequency deviants. A recent study has shown that a visual environment that is positive and non-threatening elicits a smaller MMN to auditory deviant stimuli compared to a negative or neutral visual environment [Surakka et al., 1998]. Whether this works on the input to the MMN system or on the MMN system itself remains an open question.

To evaluate the effects of visual processing load on the processing of large frequency deviants occurring at short or long ISIs, we have recently examined MMN amplitude while the subject was engaged in a concurrent visual task with two levels of difficulty [Otten et al., in press]. Red and green colored numbers (1, 2, 3, 4, 6, 7, 8 or 9) were presented visually at intervals ranging between 1.4 and 1.9 s. The easy visual task simply involved responding with one hand when the visual stimulus (regardless of color) was less than 5 and with the other hand when the stimulus was greater than 5. The difficult visual task required the subject to give a response on the basis of the magnitude of the currently presented digit if the digit was of one color and on the basis of the magnitude of the previously presented digit ('one-back') if the digit was of the other color. This involved a continuous and effortful allocation of both memory and attentional resources. Visual task performance verified the increased demands of the difficult visual task, with the reaction times being significantly longer for the more difficult task. Auditory evoked potentials were recorded at two ISIs while the subjects performed the visual tasks. The results (fig. 4) showed no clear difference in the MMN recorded at the mid-frontal electrodes over the latency range of 150–200 ms. However, there were two clear effects of visual processing load on the difference waveforms.

First, a large late negative wave peaked around 450 ms in the difference waveform for the fast stimulus rate during the easy visual task. This might represent further evaluation of the irrelevant deviants when they occur more frequently and when the concurrent visual task demands are low. The call to attention might thus be 'heeded' when attentional resources are available. Schröger and Wolff [1998a] have recorded a similar late frontal negative wave in a paradigm wherein certain stimulus features were irrelevant but distracting. Stimuli were equiprobably of long or short duration. Ten percent of the stimuli had a deviant frequency from the others. Subjects were asked either to discriminate whether tones were of short or long duration (while ignoring the occasional deviations in frequency) or to ignore all auditory stimuli and read a book. A typical MMN occurred in response to the frequency deviant in both conditions. In the attend/distract condition a later negative wave occurred in response to the irrelevant deviant. This might represent a re-orienting from the task-irrelevant processing (frequency) back to the relevant processing (duration) [Schröger, 1998b]. Escera et al. [1998] and Alain and Woods [1997] described a frontal negative wave with a peak latency at 400 ms in addition to the typical MMN in the deviant-standard waveform, but neither speculated on its meaning.

Fig. 4. Effects of attention on the MMN. The figure shows the deviant-standard difference waveforms recorded in response to auditory stimuli while the subject paid attention to an easy or a difficult visual task [Otten et al., in press]. The auditory responses were obtained at two different ISIs. There is no clear difference in the MMN recorded from Fz in relation to the different visual tasks (filled arrowhead). However, there is a later negative wave (unfilled upgoing arrowhead) recorded from Fz when the task was easy and the rate was fast. Furthermore, a small positive wave recorded from the right mastoid (RM) but not the left (LM; downgoing unfilled arrowhead) was also affected by whether the visual task required more or less attention.

Second, a small positive wave recorded over the right mid-temporal and mastoid regions was larger when the visual task was easy and the stimulus rate slow. This might represent some activity in the lateral wall of the temporal lobe in response to the deviant stimulus when the demands of the visual task are low. With respect to the classic frontocentral MMN, however, the results showed no evidence to suggest that visual processing load influenced the MMN at either short or long ISIs.

Input Systems as Modules

Fodor [1983] proposed that the brain uses information processing modules. These modules are particularly evident in the analysis of incoming sensory information. Modular systems are distinguished from central cognitive processing in many ways (table 1). These input systems can process very complicated information, such as sentence structure or lexical decisions. However, the information in the system is not affected by expectancies in other systems and the output is without meaning in relation to these expectancies. The MMN shares many of these characteristics.

Some recent evidence for the independence of the MMN from cognitive processing derived from a paradigm that presents pairs of stimuli [Ritter et al., 1999]. The first stimulus of the pair is visual and the second stimulus is auditory. Occasionally, one of the auditory

stimuli is shorter than the other auditory stimuli. The subject's task is to respond to this deviant stimulus. In the 'unpredictable' condition the visual stimuli have no relationship to the auditory stimuli other than their timing. The deviant auditory stimuli elicit an MMN and subsequently an N_{2b} and P_{300} wave as the subject recognizes the deviant. The paradigm is then altered so that there are two visual stimuli, with one of these stimuli correctly predicting the deviant auditory stimulus and the other correctly predicting the standard auditory stimulus. Now the subject responds with an N_{2b}-P_{300} complex to the visual cue that predicts the deviant stimulus, and the endogenous evoked potentials to the deviant stimulus are markedly decreased. However, the MMN to the deviant auditory stimulus is unaffected by this manipulation. The cognitive system is using the information in the visual cue to control the motor response and is paying little attention to the deviant auditory stimulus. However, the MMN system continues on its own automatic way pointing out that the deviant stimulus is different from the preceding standard stimulus even though this information is unnecessary to the cognitive system. These results indicate that the MMN occurs in a system that works automatically to detect deviance in the auditory input, regardless of whether this deviance is useful or not.

We have also looked at this paradigm using cues in the auditory modality [Picton et al., in preparation]. Since the auditory system can recognize patterns of stimuli over periods of a second, it seemed possible that the pairs of

Table 1. Characteristics of modular systems

Domain specificity	'specialized systems for specialized tasks' (p. 52)
Mandatory activation	'input systems are constrained to apply whenever they can apply' (p. 53)
Limited central access	'only such representations as constitute the final consequences of input processing are fully and freely available to the cognitive processes that eventuate in the voluntary determination of overt behaviour' (p. 56)
Fast processing	'because these processes are automatic, you save computation (hence time) that would otherwise have to be devoted to deciding whether, and how, they ought to be performed' (p. 64)
Informational encapsulation	'of all the information that might in principle bear upon a problem of perceptual analysis only a portion (perhaps only quite a small and stereotyped portion) is actually admitted for consideration' (p. 70)
Shallow outputs	'basic categorizations are the ones that you would want the input system to deliver assuming that you are interested in maximizing the information per unit of perceptual integration' (p. 97)
Fixed neural architecture	'hardwired connections indicate privileged paths of informational access; the effect of hardwiring is thus to facilitate the flow of information from one neural structure to another' (p. 98)
Specific breakdown patterns	'the agnosias and aphasias constitute patterned failures of functioning ... This is hardly surprising if, on the one hand, input analysis is effected by specific hardwired neural circuitry and, on the other, the pathologies of the input systems are caused by insult to these specialized circuits' (p. 99)
Characteristic development	'the neural mechanisms subserving input analysis develop according to specific, endogenously determined patterns under the impact of environmental releasers' (p. 100)

Quotations in the second column are from Fodor [1983].

stimuli would be treated as units when both members of the pair were auditory. We used cues in either the opposite ear or the same ear as the deviant and standard stimuli. The results with the auditory cues were similar to the results with the visual cues (fig. 5). The MMN detects the deviant stimulus without regard to the fact that this detection is irrelevant to the task. The information about what response to make is provided by the cue and the deviant auditory stimulus only confirms what the subject already knows. Even when the cue and the deviant stimulus are in the same ear, the MMN still occurs. The system does not process the stimuli as pairs even when they are in the same modality and in the same ear. Several factors need to be considered in this regard. First, the interval between the paired stimuli is longer than the 200–300 ms required to integrate an auditory event. Different results might have been obtained with a shorter interval between the paired stimuli, particularly when both stimuli were auditory. Second, the MMN system may not have been able to recognize the invariance that the cue for the deviant stimulus always preceded the deviant. Only rarely would two or more cue-deviant pairs occur in the 10- to 20-second period of auditory sensory memory. Different results might have been obtained if the cue-deviant stimuli had been more probable.

Clinical Usefulness of the MMN

We know health by illness, good by evil, satisfaction by hunger, leisure by fatigue. Heraclitus, LXVII

The MMN has been recorded in many different clinical contexts. Its advantage over the sensory evoked potentials is that it reflects discrimination and memory in addition to sensation. Its advantage over the later endogenous evoked potentials is that it occurs automatically and does not require the patient's involvement in any task. The MMN may be useful in clinical situations in two different ways. The first is to evaluate the perceptual and mnemonic processing that occurs in a group of patients with a particular disorder. This information may help us to understand what is going wrong in this disorder. A second
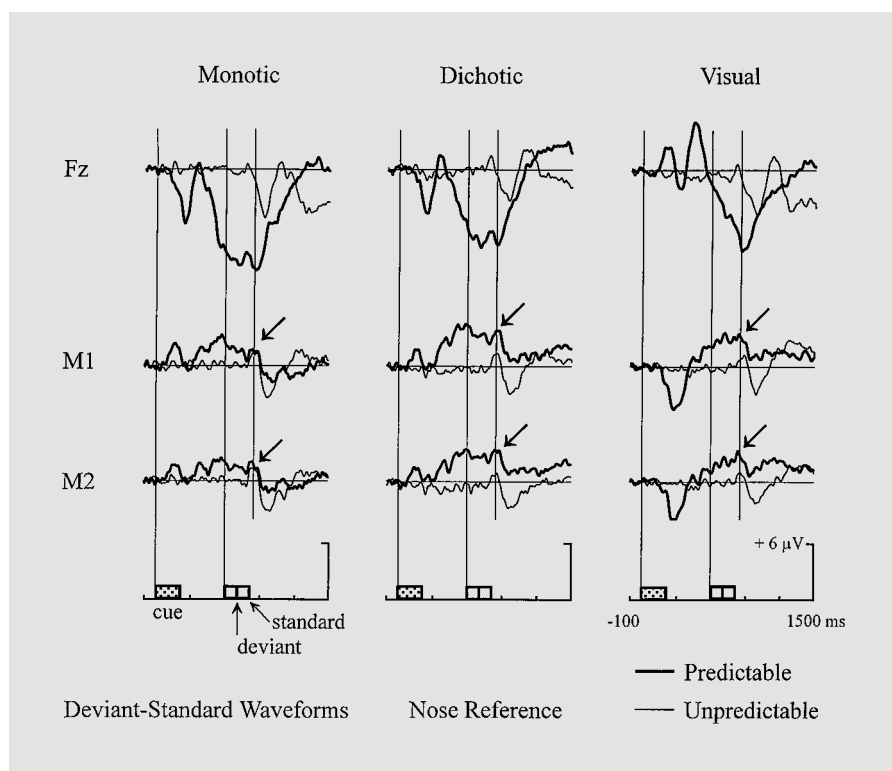
Fig. 5. MMN as a modular input system. These data represent the results from a study that extended and replicated the findings of Ritter et al. [1999]. Stimuli were presented in pairs with 600 ms between the onset of the stimuli. The first stimulus was a 'cue' and the second stimulus was one of two auditory stimuli – a probable standard stimulus and an improbable deviant stimulus. The duration of the deviant auditory stimulus was 100 ms and that of the standard 200 ms. Three types of cues were used: a visual cue (X or O) or an auditory cue that could be either in the same ear as the standard and deviant (monotic) or in the opposite ear (dichotic). Two conditions were used: in the 'predictable' condition, the cue informed the subject whether the following auditory stimulus would be a standard or a deviant: in the 'unpredictable' condition, only one cue occurred and there was no way to know beforehand whether the second stimulus would be a standard or a deviant. The subject's task was to press a button in response to the deviant stimulus. In the predictable conditions, a contingent negative variation wave occurs at Fz between the cue (first vertical line) and the standard or deviant auditory stimulus (second vertical line) as the subject prepares to make a decision about this stimulus. The arrows indicate that an MMN can be recorded in response to the deviant stimulus regardless of whether it is predictable or unpredictable. This MMN is most easily recognized as a positive (upward) deflection at the mastoids where it is not contaminated by the N_{2b} wave that occurs at Fz. The third vertical line is at 825 ms, 125 ms after the latency at which the 100-ms deviant stimulus would have been detectable.

use would be to diagnose a particular abnormality of processing or a particular clinical disorder in an individual patient. These two clinical uses require different statistics. Increased understanding of a disorder can derive from group comparisons. Diagnosing an individual patient requires that the measurements in that patient be outside the limits of what is considered normal. Because of the small size of the MMN, there are definite problems in distinguishing the response from the residual background EEG. Statements about groups are possible, but individual measurements are not yet sufficiently reliable, sensitive or specific to make statements about individual subjects.

Signals in Noise

The MMN is not as large as many other ERP waves and it occurs in high levels of background noise. The MMN varies in amplitude from fractions of a microvolt to several microvolts. Although it is only a few times larger than the auditory brainstem response, it is usually averaged over many fewer trials than the thousands used to record the auditory brainstem response clinically. How to recognize whether an MMN is present or not is the most important question to be considered in any application of the MMN to either clinical diagnosis or experimental science.

Distinguishing the MMN from the averaged background noise raises two problems. First, calculating difference waveforms increases noise in the recording since the noise of the standard is added to the noise in the deviant response. Second, it is not always clear where to look for the MMN. Multiple measurements taken at multiple latencies are much more difficult to assess statistically than arbitrary single measurements. The 'integrated MMN' [Ponton et al., 1997] and other area measurements are reasonable ways to combine multiple measurements into one.

In evaluating the MMN there are always fewer deviant responses than standard responses. The usual measurement of the MMN involves either comparing the deviant response to the standard or comparing the deviant-standard difference to zero. In both situations, the noise levels that determine whether the results are significant are primarily those of the deviant response. As McGee et al. [1997b] have pointed out, it is far better to obtain the best standard response possible by averaging all available responses rather than to make the standard response as noisy as the deviant response by only averaging a selected subsample of the standard responses. Since the standard following a deviant may contain some MMN, it might be reasonable not to include such trials in the average standard response. In certain situations, when there are stimulus-specific artefacts or sensory responses, it is necessary to compare responses to the same stimulus when it acts as an improbable deviant and when it is the probable standard [Ponton and Don, 1995]. Again, it is important to obtain the best standard response possible.

What type of measurement provides the best discrimination of the MMN from background noise? Different papers have measured the MMN peak amplitude, the mean MMN value over an arbitrarily determined latency range and the area under the curve above the baseline between the time points where the MMN first exceeds and finally returns below baseline. McGee et al. [1997a] compared the efficiency of various MMN measurements by determining both their hit rate (how many times an MMN was correctly detected in deviant-standard difference waveforms) and their false alarm rate (how many times an MMN was inappropriately identified in standard-standard difference waveforms). They found that an area measurement was the best single discriminator for the MMN. However, for the data used (phoneme mismatch in children), the discrimination was not precise for single subjects (a hit rate of 80% with a false alarm rate of 28% yielding a d' of 1.42).

The integrated MMN technique [Ponton et al., 1997] has several advantages over simple amplitude measurements. First, it integrates the measured amplitude over time (until a point which is selected a priori to remove any possible bias from picking the largest difference a posteriori). Second, it does not calculate difference waveforms but directly compares the integrated deviant response to the integrated standard response. Third, it takes advantage of the greater number of standard responses to assess the distribution of the standard response (by randomly sampling from the available standard responses) and then compares the deviant response to this distribution. Fourth, the statistical assessment is distribution free since the probability of the integrated deviant response being included within the distribution of the integrated standard responses is directly determined by how many standard responses are above or below the deviant response.

The PC1 technique for detecting an ERP signal performs a principal-component analysis of a set of ERP waveforms [Achim, 1995]. In order to apply this to the MMN, one needs a set of replicate MMN waveforms from a subject. The deviant responses may be obtained from single deviant trials or (preferably) from averages over small numbers of deviant trials. Standard responses are averaged during the period of time when the deviant stimuli occurred (thus basing the standard responses on more trials than the deviant responses). The standard responses are subtracted away from the concurrent deviant responses to give a set of difference waveforms. A principal-component analysis of the difference waveforms yields a first component that explains the greatest part of the variance of these waveforms. This first principal component is an unbiased estimate of the constant response present in the replicate waveforms. Each of the individual waveforms is then related to this first principal-component waveform by point-by-point multiplication and summing the resultant products (effectively the same as calculating 'component scores'). If there is no MMN (or other difference) present, the scores will be randomly distributed around zero; if there is an MMN, the scores will tend to share either a positive or negative polarity (depending on the polarity of the principal-component waveform). A two-tailed t test on these scores will provide an unbiased and sensitive test of whether or not an MMN is present in the recording. In principle, this should offer all the advantages of the integrated MMN approach, but it embeds the further feature that the different data points are not equally weighted: the weights are adapted to the data, being determined from the dominant waveform shared by the
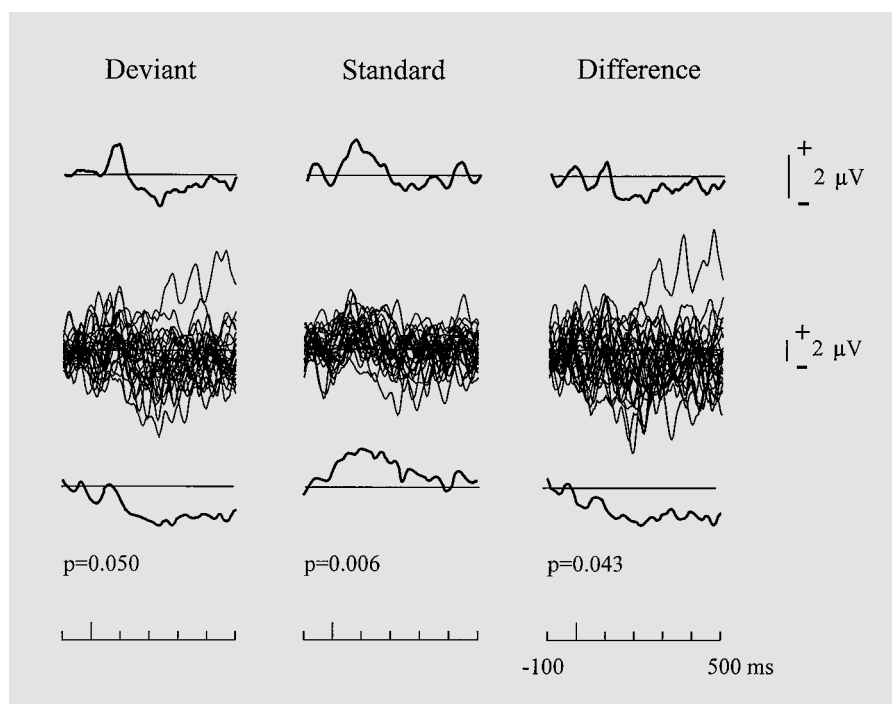
Fig. 6. Principal-component analysis of the MMN. The data are from a single subject in a single block of trials recorded during the study of Otten et al. [in press]. Stimuli occurred at a rate of 2/s. At the top of the figure are shown the mean waveforms over the recording block. The standard responses were averaged over 420 trials and the deviant responses were averaged over 140 trials. In response to the standard there is no recognizable N_1 response because at these rates the response consists mainly of a P_1-P_2 wave. In the middle of the figure are shown 28 superimposed subaverages for each of these responses. For these waveforms averaging was performed over 15 trials for the standard responses and 5 trials for the deviant responses. Difference waveforms were calculated by subtracting the subaveraged standard responses from the subaveraged deviant responses. The replications are plotted at one half the scale of the block-averaged responses. At the bottom of the figure are shown the first principal components obtained from an analysis of the subaverages. The scale for this response is arbitrary. Underneath these waveforms are shown the probabilities (t test) that there is a response in the subaverages that is consistent with the waveform of this first principal component.

various replications of the standard-deviant difference. Figure 6 shows this technique in operation.

This approach has several advantages. First, it looks for a waveform rather than for a deflection in a particular direction. Thus, the measurement of the mismatch effect is not compromised if the MMN is followed by a positive wave. (On the other hand, the technique will not necessarily detect the MMN and will just as easily detect a significant change in the N_1 or P_{300} waves.) Second, it can combine data across different scalp locations. The waveforms recorded from the different scalp locations are just concatenated prior to being submitted to the principal-component analysis. This may improve the statistical power of the test, depending on the signal-to-noise ratios in the additional channels. Third, it can be a priori limited to look only at a selected latency region, chosen on the basis of where one expects to see the MMN difference.

Whatever the technique for identifying the MMN, increasing the signal-to-noise ratio of the recording will be necessary if the MMN is to be used as a clinical test to assess individual patients. The noise level can be reduced in two ways: filtering and averaging. Most studies of the MMN do not optimally filter the recordings. Since the MMN has most of its energy in the 2- to 5-Hz frequency band, digitally filtering the recordings using a much tighter bandpass than the usual 0.1–30 Hz should be worthwhile (e.g., Tervaniemi et al. [1999b] used 2–10 Hz). Although this will distort other parts of the ERP waveform such as the N_1 and the P_{300} waves, it should provide a better look at the MMN.

Averaging more deviant responses will decrease the noise level in the recording. If the MMN were constant with decreasing interdeviant interval, the recording would be more efficient in paradigms using shorter inter-

deviant intervals since more deviant responses would be averaged within a given period of time. Since the MMN is likely to be smaller at shorter interdeviant intervals, one can calculate a measure of efficiency at each interval by dividing the amplitude by the square root of the average interval between the deviant stimuli (discussed in terms of the N_1 in Picton et al. [1977]). Such efficiency measures can be used to choose the stimulus paradigm that will provide the best signal-to-noise ratio in a given amount of testing time.

These considerations assume that the MMN has a constant amplitude. Although the MMN is replicable between recording sessions on different days [Pekkonen et al., 1995], there is sometimes a tendency for the MMN to decrease in size over a prolonged recording period [Lang et al., 1995]. This decrease may be due to adaptation of the generator process or a decrease in vigilance [Sallinen and Lyytinen, 1997]. Other studies have shown that the MMN recorded frontally (but not at the mastoid) may actually increase from one block to the next [Baldeweg et al., 1999b]. This may possibly be due to the superimposition of a frontal N_{2b} wave with changes in attention in passive subjects. Adaptation, attention and sleepiness therefore need to be considered in designing the optimal recording paradigm.

Reliability, Sensitivity and Specificity

In order for a physiological measurement to be used clinically, it must reliably and accurately discriminate between patients with a particular disorder and those without. Reliability measures the closeness of multiple measurement in a particular subject in a particular state. Several recent papers have clearly documented that the MMN is reasonably reliable in that different recording sessions provide similar measurements [Pekkonen et al., 1995; Joutsiniemi et al., 1998; Kathman et al., 1999] with correlation coefficients reaching 0.78 [Tervaniemi et al., 1999b].

While reliability looks at intrasubject variance, the differentiation between patients and normal subjects relies on intersubject variances [Sackett et al., 1991]. The discrimination of a particular patient from a group of normal subjects will depend on the limits of the normal measurements. If the limits of normal amplitude include zero, it will not be possible to consider any MMN abnormally small or absent. Although the data were available, the reliability studies mentioned in the previous paragraph did not focus on the limits of normal. The data illustrated in the papers suggest that the lower limit of MMN amplitude

in normal subjects approaches zero. The variances of the results in the normal group and in the patient group lead to measures of sensitivity and specificity. Once a criterion of abnormality (e.g., an MMN smaller than 0.5 µV) is determined, the sensitivity and specificity of a test can be estimated. Sensitivity is the probability that an abnormal measurement will be obtained in a group of patients with the disorder to be diagnosed. Specificity is the probability that the response will be normal in a group of patients without the disorder. Other approaches combine these estimates into a measurement of test accuracy [Swets, 1988]. None of these techniques have yet been applied to the MMN measurements.

Problems with Patients

Patients with clinical disorders are quite different from the normal control subjects that have provided most of our knowledge about the MMN. ERPs recorded from patients are often smaller and more variable than those recorded from normal control subjects. Indeed, the intent of a clinical ERP study is often to demonstrate that a particular ERP component is absent or smaller than in normal subjects. Demonstrating that the MMN is absent or smaller than normal will require much more averaging than simply demonstrating that it is present with normal amplitude (itself not always an easy task). This problem is compounded with the fact that the level of background EEG noise and the incidence of non-cerebral artefacts are often greater in patients than in normal subjects.

In terms of the signal-to-noise ratios, it may be worthwhile to reconsider the N_1 in terms of clinical diagnosis, since the N_1 wave can be much larger than the MMN. Martin and Boothroyd [1999] demonstrated that the N_1 wave evoked by a change in the ongoing acoustic parameters of a sound (between a tonal complex with a periodic quality and a noise with the same spectral envelope but no periodicity) displayed a significantly larger signal-to-noise ratio than the MMN evoked by a deviant stimulus showing a similar change in acoustic parameters. O'Donnell et al. [1994] found a significant difference in N_1 amplitude but no significant difference in MMN between schizophrenic patients and controls. In comparing the N_1 and the MMN the final decision will rest on both the ease of recording and the accuracy whereby the measurements predict perceptual ability. The N_1 has mainly been used to estimate hearing threshold rather than perceptual discrimination, and different paradigms will be needed for looking at discrimination [Martin and Boothroyd, 1999].

Physiologists and psychologists usually work with groups of subjects and look for cerebral processes that differ between the groups. Clinical testing needs to conclude something about each individual patient. Differences between groups may not be distinct enough to indicate anything definite about an individual subject. Group effects are interesting to the clinician by suggesting pathological mechanisms. However, these effects cannot lead to a clinical test unless they are so large that there is little overlap between the groups.

Demonstrating that a possible clinical test is worthwhile requires calculating the cost and effectiveness (which derives from sensitivity and specificity) of the test. How well does it characterize an individual patient as different from normal? How often does it characterize a normal subject as abnormal (false alarms)? How often does it incorrectly characterize a patient as normal (miss)? Choosing the best ratio of false alarms to misses will depend on the test's costs (for administering the test to all the subjects plus the cost of missing some of the patients) and the benefits (of making the diagnosis in a patient and treating the patient before a diagnosis could otherwise have been made). Cost-benefit calculations must be based on the group of subjects usually referred for testing (and not on a group of patients and a group of completely normal subjects). Patients with a similar presentation to those that are to be diagnosed (e.g., depressed as opposed to demented patients) are often far more difficult to distinguish from the target patients than completely normal subjects. Patienthood is one of the problems of clinical diagnosis. Differentiating patients from normal subjects is often much easier than differentiating patients of one kind from those of another. In this regard, the results of Catts et al. [1995], showing that the MMN was reduced in schizophrenic patients but not in patients with affective disorders, are important.

The MMN would be most useful in patients for whom there is no other clear diagnostic test. Unfortunately this makes it difficult to validate the test on the basis of diagnosis, prognosis or response to treatment. Bootstrapping is often necessary, in the sense that one may find that patients categorized on the basis of differences in their MMN may turn out to be different in other aspects, such as their response to treatment. However, intelligent boots are helpful – some theoretical justification for why the MMN is affected or not in a particular disorder will make it more likely for the measurement to be diagnostically helpful.

Disorders of Perception

Perhaps the most important clinical application of the MMN may be to demonstrate auditory discrimination in patients who are unable to respond behaviourally. The main paradigm for studying discrimination is to measure the presence or absence of the MMN as the difference between the deviant and the standard is decreased. The presence of an MMN indicates that the brain is capable of discriminating the stimuli. The lowest level at which an MMN can be demonstrated is the electrophysiological threshold for discrimination. In experimental studies of normal subjects this threshold is very similar to the subject's behavioural threshold [Sams et al., 1985]. At times it may also be possible to see an MMN at subthreshold level when the subject is uncertain [Näätänen, 1992, p. 138]. However, in testing patients whose signal-to-noise levels are much less than in normal subjects, it is not easy to demonstrate the presence of a small MMN near threshold. Measuring discrimination threshold requires that the standard and deviant stimuli be brought closer and closer together until there is no longer a recognizable MMN. The tester must be sure when a response is not present (and this is a statistical nightmare). If one sets threshold at the level where a statistically reliable MMN is detected, the electrophysiological threshold will significantly exceed the behavioural threshold. Another approach is to determine whether some parameter of the MMN measured at a suprathreshold level correlates with the subject's perceptual ability [Lang et al., 1990]. For example, if the MMN amplitude evoked by a frequency deviance of X Hz is larger than some criterion, perhaps one can conclude that the perceptual threshold is less than some fraction of X Hz.

Of particular importance is the evaluation of speech discrimination. In infants and young children it is essential to have some measure that can reliably demonstrate whether or not the child can discriminate normal speech sounds. Studies of the MMN in children have suggested that this might be such a measurement [Kraus et al., 1993; Csépe, 1995], although problems with intersubject variability and response detection remain [Lang et al., 1995]. Of particular importance is the demonstration of mismatch responses in infants [Alho and Cheour, 1997] since it is essential to find out about hearing problems as early as possible. Since many causes of abnormal discrimination occur in the cochlea, one may not need to record as late as the MMN to demonstrate the abnormality. Responses to frequency modulation can be obtained from the brainstem [John and Picton, in preparation], and the

lack of such responses could indicate that sensory analysis is not working well enough to allow a later MMN. Nevertheless, a significant proportion of patients with central auditory processing disorders probably have cortical rather than subcortical disorders, and the MMN might then be the earliest abnormality. Measurements of the MMN might also demonstrate abnormalities in children whose primary abnormalities are in the domains of learning or language rather than hearing [Kraus et al., 1996]. Baldeweg et al. [1999a] have shown that dyslexic subjects have abnormalities in the MMN to changes in frequency but not changes in duration.

Many studies have shown that schizophrenic patients characteristically have smaller MMN than normal subjects [reviewed in Gené-Cos et al., 1999]. Javitt et al. [1995] have shown that the MMN is smaller in schizophrenic patients than control subjects but that the effects of deviant probability and interdeviant interval were similar in the two groups, suggesting abnormal perceptual mechanisms rather than abnormal memory mechanisms [Javitt et al., 1998]. Alain et al. [1998b] found that the pattern MMN in schizophrenic patients has a different scalp topography than in normal subjects. This suggests that pattern perception is particularly disordered in schizophrenic subjects.

Disorders of Memory

The basic paradigm for studying memory with the MMN is to evaluate the MMN while varying the temporal parameters of memory. Pekkonen et al. [1993, 1996] found, for example, that the MMN decreases with increasing ISIs (from 1 to 4.5 s) and that this change was greater in elderly than in young subjects. The decrease was even greater in patients with Alzheimer's disease [Pekkonen et al., 1994]. These results suggest that the MMN indexes a deterioration in the persistence of auditory sensory memory with normal aging and that this is exacerbated in Alzheimer's disease. This paradigm is one case where within-patient statistics may be used, because the diagnostic sign would be the positive detection of a difference in MMN between two conditions (i.e., that the MMN is significantly smaller at the longer of two adjacent ISIs). This is simpler than making a decision on the failure to detect something.

As we have pointed out, however, the MMN is characterized by multiple temporal parameters. Among these are the time over which stimuli can be integrated, the time over which a pattern of invariance can be detected, and the time over which the representations of this invariance can be maintained. All of these need to be manipulated and evaluated in patients with disorders of memory. The simple change of the ISI is a much more complex manipulation than it seems and may not be the best approach to demonstrating memory disorders.

Disorders of Consciousness

The MMN has been used to demonstrate that consciousness may be about to return in comatose patients [Kane et al., 1996]. This is and exciting finding. However, the relationship between the MMN and consciousness is indirect and is probably mediated by some intervening variable such as the extent of brain damage. The MMN does not represent conscious processing. It represents an automatic processing of sensory information. Such automatic processing may be a necessary prerequisite of conscious processing. However, if one wishes specifically to examine conscious processing, other components of the ERP might be more important. In the patient coming out of coma, these other potentials may also relate to prognosis [Gott et al., 1991; Guérit et al., 1999; Fischer et al., 1999; Kane et al., 2000].

Conclusion

To do the same thing over and over is not only boredom: it is to be controlled by rather than to control what you do. Heraclitus, LIII

This short and selective review concludes with some comments about whither our research efforts might go. The field is vigorous and will continue to enhance our understanding of cerebral function, but it might be worthwhile to consider some particular directions – the new water in the old river.

It is always important that we make our experiments relevant to the real world. Real-world environments do not always fit easily with the technical needs for recording ERPs which requires time-locking of the recording to stimuli and repetition to allow averaging, but we should try our best to use natural stimuli. The present trend to using real stimuli is important and should be continued. The MMN system did probably not evolve to tell us about sounds that we only hear in the laboratory, and it will be important to examine how the MMN system processes speech sounds [Kraus et al., 1995; Cheour et al., 1998]. The fact that it is automatic and highly discriminative

probably means that it contributes importantly to perception. Likely candidates for this contribution are auditory scene analysis (streaming and the recognition of auditory objects) and the perception of speech (the prediction of upcoming sounds or the distinction between competing sound sequences). Scene analysis likely occurs prior to the MMN [Sussman et al., 1999a] since the MMN system can work on the basis of auditory objects [Ritter et al., in preparation]. However, the MMN may serve to monitor this processing when the auditory input is not being attended to.

Along the same vein, it might be worthwhile to pursue more intensively the functional significance of the MMN. Much of our research effort has been directed to finding out what determines the MMN. We need now to increase our efforts to understand the role played by the MMN in information processing. There are several suggestions in the literature about this role. The MMN might represent a trigger for attentional involvement with the stimuli [Näätänen, 1992] – a 'call' to attention [Giard et al., 1990] that may or may not be heeded by higher levels of the nervous system depending on the context. Giard et al. [1990] have suggested that the temporal MMN might represent the detection of a discrepancy and the right frontal MMN the call to attention. It is also possible that the MMN represents an automatic adaptation of an ongoing model of the auditory world [Winkler et al., 1996b]. Experiments that look at what happens to other cognitive processes when an MMN occurs [Schröger and Wolff, 1998a, b; Escera et al., 1998] indicate an important direction for future research.

There should be more research on the neural mechanisms of the MMN in animals [Javitt et al., 1996]. Results with animals can provide a more exact testing of the various theories of how the MMN system operates. Furthermore, such research might allow us to determine the neuronal transmitter systems involved. Mathematically modelling the processes [May, 1999] will allow the limited animal data to be extrapolated into the great variety of paradigms used in human studies.

It is probably worthwhile to use paradigms designed to look specifically at particular memory or sensory processes rather than the routine 'oddball' paradigm. There is much more to the MMN than will be found by manipulating the probability of the deviant and the ISI. Even these simple parameters are confounded in the simple oddball paradigm.

One of the advantages of the MMN is that it does not require the cognitive involvement of the subject in the task. Fewer behavioural controls and measurements are needed. The MMN can tell us a lot about the sensory processes that provide input to cognition. Indeed, there may not be an easy behavioural way to examine these sensory processes, since they are 'cognitively impenetrable'. On the other hand, the MMN cannot tell us much about conscious processing. The brain is little conscious of irrelevant sounds when it is engaged in reading a book. Since conscious cognitive processes are variable in their electrophysiological manifestations and difficult to understand, the ease of the MMN is beguiling. This is not to fault the importance of the MMN or of passive paradigms. Rather, it is to recall the importance of the later ERP waves and active paradigms. In many situations it might be worthwhile to record ERPs both when the subjects are actively attending to the stimuli and when they are not. Not only can such recordings be used to monitor what is going on in conscious processing (e.g., the differences in the contingent negative variation in fig. 5), but they may also tell us how the information analysed in the automatic MMN system is used at higher levels in the brain.

This paper derives from a presentation at a meeting on the clinical applications of the MMN held in Helsinki under the direction of Risto Näätänen. The discovery of the MMN [Näätänen et al., 1978] was an important contribution to our understanding of how the human brain works. In the context of this issue celebrating the coming of age of the MMN, it is interesting to wonder why such a discovery occurred. Näätänen was and is knowledgeable, persistent and optimistic. Knowledge allowed insight, persistence provided data, optimism gave energy, and our understanding of auditory processing has increased remarkably with our study of the MMN. As this review has indicated, we still need more details about the MMN and we need to fit these details together into a working theory of how the brain perceives the world, predicts what will happen and notices what has not been predicted. There remain many experiments to do.

Men who wish to know about the world must learn about it in its particular details. Heraclitus, IX

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