

Human cortical functions in auditory change detection evaluated with multiple brain research methods

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Abstract

The present thesis examined in human subjects the brain mechanisms involved in the detection of unattended auditory changes. According to previous results, the auditory change-detection mechanism consists of several anatomical and functional units which are activated within the first 200 ms after the onset of sound change. In order to investigate this mechanism with high temporal and spatial resolution, electroencephalography, magnetoencephalography, functional magnetic resonance imaging, and the new method of recording the event-related optical signal were used.

Näätänen's model of auditory change detection assumes that change detection is based on a memory representation of the past auditory events, which contain information about the physical characteristics (e.g., frequency) and abstract relations of sounds (e.g., ascending vs. descending tone pair). Furthermore, the model assumes that change detection occurs independently of attentional resources and may lead to a switch of attention to the change occurring in unattended sounds. The results of the present studies were in concordance with these assumptions: First, it was shown that the memory system underlying auditory change detection operates also on categorical speech information. Second, the relation of the change-detection mechanism and volitional control functions was further clarified by showing that the subject's foreknowledge of sound changes does not affect the functioning of the change-detection mechanism. Third, anatomical information about the temporal-frontal lobe network of brain areas involved in auditory change detection was provided. (The exact location of the brain areas in the frontal lobe involved in change detection was not known previously.) Furthermore, it was shown that the temporal-frontal lobe network was activated in an order that is congruent with the assumption that a temporal-lobe change-detection process triggers subsequent processes in the frontal lobe associated with the initiation of an attention switch. Finally, based on the present results, an updated version of Näätänen's model was proposed.

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1 Introduction

1.1 Auditory change detection

A wealth of information enters the auditory sensory system continuously. However, as the attentive processing capacity of the human brain is limited, only a subset of the sensory information may be evaluated under attentional control. Therefore, most theories of human auditory information processing (Broadbent 1958; Treisman 1960; Näätänen 1990; Näätänen 1992; Cowan 1995) are based on a similar core model assuming a *large-capacity system* in which the initial sound analysis is performed and a subsequent *limited-capacity system* in which the most important or relevant subset of the sensory information may be processed under attentional control (for a critical review of the core model, see Allport 1993). Auditory information may enter the limited-capacity system as a result of active selection when attention is focused according to behavioral needs on certain events in the environment. In addition, this selection of information may occur passively, triggered by a potentially important sensory event such as a sound occurring in silence or a sudden breakdown of a regular sound pattern in the unattended auditory environment. Such potentially important sensory events appear as *changes* in the sensory input. In this thesis, the brain mechanisms involved in the detection of unattended auditory changes are examined.

1.2 Electric and magnetic brain responses as indexes of the change detection mechanism

A large part of the knowledge about the brain mechanisms of auditory change detection is based on electric and magnetic brain responses observed in the non-invasively recorded electroencephalogram (EEG) and magnetoencephalogram (MEG). The EEG and MEG provide measures of brain function during various experimental manipulations. For example, both methods may be used to study sound processing in the absence of attention while the subject performs a task not involving these sounds.

Various aspects of the EEG and MEG may be used to examine brain function. A common approach is to average the signal across several presentations of the same stimulus event to reveal the evoked brain activity. Averaging enhances the phase-locked signal related to the processing of the stimulus information and reduces random electric activation. In the EEG, the evoked activity is termed the event-related potential (ERP) and in the MEG the event-related magnetic field (ERF). Both ERP and ERF are divided into components according to their latency, scalp distribution, or location of the brain generators. At the level of brain sources, the interpretation of these components is, however, often complicated as multiple processes and brain areas may be simultaneously

activated. In the following section, two prominent auditory evoked components of particular relevance for change detection will be introduced.

1.2.1 N1 and MMN: indexes of auditory change detection

Auditory change detection depends on the information available to the system at the moment when the change occurs. The detection of a change requires that the characteristics of auditory events are extracted from the external stimulation and encoded in some internal representation. The N1 and mismatch negativity (MMN) components of the auditory ERP (the corresponding components of ERF are termed N1m and MMNm, respectively) reflect the activation of two distinct change-detection mechanisms operating on different information about the preceding acoustic stimulation (Näätänen 1990; 1992). The N1 is elicited by a fast change in the stimulus energy level (stimulus onset) and its amplitude is determined by the physical properties (e.g., intensity and presentation rate) of the sounds whereas the MMN mechanism detects deviations from regular aspects of the ongoing auditory stimulation (Näätänen and Picton 1987).

The auditory N1 (Näätänen and Picton 1987), occurring in the ERP at about 100 ms from stimulus onset, has its negative-polarity maximum amplitude typically at the vertex of the head. EEG and MEG source analysis has indicated that the main N1 generators are located bilaterally in the supratemporal auditory cortex, although several different brain areas are suggested to be involved in its generation (Hari *et al.* 1982; Näätänen and Picton 1987; Woods *et al.* 1993; Giard *et al.* 1994; Picton *et al.* 1999). The N1 amplitude is largest to the first stimulus in a train and decreases with repetition (Näätänen and Picton 1987; Karhu *et al.* 1997). A large N1 is again generated if the stimulation is ceased for several seconds (Hari *et al.* 1982; Alcaini *et al.* 1994) or a large change, *e.g.*, a novel sound, occurs in the stimulus sequence (Alho *et al.* 1998; Escera *et al.* 1998). These effects can be explained in terms of stimulus-specific refractoriness of the complex neural circuits formed by large neural populations underlying the N1 generators (note that, here, the term ‘refractoriness’ does not refer to the refractoriness of action potential generation in single neurons; Näätänen and Picton 1987): The more the present and previous sounds are different from each other in frequency, the smaller the overlap between the frequency-specific neuronal populations activated by the two sounds and, therefore, the greater the N1 amplitude (Näätänen *et al.* 1988). Furthermore, the assumption that N1 is associated with stimulus-specific processing is supported by studies showing that the supratemporal N1 generator is tonotopically organized (Elberling *et al.* 1982; Yamamoto *et al.* 1992; Tiitinen *et al.* 1993; Pantev *et al.* 1995), *i.e.*, different neural populations respond to different stimulus frequencies. Thus, it may be concluded that N1 indexes the detection of the physical change acti-

vating new, non-refracted neural elements that occurs when a sound is presented in silence (i.e., after a long enough break in stimulation) or when a wide sound change (e.g., a novel sound) occurs in a repetitive sound sequence.

The other ERP component indexing auditory change detection, MMN, is elicited by changes violating some regular feature of a sound sequence (Näätänen *et al.* 1978; Näätänen 1992; Picton *et al.* 2000; Näätänen *et al.* 2001). MMN typically peaks at 100-200 ms from change onset depending on the characteristics of the sound change. In certain cases, it may be difficult to tell apart the two responses in the EEG or MEG signal as, for example, a large frequency change occurring in a repetitive sound sequence elicits a change-related response consisting of overlapping N1 and MMN (Scherg *et al.* 1989; Lang *et al.* 1990). However, the brain processes underlying N1 and MMN are functionally and anatomically clearly separable: First, N1 is elicited by a single presentation of a sound, whereas MMN is only elicited in the context formed by the previous sound sequence (Sams *et al.* 1985; Näätänen *et al.* 1989; Korzyukov *et al.* 1999). Second, while a significant MMN is elicited by a small intensity or frequency increase, the N1 enhancement to such a small sound change is typically insignificant (Sams *et al.* 1985; Näätänen 1992, 139 -143). Third, MMN is elicited by an intensity increase or decrease and is larger for larger intensity changes irrespective of the direction of change (Näätänen 1992, 139 -143) whereas the N1 amplitude diminishes when the intensity is decreased (Rapin *et al.* 1966). Fourth, although the main N1 and MMN sources are both located in the bilateral supratemporal plane, EEG and MEG source analyses have indicated that the sources are separate (Scherg *et al.* 1989; Sams *et al.* 1991; Csépe *et al.* 1992; Huotilainen *et al.* 1993; Tiitinen *et al.* 1993; Levänen *et al.* 1996). Finally, N1 is directly driven by sound-feature information whereas the MMN-generating process is based on integrated representations of auditory events (Näätänen and Winkler 1999). The use of MMN to probe these representations is clarified in the next section.

1.2.2 MMN as an index of auditory sensory information encoded in the brain

In addition to changes in physical sound features, such as duration, frequency and intensity, MMN is also elicited by abstract (non-physical) sound changes (Näätänen *et al.* 2001). This clearly shows that a refined memory system must be involved in its generation. For example, Saarinen *et al.* (1992) presented their subjects with stimulus pairs in which the second tone was higher in frequency than the first tone (*ascending* tone pair). Successive tone pairs were always different in frequency so that there was no physical constancy in the tone sequence. Occasionally, however, the order of the stimulus pair was reversed so that the second tone was lower than the first tone. These occasional *descending* tone pairs presented among repetitive ascending tone pairs elicited

MMN, indicating that the temporal relationship between the successive sounds was encoded by the MMN generation mechanism.

Näätänen *et al.* (1993) showed that a representation of a complex sound may develop via a learning process, suggesting that the memory representations underlying MMN elicitation are stored for extended periods of time and are therefore linked to some long-term memory storage. In their study, subjects were presented with a repetitive complex tone pattern consisting of 8 consecutive 50-ms segments of different frequencies. The complex tone pattern was occasionally replaced by an otherwise similar pattern but one in which the sixth segment was slightly higher in frequency. These sound changes were very difficult to detect. Some of the subjects could not discriminate the changes in the beginning of the study but learned the required discrimination during the 2-3-h session consisting of alternating blocks of passive exposure to the sounds (ERP recording) and an active discrimination task. In this group of subjects, no MMN was elicited by the changes in the complex tone pattern in the beginning of the study but MMN appeared during the course of the session.

The results reviewed in this section demonstrate the importance of MMN for cognitive neuroscience: MMN can be used to probe the fundamental cognitive process of how the auditory environment is encoded into the internal representations by the brain.

1.2.3 MMN as an index of preattentive processing in the brain

An important feature of MMN is that it is elicited irrespective of whether or not the subject performs a task with the sounds. During the recording of MMN, the subject may be reading a book, watching a video, or is engaged in a difficult discrimination task involving other auditory or visual stimuli (Alho *et al.* 1992; Näätänen 1992). Therefore, it is generally assumed that MMN can be used to probe the early, attention-independent stages of auditory processing. Nevertheless, the attention independence of MMN has been questioned by studies reporting that MMN is smaller in amplitude when subjects strongly focus their attention on one sound sequence while changes occur in another sequence than when subjects attend to the sequence in which the changes occur (Woldorff *et al.* 1991; Näätänen *et al.* 1993; Trejo *et al.* 1995; Alain and Woods 1997; Woldorff *et al.* 1998). However, an open question is whether attentional (top-down) control in these studies directly affected the MMN system itself or the sensory information entering this system (Ritter *et al.* 1999).

1.2.4 MMN and attention switching

It is assumed that the MMN mechanism may trigger a switch of attention to sound change occurring in the unattended auditory environment (Näätänen and Michie 1979). This assumption is supported by the results of Lyytinen *et al.* (1992) who showed that the sound changes eliciting MMN tend to cause autonomic nervous system responses associated with involuntary attention switching. Indirect support for the link between MMN and the control of attention is provided by the studies showing that a lesion in frontal areas, known to have an important role in the control of attention (Fuster 1989), selectively diminish the MMN amplitude (Alho *et al.* 1994; Alain *et al.* 1998). Further evidence for the role of the MMN mechanisms in attention switching comes from studying the subject's performance during the presentation of unattended sound changes that elicit MMN. Schröger (1996) used an auditory distraction paradigm to examine whether the changes occurring in an unattended sequence of sounds distract the subject's performance in a simultaneous discrimination task involving other sounds. In his study, subjects were instructed to ignore the left-ear sounds and to discriminate two equiprobable intensities amongst the right-ear sounds. The left-ear sounds consisted of a repetitive, standard sound with occasional large and small changes in frequency. The stimulus sequences were arranged so that a sound presented to the left ear was followed by one in the right ear. As expected, changes in the left-ear sound sequence elicited MMN. Furthermore, the discrimination performance of those right-ear sounds, that were preceded by the unattended left-ear sound changes was lower compared with the performance after the repetitive left-ear stimulus and more reduced after large than small sound changes.

Corresponding results have been obtained in other similar studies using slightly different paradigms: Escera *et al.* (1998) found that auditory changes (eliciting MMN) distracted performance in a visual discrimination task. In another study by Schröger *et al.* (2000), subjects were required to discriminate two equiprobable sounds of different durations. The performance in the discrimination task was lower when small frequency changes (eliciting MMN) occurred in the same sounds. Taken together, the results reviewed in this section strongly support the assumption that MMN is generated by a sound change detection process which may lead into an involuntary attention switch.

As the frontal lobes are known to be involved in the control of attention (Fuster 1989), it may be assumed that they contribute to involuntary attention switching. Indeed, it has been suggested that an MMN source in the frontal lobes is associated with the switching of attention to sound change whereas the temporal-lobe MMN source is related to the change-detection process *per se* (Näätänen and Michie 1979; Giard *et al.* 1990; Näätänen 1992). Although a frontal MMN generator was proposed for the first time over 20 years ago, the precise brain structures in the frontal lobes involved in MMN generation and their functional role are not known.

1.3 Näätänen's model of the role of auditory change detection in the control of attention

Näätänen (1990; 1992) proposed a model of stimulus-driven auditory change detection, which was primarily based on ERP data (Fig. 1). According to the model, primitive automatic processes extract information about physical sound features from the auditory sensory input (Fig. 1, 1). The *transient-detector system* (2) is activated by changes in the energy level of the sensory input. N1 is generated (3) by a process that signals the executive mechanism (4) about an abrupt change (stimulus onset) in the stimulus energy level. The N1 generation mechanism detects such sound changes on the basis of stimulus-specific refractory patterns in the auditory cortex. A large frequency change or a sound occurring in silence is detected as activation of non-refracted neural populations. The *permanent feature-detector system* (5) passes the information extracted from the physical sound features to sensory memory (6) where the representations of the auditory events are formed. These representations are strengthened by repetitions of identical events. MMN is generated (7) when the incoming sound mismatches with the representation of the past regularity. The MMN generation mechanism detects changes violating some regular feature of the previous sound sequence by comparing the incoming stimulus to the representation formed on the basis of the previous stimuli. Such a regular feature could be, for example, a repeating single sound, a repeating tone pattern, or an invariant higher-level relationship between the sounds. As the N1 mechanism, the MMN generation process provides an attention-switch signal to the executive mechanism.

The function of the N1 and MMN mechanisms is to direct attentional resources to potentially meaningful events, i.e., changes occurring in the unattended auditory environment (cf. passive attention, James 1890). Both the N1 and MMN mechanisms

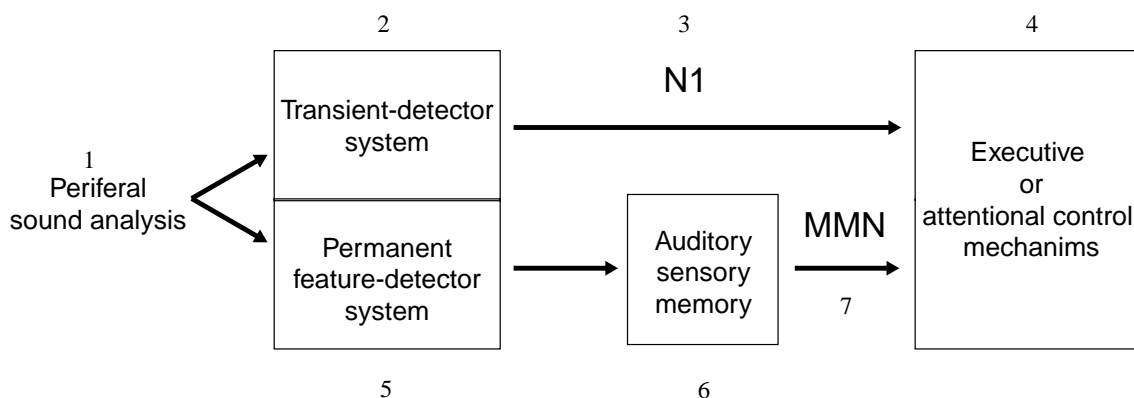


Fig. 1. A schematic model of auditory change detection (adapted from Näätänen 1990).

signal the executive mechanism so that, if a momentary threshold is exceeded, a switch of attention to the sensory events may be triggered. The assumption of threshold-based switching of attention is important as it explains why attention is not necessarily switched every time when a change is detected by the central auditory system and, thus, N1 or MMN generated.

1.4 Aims of the present study

The present study evaluated the cortical functions involved in auditory change detection by testing several hypotheses based on Näätänen's model. It is assumed that the auditory change-detection mechanism consists of several anatomical and functional units in the temporal and frontal lobes which are activated within the first 200 ms after the onset of sound change. Therefore, in order to investigate this mechanism, it is necessary to measure brain activation with high temporal and spatial resolution. The requirement of high spatiotemporal resolution, however, is a serious challenge to any single non-invasive brain-research method; therefore several methods have to be used in combination. In the present study, EEG, MEG, functional magnetic resonance imaging (fMRI), and the recording of the event-related optical signal (EROS) were used. An introduction to these methods is given in Section 2.

The specific hypotheses were as follows:

Study I (EEG) was aimed at determining whether categorical speech information is represented in the memory system indexed by MMN. Previous studies using positron emission tomography (PET) and fMRI have revealed activity in the left temporal cortex related to attentive processing of phonetic or semantic contents of stimuli (Zatorre *et al.* 1992; Binder *et al.* 1995). However, the limited time-resolution of PET and fMRI did not permit one to determine whether these language-specific processes are activated during the brief pre-attentive phase of the early auditory analysis or later. It was hypothesized that if the processing of phonetic stimuli is specialized as early as during the MMN time range (100-200 ms after stimulus onset), then the hemispheric dominance of MMN should change when the stimuli are gradually changed from non-speech to speech. Such a difference between MMN to speech and non-speech sounds would indicate that the MMN system operates, in addition to physical and abstract sound features, on long-term representations of speech sounds.

Study II (EEG) examined whether the MMN generation process can be directly influenced by top-down control. It is often argued that the MMN cannot be fully independent of volitional control as the MMN amplitude is modulated when subjects are strongly focusing attention away from the MMN-eliciting sound sequence. However,

it is not exactly known whether attentional control affected the MMN system *per se* or the sensory information entering this system (Ritter *et al.* 1999).

Some previous studies suggested that no MMN is elicited when the sound changes can be modeled (extrapolated) on the basis of the previous stimulus sequence (Sussman *et al.* 1998) or when the probability of the deviant stimulus is high (Sinkkonen *et al.* 1996). Therefore, it may be assumed that by providing predictive information about the sound changes to the subject it would be possible to reveal the hypothesized top-down access to the MMN mechanism. In a previous study, Ritter *et al.* (1999) found no difference between MMNs elicited by predictable and non-predictable sound changes when the changes were visually cued. This result either indicates that the visually presented predictive information did not reach the auditory system or that there is no direct top-down access to the MMN system in general. This was re-examined in Study II by making the predictive information directly available to the central executive control by requiring subjects to produce the auditory stimulus sequences themselves. That is, subjects controlled, and thus had full foreknowledge of, the occurrence of the infrequent deviant sounds. It was hypothesized that if the predictive information entered the MMN-generation process no MMN should be elicited. In contrast, if predictable and unpredictable sound changes elicit similar MMNs, it would suggest that there is no direct top-down control over the MMN-generating process.

Study III (EEG and MEG) tested the hypothesis that the frontal MMN generator is triggered as a result of the temporal-lobe change-detection process. If this was true, then the frontal MMN source should be activated later than the temporal one. To test this possibility, the time behaviors of the temporal and frontal MMN generators were estimated.

Study IV (fMRI) aimed to determine the precise locus of the frontal brain structures involved in auditory change detection. In addition, this study examined whether the amount of the frontal activation depends on the magnitude of the sound change. It was hypothesized that the frontal activation should be stronger the larger the informational significance, i.e., the magnitude of change.

Study V (EROS) determined whether a new brain-research method, the recording of the event-related optical signal (EROS), could be used to study the auditory change-detection mechanism. Previously, this method was successfully applied to study visual processing: signals could be recorded from areas of the visual cortex which were located in the depth of 1 cm. However, it was not known whether EROS could be measured from the auditory cortex, which is located approximately 2-3 cm below the scalp surface.

2 Non-invasive brain research techniques

2.1 Introduction

Non-invasive brain-research techniques, allowing the recording of brain activation from human subjects during experimental manipulations, have rapidly developed during the past 20-30 years: EEG, introduced over 70 years ago (Berger 1929), continues to be one of the most commonly used methods both in research and in clinical applications (Regan 1989; Näätänen 1992; Picton *et al.* 1995). Recent advances in the EEG technology include high-spatial resolution systems recording the scalp potential with a dense grid of sensors (electrodes). MEG (Cohen 1972; Hämäläinen *et al.* 1993) provides signal quality and spatial resolution exceeding those of EEG. The emergence of MEG has been accompanied by the development of sophisticated source analysis tools for both MEG and EEG. Magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI; Belliveau *et al.* 1991; Kwong *et al.* 1992; Ogawa *et al.* 1992) have in a short time become important tools in cognitive neuroscience, offering a revolutionary spatial resolution for imaging brain tissue and neural activation. In the near future, methods based on optical imaging combining excellent temporal and spatial resolutions in a single measure, such as the event-related optical signal (EROS; Gratton *et al.* 1995), might also be included into the toolkit of cognitive neuroscience. In addition, positron emission tomography (PET; Mazziotta 1995), which requires the administration of a radioactive tracer into the subject's blood circulation, can be used to examine cognitive processing in the intact human brain. In the next section, EEG, MEG, fMRI, and EROS, which were used in the present studies, will be dealt in more detail.

2.2 EEG and MEG

EEG is a measure of the potential difference between two scalp locations as a function of time. It is recorded with conventional electrodes connected to the scalp with conducting paste. When high spatial resolution is desired, a dense grid of electrodes (32 - 256 or more) covering the whole scalp area (Gevins *et al.* 1995) is applied. The amplitude range of the spontaneous EEG activity is approximately 1 mV. MEG is a measure of extremely small fluctuations of the magnetic fields produced by the electrical currents within the brain (Hämäläinen *et al.* 1993). A contemporary MEG system has 122 - 306 sensors (superconducting quantum interference devices) recording the magnetic field and its gradient from the whole head area. The amplitude range of the spontaneous MEG activity is approximately 1 pT. Both EEG and MEG record the synchronous electric activity of large groups of pyramidal neurons in the brain (Regan

1989; Hämäläinen *et al.* 1993; Picton *et al.* 1995). Because the majority of pyramidal neurons are systematically aligned perpendicular to the cortical sheet, the electric activity of groups of neurons summate to generate signals large enough to be observable outside the head.

As both EEG and MEG are measures of electric brain activity with high temporal resolution, these methods are well suited to study the various processes of early sound analysis briefly occurring within the first 200 ms after stimulus presentation. In contrast to the excellent temporal resolution, however, the spatial resolution of EEG and MEG is limited due to the characteristics of the methods: EEG is severely influenced by volume conduction and the anisotropic conductivity of the head structures (brain tissue, skull, and scalp), which make it difficult to disentangle sources activated at the same time from one another. The low-conducting skull acts as a low-pass filter for EEG, removing the high spatial frequency components of the signal. Generally, the spatial resolution of MEG is better than that of EEG, as MEG is not affected by the conductivity of the head structures. The information obtained with MEG is, however, limited by other reasons: The MEG signal primarily arises from superficial sources tangentially oriented with respect to the scalp; thus, deep (Tesche and Karhu 2000) or radially oriented sources are difficult to detect with MEG.

2.2.1 EEG and MEG source analysis

In order to estimate the parameters of the brain sources of EEG and MEG, it is necessary to assume a source and a head model. The accuracy of these models directly affects the spatial resolution that can be achieved with EEG and MEG.

A spherical head model with three concentric spheres, approximating the boundaries between the scalp, skull, and brain, is commonly used to model the effect of the low-conducting skull on the measured EEG signals. In contrast, a single-sphere model fitted to the local head curvature above the assumed source location is often applied in MEG. In the case of superficial cortical sources, the use of a simple MEG head model is justified, as the magnetic field is not affected by the head structures and is limited to a small region outside the head (Okada *et al.* 1999). However, a realistically shaped boundary-element model, constructed on the basis of an individual MRI, has to be used in the case of deep sources, and it yields more accurate results than spherical models for both EEG and MEG. The realistically shaped head model is especially important when the sources are located in areas that are not approximated accurately with a sphere such as the apex of the temporal lobes (Crouzeix *et al.* 1999). Recently, finite-element head models taking into account the tissue heterogeneity of the head are being developed (Haueisen *et al.* 1997).

Theoretically, there is an infinite number of different source patterns that could generate the extra-cranially recorded EEG and MEG signals (the so-called inverse problem). To determine the sources of these signals, the unlimited number of possible source distributions has to be reduced by using *a priori* information or by applying anatomic or neurophysiological constraints to the model (Ilmoniemi 1993). A model based on equivalent current dipoles (Scherg and von Cramon 1986; Cuffin 1998) is used when it can be assumed that a limited number of spatially restricted regions are active during the time of interest. Due to the systematic organization of the pyramidal neurons of the cortex, the dipole is considered to adequately represent the center-of-gravity of such regional sources although the activated cortical area may spread over several tens of millimeters. For example, the main sources of the auditory N1 and MMN may be modeled with dipoles located in or near the primary auditory cortex in the bilateral supratemporal planes (Scherg *et al.* 1989). A continuous current model, such as the minimum norm estimate of the source currents (Hämäläinen and Ilmoniemi 1994), may be used when the number of the individual sources is not known or when a dipole model is not appropriate for other reasons. For example, a physiologically relevant continuous current model could be constructed by constraining all source current to the cortical sheet. Such a model is often used as the basis of more specific hypotheses about the source structure or for the purpose of visualization.

2.3 FMRI

Magnetic resonance imaging (MRI) utilizes a strong and uniform magnetic field (typically 1.5 T) and a sequence of low-power radio-frequency (RF) pulses and magnetic-field gradients to create images of brain anatomy with high spatial accuracy. The MRI signal is based on the behavior of hydrogen nuclei in strong magnetic field when the nuclei are perturbed with the RF pulses. The emitted signal is detected by an RF coil closely fitted around the subject's head. Spatial information is coded directly into the MRI signal by using magnetic field gradients, which is the basis of the localization power of MRI. Images of brain anatomy are constructed on the basis of the distinctive magnetic-resonance parameters of the various brain tissues (gray and white matter, fat, and cerebrospinal fluid).

In functional MRI (fMRI), special pulse sequences are used to measure with a standard MRI scanner physiological responses related to brain activation. In general, functional images are achieved using blood-oxygenation-level -dependent (BOLD) fMRI. At the microscopic level, the BOLD-fMRI measures the change in the magnetic properties of the hemoglobin of blood when the hemoglobin changes from the oxygenated to the deoxygenated state during oxygen metabolism. BOLD-fMRI utilizes deoxyhemoglobin

which is paramagnetic and can be sensed with MRI as an endogenous contrast agent for the functional images. At the macroscopic level, the underlying mechanism of the fMRI signal is not yet fully understood as it is a complex reflection of various physiological changes in blood volume, blood flow, and cell metabolism during neural activation (Weisskoff 1999).

Because the hemodynamic changes associated with neuronal activation are quite focal and the spatial information is directly coded into the MRI signal, the spatial specificity of fMRI is generally good. In practice, however, the spatial resolution is often limited to the 10-mm range by several factors such as motion artefacts, blood-flow effects (which may move the locus of fMRI signal from the actual site of the activity) and the properties of the imaging system and data-analysis procedure (Kim *et al.* 1999). On the other hand, the resolution of the cortical columns (~1mm) may be reached using special techniques (Menon *et al.* 1997; Kim *et al.* 2000).

Compared with EEG and MEG, fMRI is poor in detecting the temporal dynamics of brain activation. The temporal resolution of fMRI is limited by the characteristics of the BOLD response which evolves over a time period of several seconds (Blamire *et al.* 1992; Buckner *et al.* 1996; Miezin *et al.* 2000). However, a recently introduced technique, termed as event-related (ER) fMRI, makes it possible to examine the response to single events, separated by only a few seconds, in a sequential stream of stimuli (Dale and Buckner 1997; Friston *et al.* 1998; Rosen *et al.* 1998). ER fMRI has been successfully used to measure the relative timing of activation in different brain areas in the sub-second range (Menon *et al.* 1998; Miezin *et al.* 2000). The ER fMRI technique enables the use of paradigms that closely match those used in ERP and ERF studies (Linden *et al.* 1999; Stevens *et al.* 2000).

Compared with the “blocked design” scheme (BD), used in the previous fMRI and PET studies of auditory change detection (Opitz *et al.* 1999; Tervaniemi *et al.* 2000) the ER scheme offers several advantages. First, in BD, change-related activity is revealed by comparing the response to stimulus blocks containing the sound changes with blocks containing only the repeating sounds. It is assumed that a steady state is maintained within the blocks, i.e., that the signal differences between the blocks are due to the presentation of sound changes and not due to block-level differences. In the ER design, this assumption is not needed. Second, it seems probable that a higher signal quality is achieved using the ER-design scheme: In the blocked design, alternating relatively short blocks of frequent sounds and blocks including both frequent and infrequent sounds (i.e., sound changes) are presented. To benefit from the summation of the hemodynamic responses to the subsequent presentations of the infrequent sounds in BD, there would have to be many infrequent tones in a block, which increases the

probability of the change and thus decreases the amplitude of the MMN-related response (Näätänen 1992). In the ER design with relatively short intervals between the presentations of the sound changes, the response summation takes place without this problem. Third, the strongest argument against using BD is that all previous knowledge is based on electromagnetic studies using the ER design. Although the mapping from the generators of the hemodynamic response to those of the electric signals may not be one-to-one, experimental procedures should be as similar as possible in order to combine the results obtained in EEG, MEG, and fMRI.

2.4 EROS

Changes in the optic parameters of the brain tissue caused by neural activation can be used as an index of brain function. Non-invasive optical imaging (Villringer and Chance 1997) is based on the measurement of the properties of near-infrared (NIR) light that is directed through the head and brain tissue. Several substances involved in neuronal metabolism, such as oxy- and deoxyhemoglobin, have distinctive light absorption spectra and scattering properties in the NIR range. However, the changes in metabolism are relatively slow lagging electric neural activation by several hundreds milliseconds. Interestingly, rapid optical changes with a time course following that of electric neural activation have also been reported (Rector *et al.* 1997). It has been suggested that these rapid changes in the light scattering properties of neural tissue may result from ionic-related changes in cell conformation and swelling during neural activation (Rector *et al.* 1997). According to Gratton and his coworkers (Gratton and Fabiani 1998), rapid light-scattering changes related to neural activation can be measured non-invasively from scalp using the EROS technique.

In an EROS recording, a source of near-infrared low-intensity (typically 1.5 mW) light and a detector are placed on the scalp a few centimeters apart from each other. The light emitted by the source diffuses through the skin, bone, and brain, and some photons eventually exit the head reaching the detector. EROS is based on the measurement of the time taken by the photons to migrate from the source to the detector. The measurement of the photon time-of-flight is based on the use of intensity-modulated (> 100 Mhz) light. EROS is a measure of the phase-shifts (i.e., time delay) in the modulation envelope of the light as the photons migrate through the brain tissue which is optically modified by the neural activation. The amplitude range of the EROS is approximately 1°.

In typical EROS recording, the signal, i.e., the phase shift, is estimated every 20 ms even though a higher sampling rate could theoretically be used. Therefore the temporal resolution of EROS is, at least technically, in the range of that of EEG and MEG. A

spatially high-resolution signal is achieved by selecting the photons on the basis of their time of flight; those photons that take similar (short) amounts of time to migrate through the medium are assumed to follow relatively similar paths.

EROS is a selective measure of superficial cortical processing as it cannot be used to record deep sources. The depth from which EROS can be obtained is limited by the source-to-detector distance so that the longer the distance the deeper the locus where the EROS is generated. Unfortunately, with longer source-to-detector distances, the signal quality decreases as less photons reach the detector. Therefore, the use of EROS is probably limited to studies of cortical processing at depths up to 3-4 cm (Gratton *et al.* 2000).

3 Methods and results

3.1 Common procedures in Studies I - V

Task. During the EEG, MEG, fMRI and EROS recordings in Studies I and III-V, subjects were instructed to ignore the auditory stimuli and to read a self-chosen text (Studies I and V) or to watch a silent movie (Studies III and IV). In Study II, subjects performed a button-pressing task.

Averaging of raw data. In Studies I-III and V, the raw EEG, MEG, and EROS epochs, time-locked to the stimuli, were separately averaged for each stimulus type and condition. Epochs with artifacts were rejected from averaging.

Data reduction. In Studies I-III and V, the electric, magnetic, and optic responses to the frequent sounds were subtracted from the corresponding responses to infrequent sound changes to reveal the MMN (Schröger 1998).

Stimuli. In Studies II-V, harmonically enriched tones (5-ms rise and fall times) consisting of 3 sinusoidal partials (500, 1000 and 1500 Hz) were used. The second and third partials were 3 and 6 dB lower in intensity, respectively, than the base harmonic. This tone structure was chosen because it has been shown to result in higher MMN amplitudes (Tervaniemi *et al.* 1999; Tervaniemi *et al.* 2000).

3.2 Study I. Analysis of speech sounds is left-hemisphere predominant at 100 – 150 ms after sound onset

3.2.1 Methods

The experiment consisted of 8 different conditions in which the frequent ($P = 0.8$) and infrequent ($P = 0.2$) tones (both of 400-ms in duration) were systematically varied, in different blocks, from non-phonetic tones to semisynthetic vowels (Fig. 2). The sounds were presented with a constant 800-ms onset-to-onset interval. Stimuli were binaurally delivered via headphones at a comfortable hearing level. EEG was recorded from 9

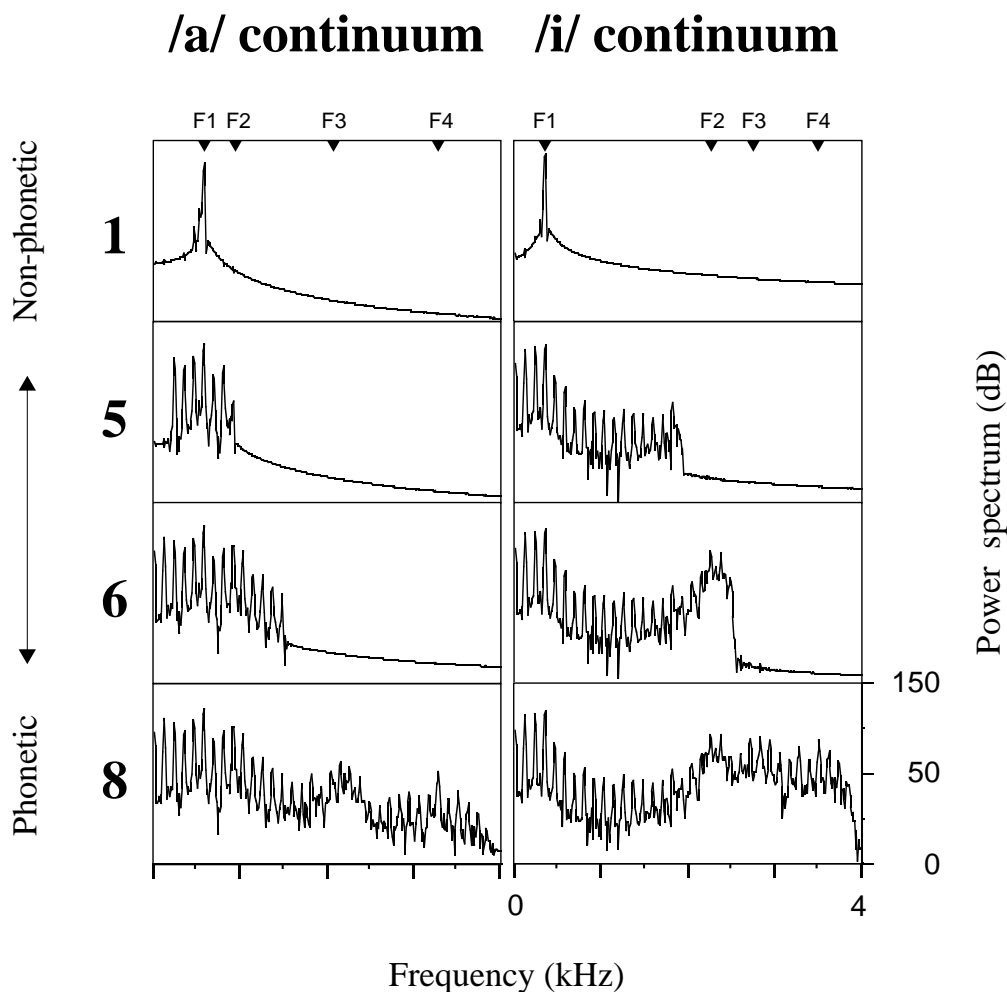


Fig. 2. The spectrograms of the sounds of conditions 1 (the most non-phonetic), 5, 6, and 8 (the most phonetic) in Study I. In the electric measurements, each sound from the /a/ continuum was presented as the frequent stimulus randomly replaced by a corresponding (on the same row) sound from the /i/ continuum. The formants of the /a/ vowel were: $F_0 = 115$ Hz, $F_1 = 530$ Hz, $F_2 = 950$ Hz, $F_3 = 2130$ Hz, and $F_4 = 3300$ Hz. The formants of the /i/ vowel were: $F_0 = 115$ Hz, $F_1 = 320$ Hz, $F_2 = 2263$ Hz, $F_3 = 2770$ Hz, and $F_4 = 3500$ Hz.

subjects (age 22–32 years, all right-handed, 4 females) with 128 scalp-attached electrodes (Virtanen *et al.* 1996). The electrode locations and anatomic landmarks were measured using a 3D-digitizer in order to map the EEG responses onto the individual MRI scans. The head was modeled using a three-layer (boundaries between scalp, skull, and brain) spherical head model. The multichannel data were reduced into measures of hemispheric MMN activation with a source model consisting of one supratemporal dipole in each hemisphere. The dipoles were constrained to be symmetrically located in the two hemispheres to yield stable models of the lateralized sources and to reduce the probability of artificial laterality effects caused by differences in the estimation of the depth of the dipoles in the two hemispheres.

3.2.2 Results and discussion

MMN activation to non-phonetic sounds was stronger in the right than in the left hemisphere. As the sounds became more phonetic the predominance of the MMN activation shifted from the right to the left hemisphere (Fig. 3; sum of Kendall's τ over subjects = 0.481, two-tailed $P < 0.001$). A separate discrimination task in which the

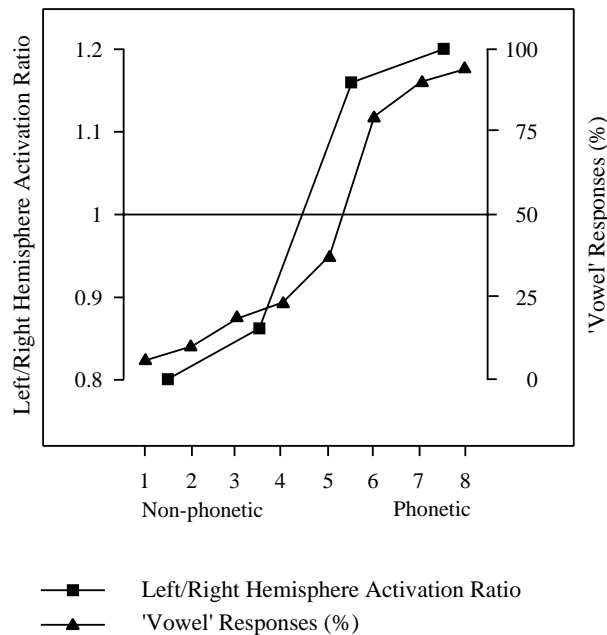


Fig. 3. The ratio of the left/right hemisphere MMN activation as a function of the stimulus condition (rectangles; scale on the left) and the percentage of the ‘vowel’ responses in a behavioral forced-choice task where subjects were asked to categorize stimuli either as vowels or non-vowels (triangles; scale on the right) in Study I. In the electric measurements, the data of the adjacent stimulus conditions were pooled to improve the signal-to-noise ratio. The neural activation of each hemisphere was determined with a model of two dipoles (one in each hemisphere).

subjects classified the stimuli as vowels or non-vowels indicated that the change of the hemispheric MMN predominance was accompanied by a corresponding change in the perception of the stimulus (Fig. 3). These results indicate that the specialization of left temporal cortex in processing speech stimuli is present as early as during the first 100 - 200 ms from stimulus onset. Furthermore, the sources of MMN activation caused by the phonetic sound changes appeared to be posterior to those of the activation caused by the non-phonetic changes. This suggests that additional posterior areas of the temporal cortex were activated by phonetic stimulation.

3.3 Study II. Mismatch negativity is unaffected by top-down predictive information

3.3.1 Methods

EEG was recorded with 32 channels in two conditions in which the subjects ($n = 13$, age 18-31, 9 females) were instructed to press one button with the forefinger and another button with the middle finger. The subjects were required to keep the temporal frequency of the button presses and the ratio of the fore/middle finger presses within predefined limits, as close to the center of the accepted range as possible. The target ranges of these two parameters were indicated on a computer monitor. Both task-relevant parameters were measured on-line and feedback was continuously provided. Subjects had to keep the average button-pressing interval within a range of 500-700 ms, and execute 15-20% of the button presses with the button assigned to the middle finger. In the Predictable condition, the “forefinger button” always triggered a 75-ms long tone, whereas the “middle-finger button” produced a 25 ms long tone. In the Unpredictable condition, each button press triggered the next tone of a prearranged sound sequence in which the 75-ms ($P = 0.8$) and 25-ms long tones ($P = 0.2$) were delivered in a random order (i.e., independent of the order in which the subjects pressed the two buttons). The stimuli were binaurally presented through headphones at an intensity of 60 dB above the hearing threshold separately determined for each subject.

3.3.2 Results and discussion

No difference between the MMNs elicited by predictable or non-predictable sound change was found (Fig. 4) although the subjects themselves produced the sound sequences and, therefore, had full knowledge about the time of occurrence of each sound change. This result suggests that the MMN-generating process is not directly influenced by top-down control.

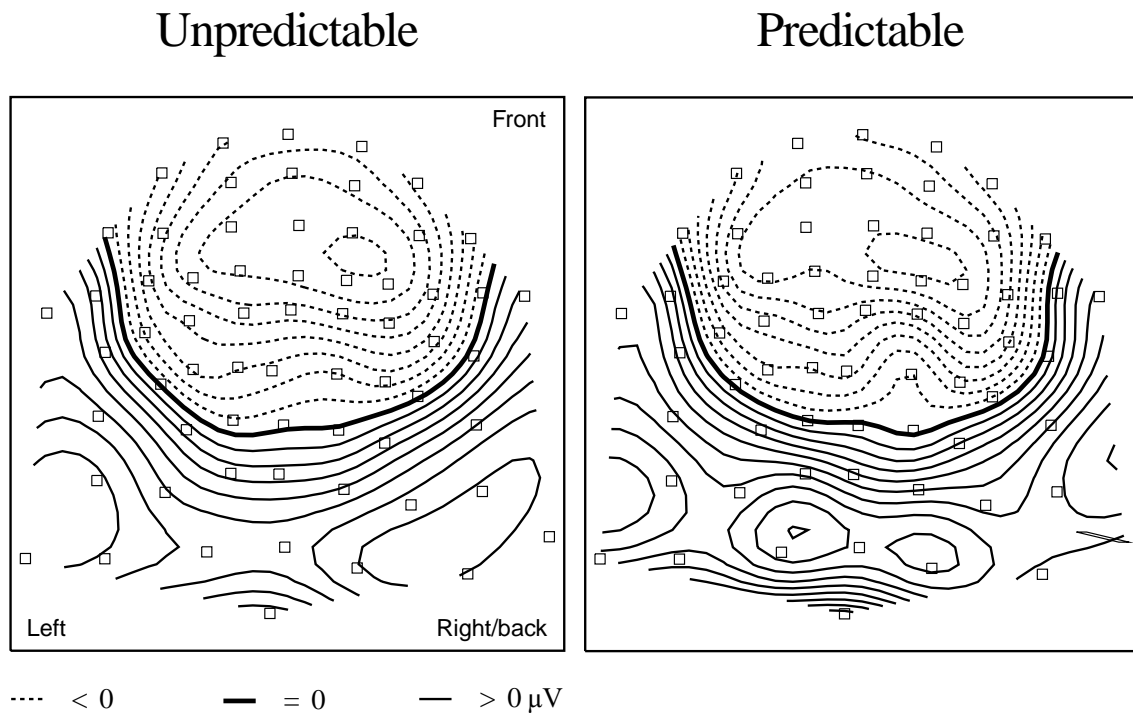


Fig. 4. Isopotential maps (increment $0,2 \mu\text{V}$, common average reference) of the grand-averaged deviant-minus-control responses ($n = 12$) at 152 ms from stimulus onset represent the MMN scalp distribution (Study II). The maps show a two-dimensional projection of the scalp potential distribution as seen from above the head. The electrodes are marked with small rectangles. In both conditions, stimulus changes elicited typical MMNs with similar scalp distributions.

3.4 Study III. Separate time behaviors of the temporal and frontal MMN sources

3.4.1 Methods

Responses to 75-ms long (fundamental frequency 500 Hz) frequent ($P = 0.8$) and 5 different infrequent tones were recorded with simultaneous EEG and MEG from 13 subjects (age 19-28 years, 7 females). The frequent tones were presented at an intensity of 60 dB above the hearing threshold separately determined for each subject. The infrequent tones ($P = 0.04$ for each type) differed from the frequent tone either in duration (25 or 50 ms), intensity (15 dB lower), or frequency (± 5 or $\pm 10\%$ change). The constant stimulus onset-to-onset interval was 300 ms. The stimuli were delivered binaurally through plastic tubes and ear pieces. Frequency distortions of the tubes were compensated for with a correction filter. The 25-ms duration deviants that elicit the most replicable MMN response (Tervaniemi *et al.* 1999) were selected for analysis. On the basis of individual MRI scans, realistically shaped head models were constructed for each subject. For each subject, minimum-norm estimation (MNE) constrained to the

reconstructed cortical sheet was performed to estimate the MMN source-current distribution as a function of time. The MNE solution was used to calculate the peak latencies of temporal and frontal activation in each hemisphere.

3.4.2 Results and discussion

EEG and MEG (Fig. 5 A) showed maximum MMN activation over the supratemporal cortex, indicating an auditory-cortex source (Fig. 5 B, left). As a function of time, the center of gravity of the EEG source currents moved in the anterior direction, revealing an additional frontal source (or sources; Fig. 5 B, top). On average, the right-hemisphere frontal MMN activation peaked later than the temporal activation (Friedman's non-parametric ANOVA, $P < 0.01$) with the mean difference being about 8 ms. However, this frontal activation pattern was not detected with MEG which showed only the temporal-cortex MMN activation (Fig. 5 B, bottom).

These results support the hypothesis that some frontal areas are activated during the MMN response and that these frontal areas are activated following the activation of the auditory cortical generator. The invisibility of this frontal activation in MEG suggests that the frontal MMN generator source is either radially oriented with respect to the scalp or located deep in the brain as these kinds of sources are difficult to detect with MEG.

3.5 Study IV. Differential Contribution of Frontal and Temporal Cortices to Auditory Change Detection: fMRI and ERP Results

3.5.1 Methods

Electric and hemodynamic brain responses were measured in separate sessions from 13 subjects (age 22-27 years, 7 males). BOLD fMRI (3T magnet) was conducted (gradient-echo EPI sequence, TE 30 ms, flip angle 90° , TR 1000 ms) using the event-related scheme. An acquisition volume consisted of 8 axial slices, parallel to the plane intersecting the anterior and posterior commissures. The most inferior slice was 15 mm below this plane. The slice thickness was 5 mm with an inter-slice gap of 2 mm. The acquired matrix was 64×64 with a field of view of 19.2 mm, resulting in an in-plane resolution of 3 mm x 3 mm. Five discarded volumes were acquired at the beginning of each run while tones were presented to allow the stabilization of magnetization. A total of 1220 volumes were synchronously acquired with the auditory stimulation. The same auditory stimulus sequences were used in both fMRI and EEG recording sessions. Subjects were presented with frequent 500-Hz tones (88%) and with 3 infrequent tones of 550-Hz, 650-Hz, and 1000-Hz (4% each; called below the small, medium

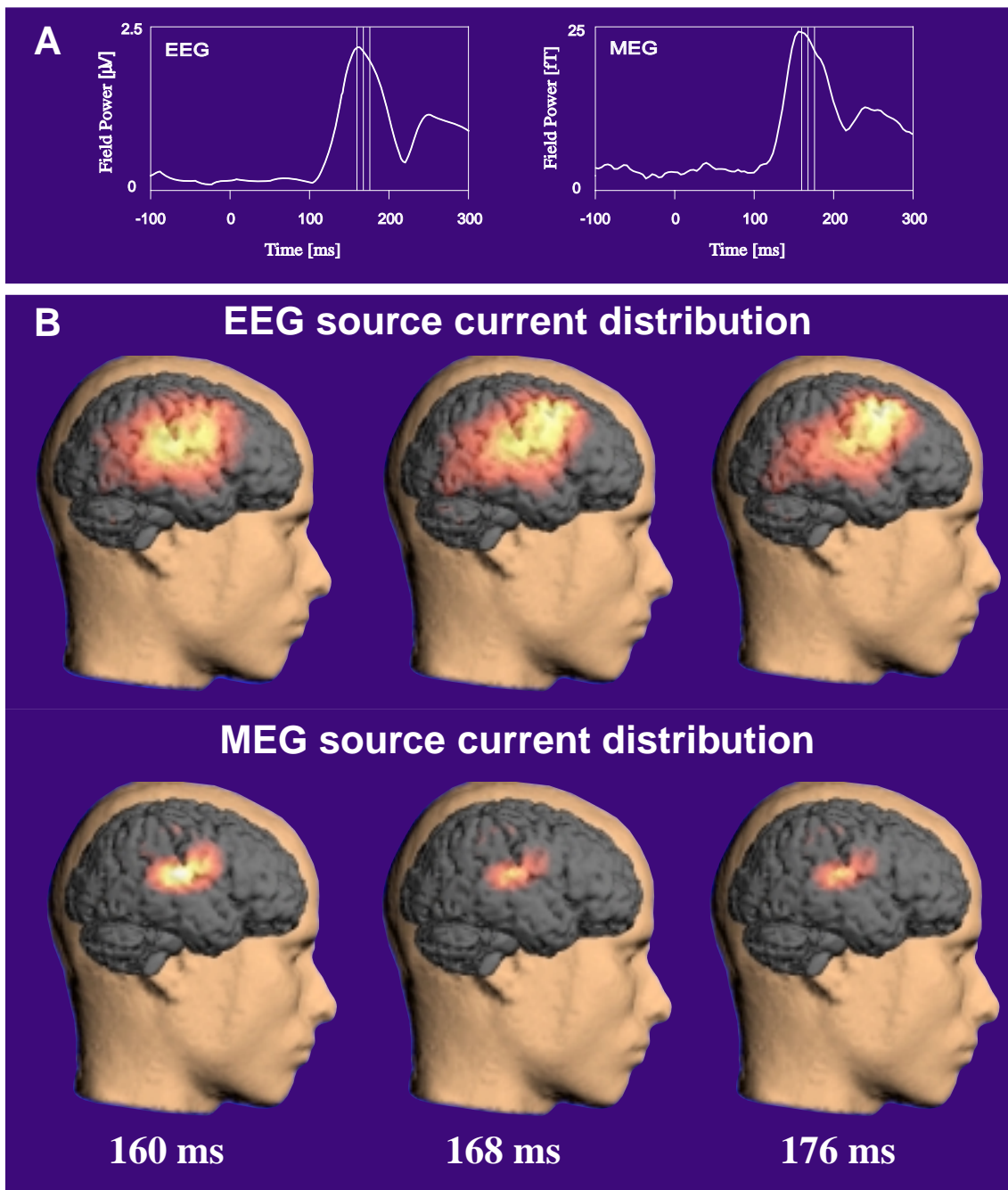


Fig. 5. A: Mean global field power (MGFP) illustrating in a single subject the strength of the MMN signal as a function of time recorded with EEG (left) and MEG (right) in Study III. The illustrated data are obtained by subtracting responses to frequent stimuli from those to infrequent stimuli. MMN is peaking at about 160 ms from stimulus onset. The three latencies shown in the subsequent figures are marked with vertical lines. **B:** The MMN source-current distribution estimated on the basis of the simultaneously recorded EEG (top) and MEG (bottom) for the same subject. At 160 ms from stimulus onset, the activation shows a temporal maximum (yellow) indicating an auditory cortex source. In EEG, the center of gravity of activation moves to a more frontal location as a function of time. In MEG, no later frontal activation is detected.

and large change, respectively). All sounds were 100 ms in duration and were presented with an onset-to-onset interval of 500 ms. The order of the stimuli was randomized with the constraint that each infrequent tone was preceded by at least 6 frequent ones, the minimum interval between two infrequent tones thus being 3.5 s. The stimuli were delivered binaurally via headphones at 70 and 85 dB/SPL for ERP and fMRI recordings, respectively. During the fMRI recording, earplugs and a passive shielding headset were used to reduce the loud noise of the fMRI scanner to 65-70 dB.

3.5.2 Results and discussion

The tones with medium and large deviation from the frequent tone elicited significant fMRI activation in the supratemporal cortex bilaterally and in the right fronto-opercular cortex (Fig. 6). In contrast, no significant activation was detected in response to the small sound changes. A follow-up ERP study indicated that this was because the small sound changes were inseparable from the repeating tones when the sounds were presented with the MRI scanner noise. The mean signal change in the bilateral temporal activation was greater for the large than for the medium sound changes (left hemisphere: $F(1,12) = 3.93$, $P < 0.1$; right hemisphere: $F(1,12) = 4.28$; $P < 0.1$). In contrast, the right hemisphere frontal activation was stronger for the medium than for the large

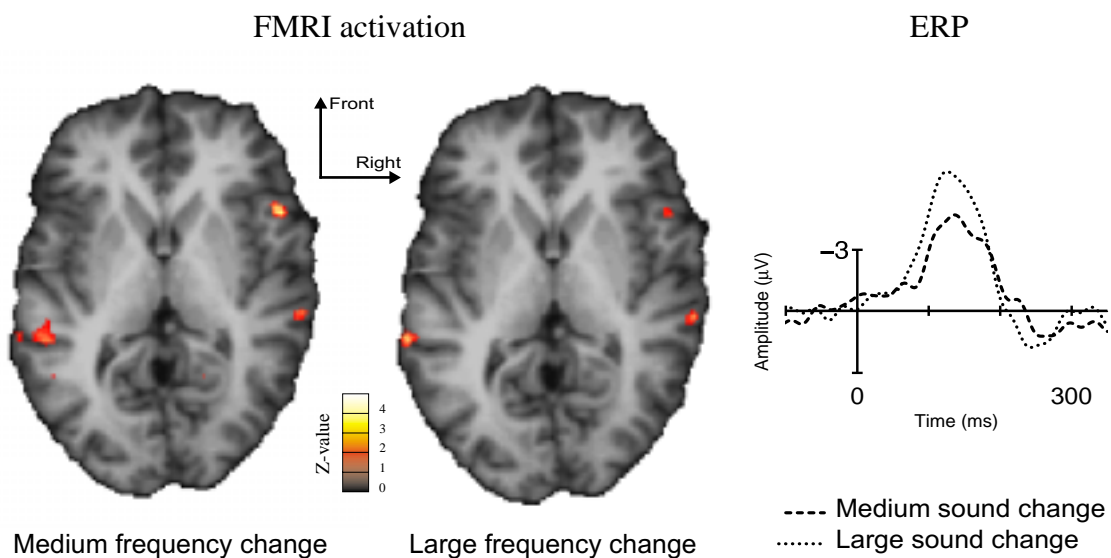


Fig. 6. Grand-averaged ($n = 13$) fMRI activation elicited by the medium (30 % increase in frequency; left) and wide (100 %; middle) deviants superimposed on an individual structural MRI in the Talairach space (Study IV). (Images were thresholded at $P < .01$.) Both deviants showed significant activation in the superior temporal gyri bilaterally and in the opercular part of the right inferior frontal gyrus. The ERP (right) recorded to the same stimuli while fMRI-noise was presented. Deviant – standard tone subtraction revealing the change-related response is shown.

sound change (right hemisphere: $F(1,12) = 9.63$, $P < 0.01$). In EEG, the medium and large sound changes elicited a change-related response which consisted of partially overlapping N1 enhancement and the MMN. The early part of the change-related response (108–132 ms), which was dominated by the N1 enhancement, correlated with the fMRI signal change in the right superior temporal cortex ($P < 0.05$). In contrast, the late part of the change-related response (140–168 ms), which was dominated by the MMN, correlated with the signal change in the right inferior frontal gyrus ($P < 0.05$).

This study provided the first direct evidence for the anatomical location of the frontal source of MMN: fMRI activation related to auditory change detection was demonstrated in the right fronto-opercular cortex. In addition, it was found that the frontal activity was stronger to the medium than to the large sound changes. This result could have been due to the fact that the large sound changes consisted of an octave frequency increase (500 Hz vs. 1000 Hz), which might have caused the medium sound changes (500 Hz vs. 650 Hz) to be relatively more different (despite the smaller physical change) than the large sound changes. This may have occurred because sounds belonging to the same pitch class (sounds separated exactly by one or more octaves) are musically more similar to each other than sounds that are of different pitch class. Alternatively, the frontal source may reflect the activation of a system specialized to, or preferring, the processing of small sound changes.

3.6 Study V. Scalp-recorded optical signals make sound processing in the auditory cortex visible

3.6.1 Methods

EROS was recorded from 6 subjects (age 21–41 years, 3 females) by 32 scalp-attached source-detector pairs so that the scalp projection of the posterior half of the supratemporal gyrus near the temporo-parietal junction of the right hemisphere was covered. A near-infrared (750 nm) low-power (< 1 mV) LED modulated at 112 MHz was used as a light source. Estimates of the phase-delay were obtained at 50 Hz. For control purposes, EEG was recorded simultaneously with the EROS from the frontal midline location. Subjects were presented with harmonically enriched tones of 75-ms (frequent; $P = 0.8$) and 25-ms (infrequent; $P = 0.2$) in duration at a constant 400-ms onset-to-onset interval. Stimuli were binaurally presented via headphones at a comfortable hearing level (approximately 70 dB above the subjective hearing threshold).

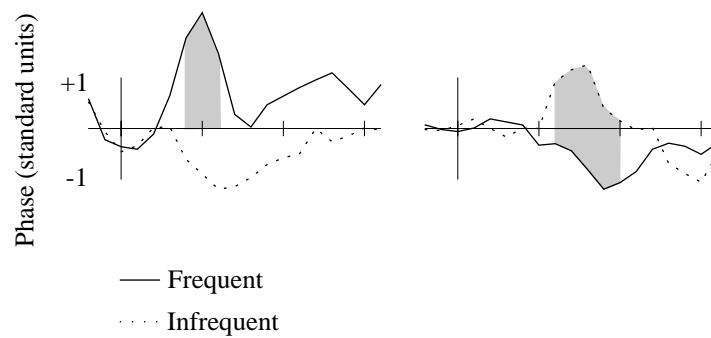


Fig. 7. The left and right panels show EROS responses to sound stimuli from different source-detector pairs (Study V). On the left, grand-averaged ($n = 5$) EROS to the frequent 75-ms long sounds (solid line) shows a significant signal peaking at about 100 ms from stimulus onset. On this source-detector pair, no significant signal in response to the infrequent 25-ms long tones (dotted line) was observed. On the right, grand-averaged ($n = 6$) EROS from a lower source-detector pair reveals a response peaking at about 160 ms to infrequent 25-ms long tones (dotted line).

3.6.2 Results and discussion

Two distinct EROS responses were elicited by the test sounds (Fig. 7). The first response ($n = 5$, $t(4) = 6.79$, $P < 0.05$ with Bonferroni correction) peaked at about 100 ms from stimulus onset. This response was elicited by the repetitive 75-ms long tones but not by the shorter 25-ms tones (Fig. 7, left). The second response ($n = 6$, $t(4) = 5.87$, $P < 0.05$ with Bonferroni correction) peaked at about 160 ms from sound onset and was elicited by changes in the sound sequence (Fig. 7, right). These two responses were recorded from different sensors, suggesting different cortical generators for these responses. The sensors that showed the maximal change-related EROS (at 160 ms from stimulus onset) were located on the average 10.4 mm inferior to the sensors showing the strongest EROS effect at 100 ms (two-tailed t test, $t(4) = 8.92$, $P < 0.0001$). The temporal and spatial characteristics of these two responses corresponded to those of the electric N1 and MMN responses. The finding that no EROS was recorded at 100 ms in response to the short 25-ms tones corresponds to the behavior of the electric N1: the N1 amplitude is diminished when stimulus energy is reduced by decreasing the sound duration (Kodera *et al.* 1979).

4 Discussion

4.1 Evaluation of cortical functions in auditory change detection

4.1.1 Auditory change detection and phonetic sound information

Näätänen's (1990) model of auditory change detection assumes that MMN is generated by a process involving memory representations of auditory events. Previously it has been shown that these representations may contain information about the physical characteristics (e.g., frequency) and abstract relations of sounds (e.g., ascending vs. descending tone pair). In Study I, it was found that MMN to phonetic changes was generated predominantly in the left-hemisphere, while MMN to non-phonetic changes was right-hemisphere dominant. This result indicates that the phonetic sound changes were processed, at least partially, separately from the non-phonetic ones and, thus, that the memory representation underlying MMN generation encode also phonetic sound information. This interpretation is supported by other studies examining MMN to changes in phonetic, complex, and musical tones. First, the finding that MMN activation to changes in native-language stimuli is stronger in the left than in the right hemisphere is reported by several other studies (Näätänen *et al.* 1997; Alho *et al.* 1998; Tervaniemi *et al.* 1999; Shtyrov *et al.* 2000). Second, studies demonstrating the right-hemisphere dominance of MMNs to complex, musical or non-native language stimuli rule out the alternative interpretation that the left-hemisphere dominance of MMN to vowel changes is simply caused by the complexity of the stimuli (Alho *et al.* 1996; Näätänen *et al.* 1997; Tervaniemi *et al.* 1999; Shtyrov *et al.* 2000). It has been proposed that speech perception is based on long-term categorical representations of speech prototypes that develop during early childhood prior to word acquisition (Kuhl 2000). The results of Study I together with the aforementioned studies show that MMN may be used to probe these representations and, thus, the basis of speech-sound processing in the brain.

4.1.2 Auditory change detection and top-down control

It is generally assumed that MMN can be used to probe the early stages of auditory processing occurring in a stimulus-driven manner independently of attention-dependent resources. This is supported by the fact that MMN is elicited even by sound changes occurring outside the focus of attention. On the other hand, it has been shown that the MMN amplitude is modulated when subjects are strongly focusing their attention away from the sound changes. Study II aimed at clarifying this apparent contradiction by testing whether predictive information about sound changes affects MMN in a top-down manner (Sussman *et al.* 1998). In Study II, the stimulus sequences were

produced by the subjects themselves so that the predictive information was directly available for the central executive (Fig. 1). In a study by Ritter *et al.* (1999) the predictive information was presented in the visual domain (sound changes were being preceded by visual cues). Both Study II and Ritter *et al.* found no differences between MMNs to predictable and unpredictable sound changes. Thus, these results obtained using different paradigms strongly suggest that there is no direct top-down access to the MMN system itself. Recently Sussman *et al.* (submitted) showed that by changing the information given to the subject about the organization of the stimulus sequences, the MMN was dramatically affected. This suggests that, at least in ambiguous cases, the representations in auditory memory can be voluntarily affected. Therefore it may be concluded that although there is no direct top-down access to the MMN system, top-down control may modify the input to the MMN system.

4.1.3 Frontal generator of MMN

The assumption that a frontal generator, associated with switching of attention, is involved in the MMN generation process was introduced already in the late seventies (Näätänen and Michie 1979). The frontal generator was postulated on the basis of four-channel scalp-potential recordings, which showed high amplitudes on electrodes over the temporal lobe, suggesting a temporal lobe source, and on a frontocentral electrode which was taken as evidence for a frontal source. In the light of present knowledge, the logic on which this source structure was based appears inaccurate: the frontocentral scalp maximum is mainly caused by the bilateral temporal sources (Alho 1995), whereas the scalp potential generated by the proposed frontal generator is difficult to detect in the ERP (Giard *et al.* 1990). Nevertheless, the suggested temporal-frontal MMN source structure received later some support although direct experimental evidence has remained scarce. This is probably due to the difficulty of separating any MMN subcomponents from the dominant temporal MMN activation and other ERP components possibly overlapping MMN (such as N1 enhancement to infrequent frequency increments). First, some studies (Giard *et al.* 1990; Deouell *et al.* 1998; Gomot *et al.* 2000) have used scalp current density mapping (SCD) to reveal a right-hemisphere or bilateral frontal contribution to the scalp potential distribution of MMN. (SCD “displays the distribution of the sinks and sources of radial scalp current responsible for the potential maps, and eventually allows the dissociation of components overlapping in potential maps” (Giard *et al.* 1990, 180)). Second, two studies (Alho *et al.* 1994; Alain *et al.* 1998) which compared ERPs in normal subjects with those in patients with focal unilateral lesions suggest that the frontal lobes contribute to the MMN generating process as the MMN amplitude was diminished in these patients while other ERPs were not affected by a frontal lesion. Third, one study (Liasis *et al.* 2001) recording intracranial electric activation over lateral prefrontal areas during presurgical

evaluation, showed frontal activation in response to changes in an unattended sound stream. However, the unknown relation of the intracranial signals and the scalp-recorded ERPs, which was not systematically examined in the study, makes the interpretation of this frontal activation difficult. Consequently, Studies III and IV are so far the only ones that directly examined the functional role of the frontal MMN component.

Study III found that the frontal MMN activation peaked later than the temporal activation, which is consistent with the assumption that the frontal MMN generator is activated as a result of the activation of the temporal change-detection mechanism (Näätänen and Michie 1979). However, a recent study of Yago *et al.* (2001) on MMN to infrequent frequency changes in a repetitive tone reported an opposite activation order of the temporal and frontal MMN sources, i.e., that the frontal MMN source was activated *before* the temporal one. It is possible, as the authors themselves suggest, that their frontal activation preceding the activation of the temporal MMN source was actually due to N1 activation (Giard *et al.* 1994) elicited by the infrequent frequency increases. This interpretation of Yago *et al.*'s data is supported by the finding that the frontal activation they found started during the typical N1 time range, which is rather early for MMN. A careful inspection of Yago *et al.*'s data indicates that the frontal activation continues longer than the temporal MMN activation, suggesting that the late part of the frontal activation might have been caused by the activation of a frontal MMN generator, which is in agreement with the results of Study III.

Study IV provided accurate anatomical information about the location of the frontal MMN generator. Significant frontal activation elicited by sound changes was found in the opercular part of the right inferior frontal gyrus. This result is in concordance with previous studies reporting frontal activation to auditory changes in different paradigms (Celsis *et al.* 1999; Downar *et al.* 2000; Dittmann-Balçar *et al.* 2001). Contrary to our hypothesis, however, the frontal activation in Study IV was smaller to the large (100% increase in frequency) than to the medium (30 %) sound change used in the study. As this finding was unexpected, all interpretations of it are necessarily post hoc. In section 3.5, it was discussed that this result might be due the fact that large sound changes consisted of an octave change (100%), which might have caused the medium sound changes, consisting of standard and deviants sounds belonging to different pitch classes, to be relatively more different than the large sound changes. This interpretation is supported by the studies showing that MMN is determined by the perceived pitch of the sound stimuli (Winkler *et al.* 1995; Winkler *et al.* 1997). Alternatively, it might be possible that the MMN and N1 mechanisms are differentially tuned to small and large frequency changes, respectively. Because of this selective tuning, the medium sound changes caused stronger MMN activation in the frontal lobe than the large changes. This possible account receives some support from the results of Escera *et al.* (1998; see also Jääskeläinen *et al.* 1996). Their subjects performed a visual discrimination task

during the presentation of repetitive auditory stimuli and infrequent large (novel sounds) as well as small (16% frequency increase) deviant stimuli. The sound changes elicited a change-related response consisting of partially overlapping N1 and MMN: The response to small deviants was dominated by MMN, whereas that to the large changes was dominated by N1. The reaction time to the visual stimulus preceded by a large sound change was prolonged as compared with that to the visual stimulus preceded by a repeating tone or a small sound change. In contrast, after a small sound change, the hit rate was decreased due to an increased number of wrong responses to the visual stimulus. This results suggests that the small and large sound changes differentially engage the N1 and MMN mechanisms. It should be noted that although the distraction caused by unattended and task-irrelevant sound changes (Schröger 1996; Escera *et al.* 1998; Escera *et al.* 2000; Schröger *et al.* 2000) is a reliable effect, further research is needed to establish the proposed different roles of N1 and MMN mechanisms in detecting small and large sound changes occurring in repetitive auditory stimulation. In conclusion, Studies III and IV together with previous results support the existence of a frontal generator(s) contributing to the MMN elicitation. The function of the frontal MMN has been traditionally assumed to be linked with attention switching to the acoustic change (Näätänen 1990). However, it is also possible that the frontal MMN source represents the activation of an amplification or contrast-enhancement mechanism tuning the temporal-lobe change-detection system (the temporal-lobe MMN generator) or it may play a role in maintaining the auditory memory traces active for comparison with incoming stimuli (Alain *et al.* 1998).

4.1.4 Update of Näätänen's model

On the basis of the results discussed in this section, an updated version of Näätänen's model, focusing on the MMN mechanism and the detection of changes occurring in the context of repetitive sound sequence, is presented in Fig. 8. As compared with the original Näätänen's model (Fig. 1), this version explains results showing top-down effects on the MMN process and incorporates the frontal MMN generator. According to this updated model, the MMN generation process *per se* occurs independently of attentional control but top-down processes can modify the auditory representations underlying MMN elicitation. The model assumes that the temporal-lobe change detection mechanism triggers a subsequent frontal-lobe process, which may lead to the initiation of the switch of attention to unattended sound changes. Näätänen originally proposed that the switch of attention occurs only when a momentary threshold is exceeded. However, it is not known whether this threshold lies between the temporal and frontal generators or between the frontal generator and the executive mechanisms. Furthermore, presently there exists no experimental support for the critical assumption that the activation of the frontal generator is a prerequisite for the initiation of attention switch to sound change.

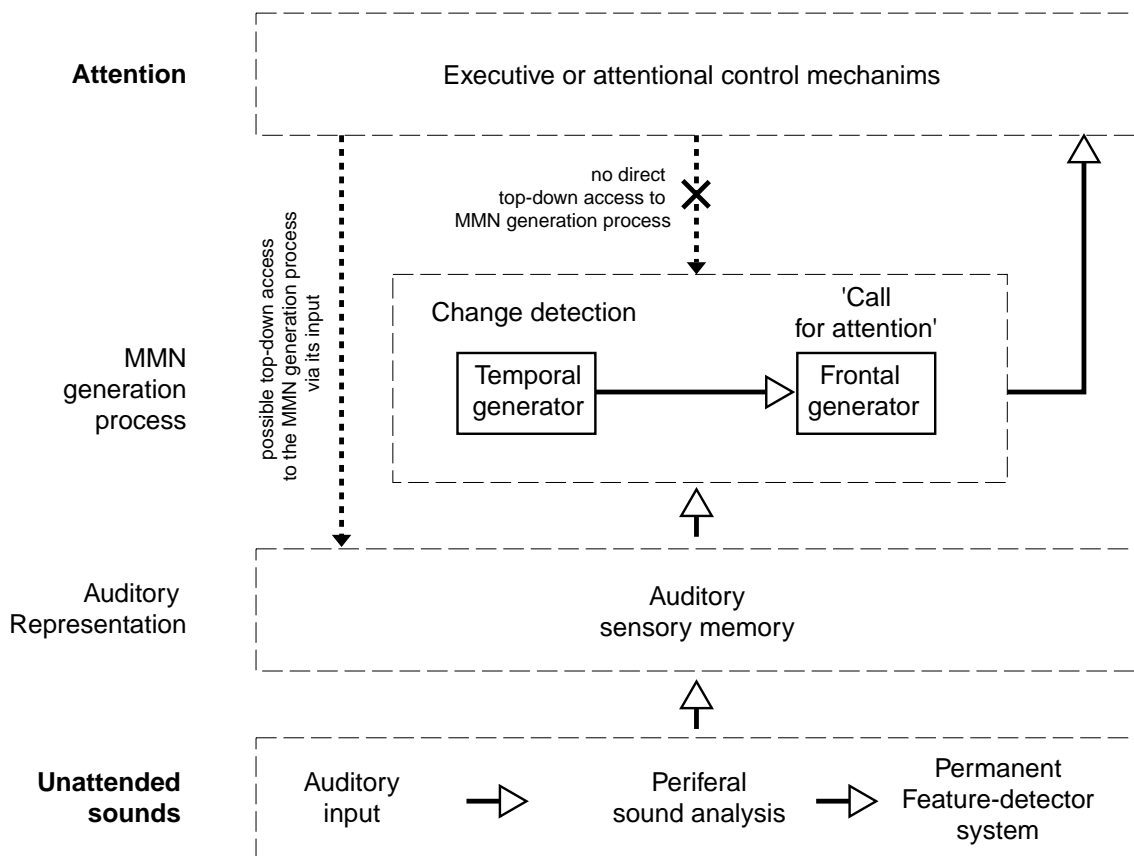


Fig. 8. An update of Näätänen's model of auditory change detection. The update focuses on the MMN mechanisms and detection of sound changes in the context of a repetitive sound sequence. As compared with the original model (Fig. 1), this version explains results showing top-down effects on the MMN process and incorporates the frontal MMN generator.

4.2 EEG, MEG, fMRI, and EROS in studies of auditory change detection

Although Studies I-V were not designed for the direct comparison of the different non-invasive brain research methods, some conclusions about how the applied methods suited for studying the auditory change-detection mechanism may be made.

First, Studies I and III demonstrated that by means of source-analysis techniques, EEG can be successfully used to study the temporal and *spatial* dynamics of the auditory change-detection mechanism. It was shown that the resolution of the EEG signal is high enough to allow the analysis of hemispheric specialization and the temporal dynamics of the MMN sources in the temporal and frontal lobes. Previously published studies (prior to Study I and III) did not promote the idea that such analyses would be possible. For example, although Näätänen *et al.* (1997) found an amplitude difference

at a frontal midline electrode between the MMNs elicited by native and non-native language phonemes, they used MEG to further study the hemispheric differences. Giard *et al.* (1990) who first provided convincing evidence for a frontal MMN generator found that the noise level in their SCD maps did not allow the analysis of the activation order of the temporal and frontal MMN generators. Accordingly, the initial data analysis in Studies I and III confirmed that a detailed EEG source analysis is rather difficult. It was impossible to obtain reliable unconstrained dipole models of the bilateral MMN sources for individual subjects. This difficulty was probably mainly due to the relatively low amplitude of the MMN signal compared with the normal noise level of EEG. In addition, the spatial resolution of the MMN source models may have been affected by the fact that bilateral symmetrical sources are active at the same time (Yvert *et al.* 1997). A source pattern of symmetrical superficial sources is difficult to tell apart from a pattern generated by a single large source in the middle of the head, especially when the signal is noisy. Therefore additional constraints had to be used to obtain stable models for each subject. In Study I, the dipoles of a simple two-dipole source model were constrained to be symmetrically located in the two hemispheres. By contrast, the use of a dipole model was not possible in Study III: The frontal source was considerably weaker than the temporal source and as no *a priori* information was available to define the spatial constraints for the frontal dipole, it would have been difficult to keep the temporal and frontal dipoles independent of each other. Therefore, a continuous current source model was used in which no assumptions about the location or number of the sources are needed. The use of the continuous source-current model, in which activity was constrained to the reconstructed cortical sheet, made it possible to visualize and examine the order of activation of the temporal and frontal MMN sources. It should be noted that the *exact* location of the sources was not in the focus of interest in Studies I and III. Instead, these studies aimed at testing hypotheses about the *relative* locations of the sources.

Second, it was found that EEG and MEG provide, to some extent, different information about the MMN mechanisms, as the frontal MMN activation in Study III was detected only with EEG and not with MEG. This result indicates that the differences between the two methods are of high practical significance in studying auditory change detection. MEG provides very detailed information about the temporal MMN mechanism but EEG, although its spatial resolution is inferior to that of MEG, has to be used when the temporal-frontal network of the brain areas contributing to the MMN generation is examined.

Third, neither EEG nor MEG could provide accurate information about the location and amplitude of the frontal MMN generator which is needed to clarify its functional role. Study IV showed that ER-fMRI is capable of detecting temporal and frontal neural activity in response to infrequent sound changes and may be used to measure the frontal component as a function of the experimental manipulations.

A fourth conclusion concerns about the problems encountered in Study IV, which pioneered the use of fMRI for determining the temporal-frontal MMN source structure. The noise generated by the fMRI scanner during the measurement (Ravicz *et al.* 2000) is a major difficulty in fMRI. Although it has been shown that auditory ERPs can be recorded in the noise of the recording system (Novitski *et al.* 2001), auditory studies are certainly seriously affected by the noise. The scanner noise causes activation in the auditory system and might mask or modify the perception of auditory stimuli (Bandettini *et al.* 1998; Shah *et al.* 1999). In Study IV, frequency changes were used for it was assumed that the noise of the fMRI recording system might mask the short-duration sounds (25 ms) used in Studies I-III and V. Unfortunately, it was found that small frequency changes, commonly used in ERP studies, did not elicit a reliable fMRI signal. A follow-up study (IV) revealed that the small sound changes used in this study did not elicit a significant MMN in EEG either, when the stimuli were presented together with fMRI noise. This finding suggests that small frequency changes cannot be used in fMRI studies. (Note that several techniques aiming to reduce the acoustic noise and its effects on auditory processing are currently being developed, see Ravicz *et al.* 2000; Di Salle *et al.* 2001; Ravicz and Melcher 2001). Using large frequency changes is also problematic: A large frequency change elicits both an N1 enhancement and MMN in ERP. Thus, the interpretation of the results is difficult because N1 and MMN types of fMRI activation are hard to disentangle from each other. Although ER-fMRI was used in Study IV, no attempt to analyze the temporal behavior of the activation sources was made. It is unlikely that the N1 and temporal and frontal MMN components could be separated from each other in time with the currently available techniques.

Fifth, Study V showed that the EROS correlates of N1 and MMN are temporally and spatially separable *directly* on the basis of the scalp-recorded signals without the use of source-analysis procedures to disentangle the sources from each other. This suggest that, in future, EROS could be used to study the temporal and frontal generators of the auditory change-detection mechanism. However, the EROS method is currently under development and used only in a few laboratories in the world. Therefore, the main results on which the method is based still need to be replicated by independent laboratories (Villringer and Chance 1997). In addition, with the presently available EROS system, the mapping of extensive brain areas is difficult, as a whole-head EROS scanner would be needed.

4.3 Future directions: combined use of the methods

The brain-research methods used in this study differ in their ability to separate sources in time and space. Logically, a combination of two methods, one with high temporal and another with high spatial resolution, should be used to obtain the desired spa-

tiotemporal accuracy. Although this idea is appealing, there are several problems involved in the combined use of the methods.

With EEG and MEG, the separation of adjacent sources that are activated at about the same time is difficult. The obvious solution would be to measure the location of the active brain areas using fMRI, which has a good spatial resolution, and then to use these locations to restrict the electromagnetic source model that would reveal the temporal dynamics of the response. However, it is not exactly known how the hemodynamic (slow) and electromagnetic (fast) responses correspond to each other. Although the BOLD-response, or at least some components of it, seems to correspond to the observable electric activity (Vanzetta and Grinvald 1999; Grinvald *et al.* 2000; Logothetis *et al.* 2001), the results obtained with fMRI and EEG/MEG may have only partially overlapping sources (Liu *et al.* 1998). It has been suggested that the electric and magnetic evoked responses are actually compounds of the superposition of different oscillatory responses (Karakas *et al.* 2000). Therefore, it may be possible that an analysis of sources of these oscillatory responses would yield results that correspond better to those obtained with fMRI.

To achieve a measure of the auditory change-detection mechanism with high spatiotemporal resolution, it appears that the combination of EEG and fMRI is preferable, as MEG does not seem to detect the frontal activation. However, for a refined spatiotemporal EEG analysis, it is necessary to further improve the quality and spatial resolution of the EEG signal. First, the design of the experimental setup should be optimized so that the highest possible signal quality is achieved. Second, accurate anatomical information should be used to model the head and brain structures and to constraint the source-current parameters. To benefit from the use of such constraints, it is necessary to accurately overlay the electric measurements and anatomic information from MRI. A common procedure is to use a 3-D digitizer to measure the EEG-electrode position with respect to three anatomical landmarks which can be identified on the MRI. This procedure appears to be error-prone as the 3-D digitizers are easily affected by magnetic artefacts (computer screens, metal objects) and because it is often difficult to accurately define the anatomical landmarks from the head and MRI. Third, the head models should be improved. Head-modeling errors such as ignoring the high-conductivity compartment formed by the ventricular system and under-estimating the skull conductivity produce considerable errors in dipole localization (Vanrumste *et al.* 2000). According to a recent study (Oostendorp *et al.* 2000), the relative skull conductivity (1, 1/80, 1 for skin, skull, and liquid, respectively) used in present Studies I and III (and in many others) is considerably underestimated (1, 1/15, 1, respectively, is instead suggested). Finally, a physiologically constrained continuous current model constructed so that the locations indicated by fMRI are given higher weights than the other locations might be a natural way to deal with the not fully known correspondence between hemodynamic and electromagnetic sources (Liu *et al.* 1998; Wagner *et al.* 1998; Dale *et al.* 2000).

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