Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained

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Abstract

The current review constitutes the first comprehensive look at the possibility that the mismatch negativity (MMN, the deflection of the auditory ERP/ERF elicited by stimulus change) might be generated by so-called fresh-afferent neuronal activity. This possibility has been repeatedly ruled out for the past 30 years, with the prevailing theoretical accounts relying on a memory-based explanation instead. We propose that the MMN is, in essence, a latency- and amplitude-modulated expression of the auditory N1 response, generated by fresh-afferent activity of cortical neurons that are under nonuniform levels of adaptation.

Descriptors: Mismatch negativity (MMN), N1, N100, Event-related potential, Event-related field, Electroencephalography, Magnetoencephalography, Human, Auditory, Memory, Attention, Computational modeling, Cortex, Adaptation, Lateral inhibition

1. Introduction

Recently, Näätänen, Jacobsen, and Winkler (2005) eloquently delineated the prevailing position that the mismatch negativity (MMN) of the event-related potential and field (ERP and ERF, respectively) is a memory-based process rather than one reflecting merely the activity of new (or fresh) afferent neuronal populations. Here, in a spirit of constructive dialogue, we present a view that is almost, but not quite, entirely unlike that advocating the memory-based interpretation.

An auditory stimulus, such as a pure tone, elicits a characteristic series of waves in the ERP labeled according to their latency and polarity (Davis & Zerlin, 1966). The most prominent response is the N1, which peaks about 100 ms after stimulus onset and lasts for approximately 100 ms. The electrically recorded N1 (or N100) response is a fronto-centrally distributed negative wave that is generated mainly in the auditory cortices (for a review, see Näätänen & Picton, 1987). Its magnetically recorded counterpart (N1m/N100m), first documented by Elberling, Bak, Kofoed, Lebech, and Saermark (1980) and Hari, Aittoniemi, Järvinen, Katila, and Varpula (1980), has been shown to originate from deep within the Sylvian fissure (Pantev et al., 1990; Papanicolaou et al., 1990; Yamamoto, Williamson, Kaufman, Nicholson, & Llinas, 1988) in tonotopically organized areas (Cansino, Williamson, & Karron, 1994; Elberling, Bak, Kofoed, Lebech, & Saermark, 1982; Lütkenhöner & Steinsträter, 1998; Pantev, Eulitz, Elbert, Hoke, 1994; Pantev et al., 1988; Yamamoto et al., 1988). The N1m has multiple sources (Elberling et al., 1982; Lu, Williamson, & Kaufman, 1992b; Zouridakis, Simos, & Papanicolaou, 1998) comprising secondary areas (Pantev et al., 1995; Pelizzone et al., 1987). These include parts of Heschl's gyrus (HG), the superior temporal gyrus (STG), and the planum temporale (Jääskeläinen et al., 2004; Yvert, Fischer, Bertrand, & Pernier, 2005), with especially the planum temporale (PT) providing a major source (Inui, Okamoto, Miki, Gunji, & Kakigi, 2006; Liégeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994; Lütkenhöner & Steinsträter, 1998). In the following, the term N1 refers both to the electroencephalography (EEG)- and magnetoencephalography (MEG)-recorded response.

The N1 is exceptionally sensitive to stimulation rate: The amplitude of the response to a stimulus following a long silence is large, but, as the stimulus is repeated, the N1 response attenuates to a magnitude that is an increasing function of the interstimulus interval (ISI; Budd, Barry, Gordon, Rennie, & Michie, 1998; Davis, Mast, Yoshie, & Zerlin, 1966; Frühstorfer, Soveri, & Järvilehto, 1970; Hari, Kaila, Katila, Tuomisto, & Varpula, 1982; Ioannides, Popescu, Otsuka, Bezerianos, & Liu, 2003; May & Tiitinen, 2004a; Milner, 1969; Nelson & Lassman, 1968; Picton, Goodman, & Bryce, 1970; Picton, Woods, & Baribeau-Braun, & Healey, 1976). With very short ISIs (< 300 ms), the N1 becomes minute and difficult to observe (e.g., Tiitinen, May, Reinikainen, & Näätänen, 1994; Yabe, Tervaniemi, Reinikainen, & Näätänen, 1997; Yabe et al. 1998). This attenuation of the N1 amplitude is thought to indicate a memory trace left by the previous repetitive stimuli (Lu, Williamson, & Kaufman, 1992a, 1992b; Näätänen & Picton, 1987).

When the monotony of repetitive stimulation is interrupted by a stimulus audibly differing from the preceding ones, something interesting happens. In this so-called oddball paradigm, the differing stimulus (usually termed the "deviant") results in an ERP and ERF similar to that elicited by the repetitive stimulus (the "standard") but, importantly, with an enhanced negative potential and strength of magnetic field gradient in the 100–200-ms poststimulus latency range. This differential response, first found by Butler (1968), and subsequently described by Squires, Squires, and Hillyard (1975), was suggested by Snyder and Hillyard (1976) to reflect the function of a "mismatch detector." Subsequently, Näätänen, Gaillard, and Mäntysalo (1978) subtracted the N1 to the standards from the response to the deviant and christened the resulting difference wave the mismatch negativity (MMN) and suggested that it reflects an automatic "physiological mismatch process caused by a sensory input deviating from the memory trace ('template') formed by a frequent 'background' stimulus" (p. 324). MMN, then, is a response to stimulus change observed indirectly in the ERP and ERF by off-line manipulation of the data employing the simplest of arithmetical procedures. It has been documented for any discriminable change in the physical feature of repetitive stimulation, for example, when the frequency, intensity, or duration of sinusoidal tones is changed or when the structure of spectrotemporally complex stimuli such as speech is modulated (for reviews, see Näätänen, 1990, 1992; Näätänen, Paavilainen, Rinne, & Alho, 2007; Picton, Alain, Otten, Ritter, & Achim, 2000).

From its beginnings as an indirect index of cortical change detection, MMN has grown in importance, and the number of cognitive phenomena it is thought directly to reflect continues to increase. These phenomena now include auditory sensory (echoic) memory, short- and even long-term memory stores, automatic (pre-attentive) analysis of the auditory environment, involuntary attention switch to sound change, the temporal window of integration in audition, sensory (primitive) intelligence, language-specific memory traces for phonemes, memory traces for syllables and words, language laterality, grammar processing, phonotactic probability, language development, perceptual learning and plasticity, voice familiarity, musical processing, perceptual streaming and stream segregation, feature integration, stimulus grouping, discrimination accuracy, audio-visual integration, visual processing, somatosensory processing, and olfactory processing (for reviews, see Näätänen, 1990, 1992; Näätänen & Alho, 1995; Näätänen et al., 2005, 2007; Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001; Näätänen & Winkler, 1999; Winkler & Cowan, 2005). Also, the MMN has been suggested to be an objective indicator for a plethora of clinical conditions, such as aging, alcoholism, Alzheimer's disease, attention deficit hyperactivity disorder, autism, coma, depression, diabetes mellitus, dyslexia, dysphasia, frontal-lobe damage, HIV, multiple drug effects, neglect and auditory extinction, Parkinson's disease, schizophrenia, somatization, thalamic infarctions, and Tourette syndrome (for reviews, see Näätänen, 2003; Näätänen & Escera, 2000). This noncomprehensive list of possible significances and applications is impressive, not least because the MMN boils down to a particular deflection elicited by a rarely occurring auditory stimulus presented in the oddball paradigm. The number of items in the MMN wardrobe indicates, at the very least, that the response should not be ignored.

It is, then, an empirical fact that a sudden change in repetitive stimulation causes an enhancement of the ERP/ERF. However, it would seem that the interpretation of the underlying cognitive and physiological mechanisms of the MMN is far from straightforward. Previously, we suggested that the MMN could be due to adaptation and lateral inhibition operating on topographic maps in auditory cortex so that cells responding to the repetitive stimuli become suppressed through stimulus repetition; the deviant then activates cells that are less suppressed and therefore elicits a larger ERP/ERF response (May, 1999; May & Tiitinen, 2001, 2004b; May et al., 1999). This adaptation model of MMN has gained support from the experimentation documented by, for example, Jääskeläinen et al. (2004) and Ulanovsky, Las, and Nelken (2003). It is essentially equivalent to the "fresh-afferents" explanation of MMN originally proposed by Butler (1968), according to whom the larger N1 responses (i.e., the "V" potential) elicited by frequency deviants (test tones) during oddball stimulation is due to the activation of "new neural units" not habituated by the preceding standards (intervening tones). Rephrasing this, Näätänen (1990, 1992) stated that the memory-based model rules out the "new afferent element" explanation whereby MMN is due to the activation of "fresh" afferent elements not under the influence of "refractoriness" (pp. 206 and 139, respectively). This vocabulary has been inherited by the current debate on the origin of the MMN (e.g., Näätänen et al., 2005, 2007). Since the 1970s, the adaptation/fresh-afferents explanation has repeatedly been refuted by the predominant theory of MMN generation, according to which MMN reflects the operation of auditory sensory memory (e.g., Näätänen, 1990, 1992; Näätänen & Alho, 1995; Näätänen et al., 1978, 2007; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989; Näätänen & Winkler, 1999). Recently, Näätänen et al. (2005) elaborated on this memory-based interpretation and concluded once again that the balance of the evidence heavily favors the memory-based explanation.

The memory-based interpretation of the MMN has, indeed, been very influential. Of the more than 1000 articles on MMN in refereed international journals ($N = 1{,}140$, PubMed search date December 6, 2008; search phrase: "mismatch negativity"), representing theoretical work, basic research, and clinical applications, the vast majority treat the MMN as an ERP/ERF component in its own right. As discussed below, the results of numerous studies have been afforded the memory-based interpretation, and, indeed, many experiments have been designed specifically to verify this particular interpretation. However, although the memory-based interpretation is a widely accepted one, it has problems that should not be overlooked.

Here, we take a look at this debate and review the literature in light of the adaptation model, that is, the proposal that MMN is part of an amplitude- and latency-modulated N1 response. We first delineate the memory-based interpretation of the MMN and discuss its inherent problems. Thereafter, we describe the adaptation model as proposed by previous studies and evaluate its plausibility in terms of physiological evidence. We then show that the arguments used against the adaptation model do not stand up to scrutiny. Having made our case, we elucidate the theoretical benefits of the adaptation model and suggest future directions for cognitive brain research.

2. The Memory-Based Interpretation of MMN

Näätänen (1990, 1992) suggested that the MMN can, in principle, be explained in two ways. According to the memory-based model (Figure 1, top), MMN reflects the operation of a memory mechanism whose representations of the environment are used

by a neural comparison process to detect auditory changes. The alternative explanation is the adaptation (i.e., "fresh" or "new" afferents) model (Figure 1, bottom), whereby the differential responding to the standard and deviant is due to adaptation ("refractoriness") of the neuronal population mapping the standard, leaving the populations mapping the deviant to respond more

strongly as the deviant is presented. Not only are these two explanations alleged to be mutually exclusive, but it is also claimed that they form an exhaustive set of models in MMN-theory space: For example, Näätänen and Alho (1995) stated that the memory-based model "is the only possible explanation for the MMN remaining after the one based on the activation of new, non-refractory afferent elements has been ruled out" (p. 320). A central task for the memory-based interpretation has therefore been to identify findings that would refute the adaptation model.

The arguments against the adaptation/fresh-afferents explanation of the MMN are numerous (Näätänen, 1990, 1992; Näätänen & Alho, 1995; Näätänen & Winkler, 1999; Näätänen et al., 2005, 2007). For example, the MMN occurs too late to be an N1; the source locations for the magnetically measured N1 and MMN are different; the MMN can be elicited by changes in temporal and abstract features of stimulation, such as decrements in stimulus duration and ISI, or by infrequent stimulus omissions; there is no MMN elicited by any one stimulus per se. Consequently, MMN is explained by the memory-based model, according to which the N1 reflects an "afferent," exogenous process due to the activation of cortical feature detectors and MMN is due to a complex "cognitive," endogenous process that reflects the operation of auditory sensory memory and cortical change detection. This sharp functional distinction between the N1 and MMN arises from the premise that the MMN (derived by subtraction) should be treated as an ERF/ERP component independent from the N1 (one element of the subtraction), so that the response to the deviant is the linear sum of the N1 and the MMN.

The distinction between the N1 and MMN underlies the theory of basic sensory analysis (Näätänen, 1990, 1992), according to which an auditory stimulus is analyzed by two parallel channels. The N1-generating "transient detector system" registers sudden energy changes in the auditory environment, such as stimulus onsets and offsets. The "feature-detector system" analyzes auditory stimuli fully for their physical features (frequency, intensity, duration, etc.) and encodes the results in auditory sensory memory. A comparison process then compares
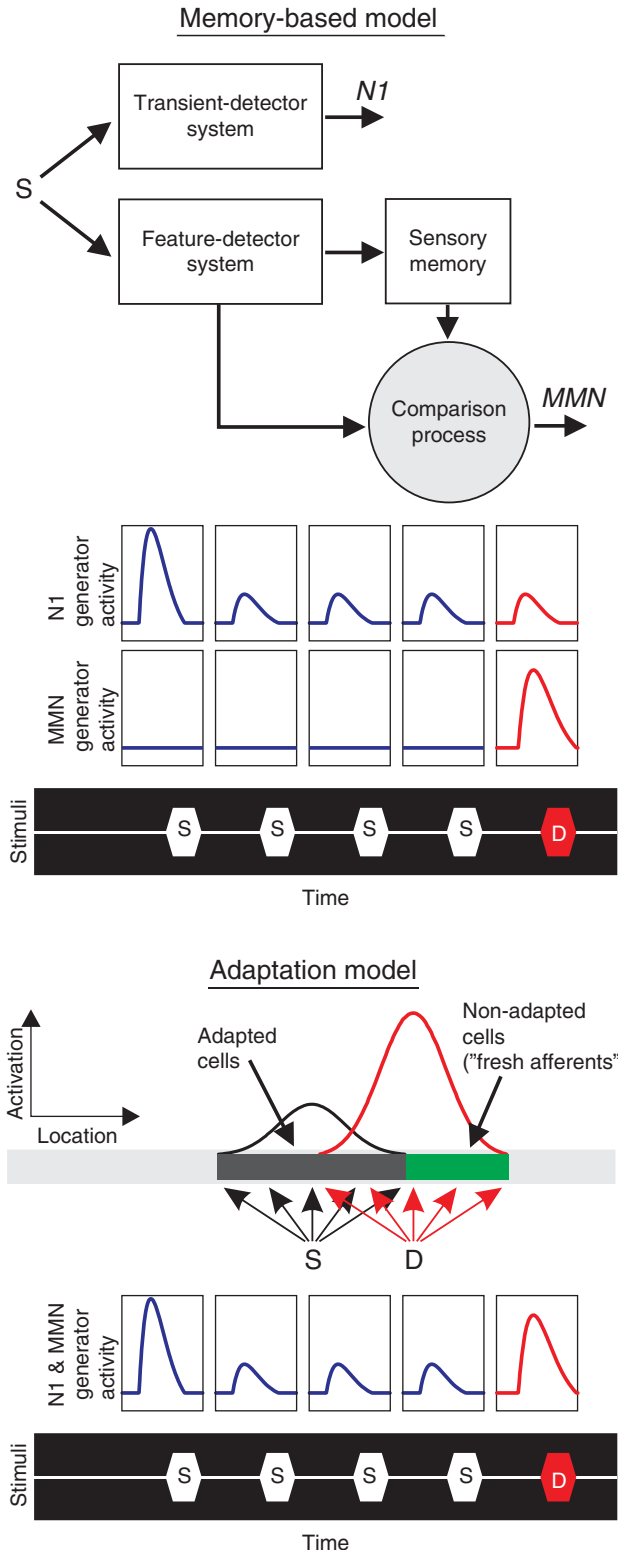

Figure 1. Schematic representations of the memory-based and adaptation model of the MMN. Top: In the memory-based model, a stimulus is analyzed by an N1-generating transient-detector system and a separate, MMN-generating system that first analyzes the stimulus for its features (frequency, intensity, duration, etc.). The result is deposited in sensory memory. A comparison process compares the features of incoming stimuli with representations of past stimuli in the sensory memory store, and, when the two differ, an MMN response is generated. Also shown is the beginning of a stimulus sequence, four standards (S) followed by a deviant (D), and the event-related responses produced by the separate N1 and MMN generators to the stimuli. The N1 is largest for the first standard. In contrast, the MMN generator reacts only when the deviant follows an already established memory trace for the standards (red curve). Therefore, it produces no response to any of the standards, including the first stimulus in the sequence. Bottom: In the adaptation model, the standards and deviants activate overlapping neural populations. The repetitive standard leads to cells tuned to the standard to become adapted. When the deviant is presented, nonadapted cells—"fresh afferents"—contribute to an enhanced response. Being in a nonadapted state, the MMN generator responds vigorously to the first standard of the sequence. It also produces attenuated responses to the subsequent standards. In this model, the N1 and MMN are generated by the same neural populations, and the MMN is, essentially, an enhanced N1 response.

the physical features of incoming stimuli to the model and, if the two differ from one another, the result is a mismatch signal that, in ERP/ERF measurements, becomes visible as the MMN. The outputs of both the transient- and feature-detector system are fed to executive mechanisms, thereby leading to involuntary redirection of attention. These sensory analysis processes are claimed to operate independently of attention, that is, automatically (see Sections 7.5 and 7.8).

3. The Problems with the Memory-Based Interpretation of MMN

First, even though the MMN is thought to index sensory memory, there are problems linking the subtraction curve with the psychological concept. Principally, several presentations of the repetitive signal are needed before a deviant elicits the MMN (Cowan, Winkler, Teder, & Näätänen, 1993; Horváth, Czigler, Sussman, & Winkler, 2001; Näätänen, 1992; Sussman, Sheridan, Kreuzer, & Winkler, 2003; Winkler, Schröger, & Cowan, 2001). This is a major problem for the memory-based interpretation because any audible stimulus *always* forms a behaviorally measurable memory trace. One could, of course, make an ad hoc suggestion that the memory trace is indeed formed after merely one presentation of the standard stimulus but that it becomes available to the comparison process only after repetitions of the standard stimulus. However, the fact would remain that the MMN is not a necessary indicator of the presence of an auditory sensory memory trace. This would be a curious extra feature of the sensory memory system that any physiological model of MMN generation would have to account for, and it diminishes the credibility of the MMN as an objective index of auditory sensory memory.

Second, the memory-based model proposed by Näätänen (1990, 1992) is rather complex. It postulates the existence of many functionally different types of cells in auditory cortex: (a) those, in a transient-detector system generating the N1, only sensitive to stimulus onsets and offsets but that are stimulus specific to some degree (accounting for enlarged N1 responses at large separations between the standard and deviant); (b) those in a permanent feature-detector system producing a full analysis of the physical features of auditory stimuli (but which, despite their stimulus-specificity, presumably do not contribute to enlarged N1 responses to the deviant); (c) those forming predictions of repetitive events (so called extrapolatory neurons) on the basis of the information provided by the permanent feature-detector system; (d) those in a sensory memory system storing the information provided by the extrapolatory neurons and the permanent feature-detector system; and (e) those in a system performing comparisons between the sensory memory trace and incoming stimuli (also presumably relying on information provided by the permanent feature-detector system) and generating the MMN but not contributing to the N1. Specifically, these cells react only to stimulus change, remaining inactive when a stimulus is presented alone, without the preceding standards. To account for the sensitivity of the MMN to the direction of attention, the change-detection cells in the comparison system must further be divided into (f) attention-independent "computational cells" and (g) attention-dependent "amplificatory cells" (Näätänen, 1991, 1992). Although cortical cells show a wide variety of response patterns and selectivity to stimulation, electrophysiological evidence does not support the above division. In particular, and despite claims to the contrary (Näätänen, 1992; Näätänen & Winkler, 1999;

Näätänen et al., 2005), direct evidence is lacking for change detection cells, those actually generating the MMN according to the memory-based interpretation (see Sections 6.10 and 6.14).

Third, to fit the memory-based interpretation, Näätänen (1984) proposed a model of MMN generation where a tonotopically organized neuronal population generating the MMN to frequency deviations is initially under homogenous, tonic inhibition. Repetition of the standard stimulus leads to "refractory" responses by neurons sensitive to the frequency of the standard, but neurons responsive to other frequencies are released from inhibition. Importantly, these cells are not activated by any one stimulus per se, but respond only to the deviant stimulus in the context of preceding standard stimuli. However, this disinhibition model suffers from the same problems as the adaptation one: Both rely on the existence of tonotopic maps, and, according to reasoning applied by Näätänen and his colleagues (Näätänen, 1990, 1992; Näätänen & Alho, 1995; Näätänen & Winkler, 1999; Näätänen et al., 2005, 2007), should be discarded as general models of the MMN on the grounds that the MMN can be elicited by, for example, infrequent stimulus omissions (see Section 6.4). More seriously, there is no direct physiological evidence for the disinhibition model (the results of Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo, 1996, often cited in support of the disinhibition model, are examined in Section 5.3).

Fourth, there is a problem with the rationale for extracting the MMN from the ERP/ERF. In practically all MMN studies, the N1 response to the standard is subtracted from the response to the deviant, and the resulting subtraction curve is treated as a separate component, a "genuine" brain response reflecting the activity arising out of a dedicated neural generator: The peak amplitude and latency, scalp distribution, and source location of this deflection are quantified and their behavior as a function of experimental parameter manipulation is statistically tested. This process of extracting the MMN assumes that the standard and deviant elicit near-identical N1 responses: The MMN is more sensitive to stimulus change than the N1, and, therefore, if the deviant represents only a small change from the standard, the N1 responses elicited by these stimuli are sufficiently similar—in terms of amplitude, latency, and source location—to justify the subtraction. As the physical difference between the standard and deviant stimulus is increased, the deviant activates an increasing number of fresh afferents, thereby leading to "N1 contamination," that is, to an overlap of the increased portion of the N1 with the MMN response embedded in the subtraction curve (e.g., Näätänen, 1990, 1992; Sams, Paavilainen, Alho, & Näätänen, 1985). However, to date, no evidence to support the assumption of the invariant N1 has been presented. It is unclear why the response to the deviant should contain an N1 response identical or even similar to the one elicited by the standard and, therefore, why the MMN obtained through subtraction should represent genuine brain activity. Thus, the notion of an invariant N1 which sums linearly with a change-detection MMN response is really the axiomatic *premise* in MMN research. However, because it is often—and confusingly—treated as a *conclusion*, circular arguments pertaining to the separability of the N1 and MMN have arisen, as we shall demonstrate in Section 6.

Even if the premise of the invariant N1 response is accepted, serious problems remain for MMN research because the N1 is clearly sensitive to stimulus features and stimulus rate. It is therefore unclear when the difference between the standard and the deviant is small enough to justify the subtraction procedure. Numerous studies show that the amplitude of the N1 has a large

variation (up to several hundred percent from minimum values) according to tone frequency (Antinoro & Skinner, 1968; Antinoro, Skinner, & Jones, 1969; Mäkelä, Alku, Mäkinen, & Tiitinen, 2004; Picton, Woods, & Proulx, 1978b; Stelmack, Achorn, & Michaud, 1977), and that the latency of the N1 varies tens of milliseconds (up to 60 ms) as a function of tone frequency (Mäkelä et al., 2002; May et al., 1999; Roberts & Poeppel, 1996; Stelmack et al., 1977). Similarly, stimulus intensity strongly affects both the amplitude and latency of the N1 (up to several hundred percent and 80-ms variations, respectively; Beagley & Knight, 1967; Picton et al., 1976; Rapin, Schimmel, Tourk, Krasnegor, & Pollak, 1966). Further, the amplitude of the N1 depends on sound source location (up to 100% variations; Leino, May, Alku, Liikkanen, & Tiitinen, 2007; Palomäki, Alku, Mäkinen, May, & Tiitinen, 2000; Palomäki, Tiitinen, Mäkinen, May, & Alku, 2002, 2005; Tiitinen, Palomäki, Mäkinen, May, & Alku, 2004; Tiitinen et al., 2006), vowel identity (up to 30% increases; Mäkelä, Alku, May, Mäkinen, & Tiitinen, 2004b, 2005; Obleser, Elbert, Lahiri, & Eulitz, 2003; Tiitinen, Mäkelä, Mäkinen, May, & Alku, 2005), the periodicity of the glottal excitation in vowel production (up to 30% increases; Alku, Sivonen, Palomäki, & Tiitinen, 2001; Tiitinen, Mäkelä, Mäkinen, May, & Alku, 2004; Tiitinen, Mäkelä, et al., 2005), intonation (up to 30% increases; Mäkelä, Alku, Mäkinen, et al., 2004; Mäkelä, Alku, May, Mäkinen, & Tiitinen, 2004a), and stimulus bandwidth (up to 35% increases; Leino et al., 2007). Shifts of 10–15 ms in the peak latency of the N1 can be measured by varying sound source location (Leino et al., 2007; Palomäki et al., 2005; Tiitinen, Palomäki, et al., 2004; Tiitinen et al., 2006), vowel identity (Diesch, Eulitz, Hampson, & Ross, 1996; Mäkelä, Alku, May, et al., 2004b; Mäkelä et al., 2005; Obleser, Elbert, et al., 2003; Obleser, Lahiri, & Eulitz, 2004; Roberts, Flagg, & Gage, 2004; Tiitinen, Mäkelä, et al., 2005), diphthong identity (Mäkelä, Alku, May, et al., 2004b; Mäkelä et al., 2005), consonant-vowel (CV) syllable identity (Obleser, Lahiri, & Eulitz, 2003), and stimulus bandwidth (Leino et al., 2007). Also, vowel sounds elicit N1 responses that are much larger in amplitude than those elicited by intensity-matched noise sounds (up to 100% increases; Palomäki et al., 2002) and intensity- and F0-matched tones (up to 70% increases; Mäkelä, Alku, Mäkinen, et al., 2004) and that peak up to 40 ms earlier than those elicited by tones (Mäkelä, Alku, Mäkinen, et al., 2004; Mäkelä et al., 2002). Importantly, the N1 is very sensitive to previous stimulation, with its amplitude decreasing sharply as stimulation rate is increased (e.g., Budd, et al., 1998; Davis et al., 1966; Frühstorfer et al., 1970; Hari et al., 1982; Ioannides et al., 2003; Lu et al., 1992a, 1992b; May & Tiitinen, 2004a; Milner, 1969; Nelson & Lassman, 1968; Picton et al., 1970, 1976), and becoming so attenuated with very short ISIs, below around 300 ms, that it is difficult to measure (Tiitinen et al., 1994; Yabe et al., 1997, 1998). Taken together, these observations indicate that differences between the N1 responses to the standard and deviant arise from two sources: the amount of "fresh-afferent" activity elicited by the deviant due to its rarer occurrence compared to the standard *and* the inherent variations in the N1 as a function of the physical features of the stimulus. Crucially, these fluctuations in the N1 will introduce unknown errors in the amplitude and latency estimates of the presumed MMN. Although the contribution of the inherent variations of the N1 can be controlled for by measuring the N1 responses elicited by the standard and deviant in a "standards alone" paradigm (which is very seldom done), the contribution of fresh-afferent activity poses a more difficult challenge.

This activity depends on how the cortical cell populations activated by the two stimuli overlap, and this overlap cannot be derived through measuring the respective N1 responses alone (i.e., two stimuli might activate divergent populations but still elicit a similar N1 response). What, then, constitutes a small enough difference between the standard and deviant to justify the assumption of the invariant N1 and thereby the subtraction procedure?[1]

It is occasionally acknowledged that the response to the deviant inevitably includes fresh-afferent activity, or N1 contamination, and thus the subtraction curve, being a linear sum of the MMN and N1 contamination, offers an overestimation of the "genuine" memory-based MMN (Campbell, Winkler, & Kujala, 2007; Horváth et al., 2008; Jacobsen, Horenkamp, & Schröger, 2003; Jacobsen & Schröger, 2001, 2003; Jacobsen, Schröger, & Alter, 2004; Jacobsen, Schröger, Horenkamp, & Winkler, 2003; Jacobsen, Schröger, & Sussman, 2004; Maess, Jacobsen, Schröger, & Friederici, 2007; Näätänen & Winkler, 1999; Schröger & Wolff, 1996). Indeed, intracortical measurements in humans show unequivocally that fresh-afferent activity characterizes the response to the deviant: Kropotov et al. (2000) found that stimulus specificity and rate dependence of activity in temporal cortex (in areas 41 and 42, respectively; for an assessment of activity in area 22, see Section 6.10) contribute to the deviant-minus-standard difference curve. Also, Rosburg et al. (2004), using a stimulus series comprising five 1500-Hz tones (~standards) followed by a 2000-Hz tone (~deviant), found that with an ISI of 0.5 s the intracortically recorded N1 to the fifth stimulus attenuates to an amplitude that is less than 50% of the amplitude of the N1 to the first stimulus. Crucially, the N1 to the 2000-Hz tone recovers almost fully to the level of the N1 to the first stimulus. These invasive results imply that the subtraction curve does not exclusively reflect a memory-based MMN, but that fresh-afferent activity is an inherent part of it. Recently, Horváth et al. (2008) measured MMN responses at different frequency separations between the standard and deviant and also employed measurements that purportedly control for fresh-afferent activity. They concluded that N1 contaminates the MMN even at very small frequency differences with such severity that the orderly increase in MMN amplitude as a function of deviance (starting at 2% difference) is, in fact, largely due to changes in the amplitude of the N1. Unfortunately, to obtain statistically significant MMN amplitudes, a bare minimum separation of 2% between the standard and deviant is needed (Tiitinen et al., 1994), and, so, in light of the results of Horváth et al. (2008), it is reasonable to assume that *any* measurable MMN is N1-contaminated. The above results have important, although overlooked, implications for practically all MMN studies that

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[1]The MMN is sometimes measured as the difference between the response to a stimulus presented as a deviant in one condition and the response to this same stimulus presented as the standard in a separate measurement (e.g., King, McGee, Rubel, Nicol, & Kraus, 1995; Kraus, McGee, Sharma, Carrell, & Nicol, 1992; Kraus et al., 1995). Regrettably, this method offers no solution to the current problem: Although the physical difference between the standard and the deviant is eliminated, the differences in their probability of occurrence and ISI remain. The evidence on the ISI dependence of the N1 clearly rules out the assumption that the N1 responses elicited in the two conditions are nearly identical, unless, of course, one assumes that the two physically different stimuli used in the experiment activate largely the same cells in the N1 generator. Again, the question—unanswerable through N1 control measurements—remains: What is a small enough separation between the two stimuli to justify the subtraction?

treat the subtraction curve as a separate component. Namely, as N1 contamination is almost never controlled for, most results purporting to describe the behavior of the memory-based MMN are questionable. Given the effort invested in MMN basic research and the prospect of clinical applicability of the MMN, it would be important to know what one is, in fact, measuring.

A further problem remaining—even if the small-deviance-invariant-N1 premise is accepted—can be identified in the large number of studies using experimental conditions where the physical difference between the standard and deviant stimuli is considerably beyond the values supposedly ensuring a "genuine" MMN. For example, the MMN found in studies employing vowels (e.g., Näätänen et al., 1997), CV syllables (e.g., Mathiak, Hertrich, Lutzenberger, & Ackermann, 2000), and even words (e.g., Pulvermüller, & Shtyrov, 2006; Pulvermüller, Shtyrov, Kujala, & Näätänen, 2004; Pulvermüller et al., 2001) are, arguably, seriously contaminated by fresh-afferent N1 activation due to the use of standard and deviant stimuli widely differing in their spectral and/or spectrotemporal composition. Accepting the argument that a very limited difference between the standard and deviant should be used, it is unclear why, for example, the vowel sound /e/ as a standard stimulus should elicit the *same* N1 response as /ö/ as a deviant. Vowel identity is based on articulation introducing vowel-specific resonance frequencies (formants) to the speech sound (Fant, 1970). Therefore, the frequency spectra of vowels, the basic units of speech sounds, differ drastically from each other and, consequently, lead to differences in the amplitude and latency of the N1 response (e.g., Mäkelä, Alku, May, et al., 2004b; Mäkelä et al., 2005; Obleser, Elbert, et al., 2003; Tiitinen, Mäkelä, et al., 2005). This point applies also to the MMN elicited by "novel" sounds, such as when drills, hammers, rain, bells, and whistles are used as deviants among sinusoidal standards (e.g., Alho et al., 1998; Escera, Alho, Winkler, & Näätänen, 1998). Although researchers are explicit about the presence of unquantifiable N1 contamination in these cases, the subtraction curve is—still—treated as a genuine brain response. The variations in the N1 according to spectrotemporal composition are likely to carry over to results obtained in the oddball paradigm, again making the subtraction curve and, consequently, the MMN an uncertain measure of anything that indexes something.

Fifth and finally, the memory-based interpretation is founded on a category error. The conceptual basis of the model is, as clearly stated in previous accounts (Näätänen 1990, 1992; Näätänen & Alho, 1995; Näätänen & Winkler, 1999; Näätänen et al., 2005), the presumed mutual exclusivity of the adaptation and memory-based model. This dichotomy between physiological and psychological explanations is problematic because, if accepted, it leads to comparisons being made across two separate categories. Why should a physiological, adaptation-based explanation rule out a psychological, memory-based one, or vice versa? The overarching theme of the cognitive neurosciences being to bridge, rather than to cancel out, psychological and physiological explanations and concepts, the dichotomy is clearly unworkable as a general principle. If it is intended to hold merely in the specific case of MMN, then it would need justification. For the dichotomy to be defendable, one would have to provide satisfactory answers to the following basic questions: Why cannot auditory sensory memory be, in principle, physiologically manifested as adaptation or "refractoriness" of cortical cells? Indeed, what are the criteria according to which the disinhibition model (Näätänen, 1984) offers a physiological explanation of sensory memory but the adaptation model does not? What *are* the criteria

for accepting a physiologically based model for MMN and memory?

4. The Adaptation/Fresh-Afferents Model of MMN

And now, for something completely different. The shortcomings of the memory-based interpretation of MMN could be made up for by discarding the physiology versus psychology dichotomy inherent in the memory-based interpretation and by complementing experimental MEG/EEG measurements with knowledge about the physiology of auditory cortex in computational neural models of cortical dynamics. In this vein, the physiologically based adaptation model proposed in recent research (May, 1999; May & Tiitinen, 2001, 2004b; May et al., 1999) has aimed at answering the fundamental questions left open by the memory-based interpretation: What is the physiological manifestation of the sensory memory trace underlying MMN? How does the comparison process work? How is the MMN generated?

The adaptation model suggests that in each auditory area the repetition of the standard stimulus leads to adaptation of the cells contributing to the standard-elicited N1 response, which, therefore, becomes attenuated. This leaves the deviant-selective cells in an unadapted state, and these contribute to an enhanced N1 response to the deviant. Thus, the set of cells generating the N1 to the standard is unlikely to be identical to that generating the N1 to the deviant, because some of the responding cells are highly selective in the feature dimension separating the standard and the deviant. However, these sets may also overlap because some of the responding cells are weakly selective. It should be emphasized that the adaptation model suggests that the *same* areas partake in generating the N1 to the standard and the enhanced response to the deviant, and, consequently, there is no separate cortical area generating the MMN "component." Rather, the complexity of the stimulation translates into variations in the amplitude, latency, and morphology of the auditory ERP/ERF produced by the N1 "generators."

The adaptation ("fresh-afferents") model suggests that the MMN is part of a modulated N1 response. In this view, rather than regarding the N1 as an entity originating from a restricted number of "N1 generators," one might approach it by considering the current neurophysiological evidence on what is going on in auditory cortex during the first few hundred milliseconds after stimulus presentation. In terms of cortical activations, the N1 is a latecomer: The arrival of afferent auditory information to the primary (core) areas takes around 10 ms in humans (Liége-ois-Chauvel, Musolino, & Chauvel, 1991) and is reflected by the initial middle-latency responses (e.g., Liégeois-Chauvel et al., 1994). Activation from the core flows serially, in several medio-lateral streams, and spreads into a complex network containing the secondary and associative areas, also known as the belt and parabelt areas (e.g., Guéguin, Le Bouquin-Jeannès, Faucon, Chauvel, & Liégeois-Chauvel, 2007; Inui et al., 2006). It would seem that the "component structure" of this network is manageably simple for a very short poststimulus period: As recently shown by Yvert et al. (2005), only the P0 and Na deflections, occurring within 25 ms from stimulus onset and originating from the spatially constrained core areas along HG, can satisfactorily be modeled with a single ECD. Already the P1 response, which peaks at some 50 ms, represents activity in multiple belt areas (Yvert et al., 2005), and the N1 has sources in belt and parabelt areas, which become activated after 50 ms (e.g., Inui et al., 2006).

Thus, the N1 seems to represent final, rather than initial, stages of activation in the feedforward organization of the auditory cortex. Activity in auditory areas, of course, does not end with the N1. Evidence suggests that subsequent activity develops as a result of feedback connectivity between A1 (core), STG (belt/parabelt), and the inferior temporal gyrus (Garrido, Kilner, Kiebel, & Friston, 2007), and it includes the P2 response that has sources in auditory cortex with a center of gravity on HG (Lütkenhöner & Steinsträter, 1998). On the above basis, even though the N1 is traditionally regarded as an index of the activation of "afferent" cortical cells to the onset of sound stimuli (e.g., Näätänen, 1992), it is likely that its generators have a much more profound role in the analysis of auditory information. Namely, as the N1 represents widespread activity in belt and parabelt areas, it is probable that the cells generating the N1 share the rich palette of selectivities to spectral and temporal aspects of sound structure that these areas have (see Section 5.2). It is therefore an interesting possibility that the N1 "generators" in fact directly participate in the central task of the auditory cortex: that of segregating auditory objects and integrating information over time (see Section 8). Indeed, this notion is supported by the experimental results on the sensitivity of the N1 to various aspects of speech stimuli and spatial information (see Section 3).

The problem of explaining the generation of MMN to frequency deviants was originally addressed by May et al. (1999), who proposed that the tonotopic mapping of sound frequency to cortex coupled with poststimulus suppressive mechanisms of adaptation and lateral inhibition could account for the ERP/ERF responses measured in the oddball paradigm. These authors elaborated on the traditional adaptation-based explanation by considering the effect that poststimulus suppression has on the latency of activation on the tonotopic map. As shown in Figure 2, the analyses of the neural model suggested that the strength of poststimulus suppression affects not only the peak amplitude of the ERP/ERF responses (the spatially summed activity of the neural field) but also the time-evolution of this activity: The larger the suppression, the later the peak latency. In this study, we showed that lateral inhibition leads to more complicated spatial distributions of poststimulus suppression than those due to adaptation alone. These distributions, consequently, allow for more complex behavior of the peak latency of the ERP/ERF response. Specifically, the peak latency of the response to the deviant (undistorted by subtraction procedures) can be a unimodal function of the magnitude of the difference between the standard and deviant, first increasing and then decreasing as the difference is widened. This, then, would be the reason why the MMN has a large latency variation and why it peaks at a latency that is delayed compared to the peak latency of the N1 to the standard. Our prediction was verified in EEG measurements, and the model was also able to account for the behavior of MMN amplitude, which grows as the magnitude of deviance is increased (Tiitinen et al., 1994).

Importantly, exploiting the purported N1 contamination of the MMN response at large deviances, the study of May et al. (1999) included a test for whether auditory cortex generates an exclusively deviance-related response to the deviant according to the memory-based model. Tones in the 100–5000 Hz range were presented in two conditions: In the "tone alone" condition, the stimuli (one frequency per stimulus block) were presented at
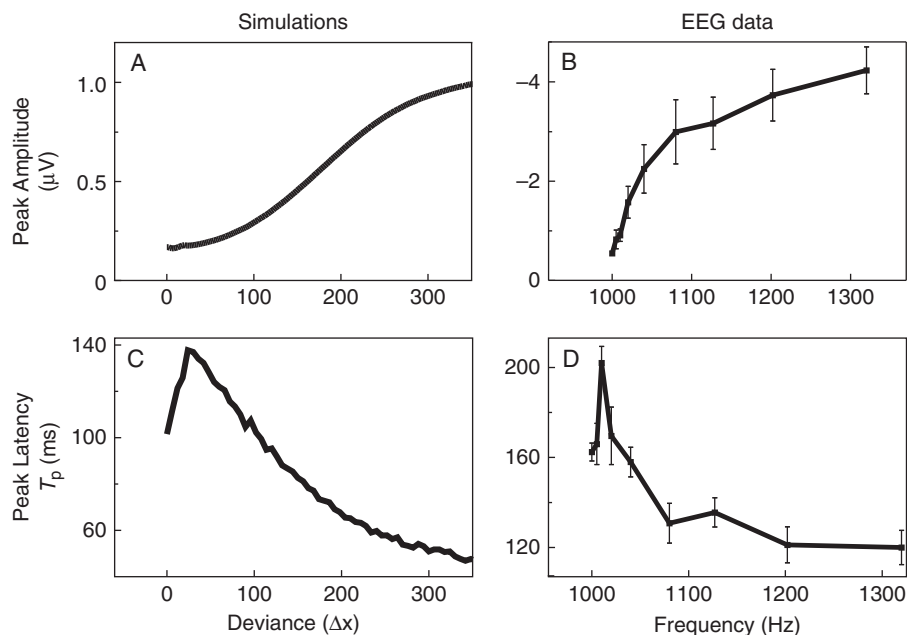

Figure 2. Experimental support for the adaptation model of MMN generation. Simulations of the adaptation model and EEG results show how the peak amplitude and peak latency of the response to the deviant (unmanipulated by the subtraction procedure) changes as a function of the frequency difference between the deviant and standard. A: In simulations, the amplitude increases monotonically as a function of frequency separation. B: Similar behavior was observed in EEG measurements where deviants in the 1005–1320-Hz range where presented among 1000-Hz standards. C: In simulations, the latency function displays more complicated behavior, first increasing and then decreasing as a function of frequency separation. This can be attributed to the presence of lateral inhibition in the model. D: Analysis of EEG data confirmed the prediction of the model: As the frequency separation grows, peak latency of the response to the deviant increases from around 160 ms to 200 ms before dropping down to around 120 ms. Adapted, with permission, from May et al. (1999). Copyright Kluwer Academic Publishers.

irregular intervals, with a relatively long mean ISI of 2.4 s. In the oddball condition, the same series of tones was presented with the silent periods between them filled with 1000-Hz standard stimuli presented at a fast ISI of 240 ms. This setup essentially tests the effect the standard stimuli have on the response elicited by the deviant. As the frequency separation between the standard and deviant is widened, the attenuating effect of the standards on the N1 response elicited by the deviant should become weaker. Consequently, this N1 response increasingly resembles that elicited by the deviant presented in the tone alone condition (although the tone-alone response should remain larger due to the contribution of cells responding nonselectively to both the standard and the deviant). In the oddball condition, the deviant-elicited N1 response should, according to the memory-based interpretation of MMN, be augmented by the deviance-related MMN response. Therefore, *sufficient* (though not necessary) evidence for the memory-based model would be a larger oddball than tone alone response. However, no such augmentation was found, supporting the adaptation model for frequency MMN generation. This result was recently verified by Jääskeläinen et al. (2004, Experiment 2), who used the same tone-alone versus oddball comparison, and it is also corroborated by the results of Elangovan, Cranfordt, Walker, and Stuart (2005), Korzyukov et al. (1999), and Umbricht, Vyssotki, Latanov, Nitsch, and Lipp (2005), none of whom found a larger oddball than tone-alone response.

The central element in the May et al. (1999) model for frequency MMN generation is the tonotopic map, whereby the cells are differentially tuned to the feature that separates the standard and the deviant. In the pure-tone stimulation used in the oddball paradigm to study frequency MMN, frequency is the primary spectral feature of the series of standard stimuli. The primary temporal feature is the stimulus presentation rate, the ISI. To expand the scope of the model, the possibility of cortical cells being differentially tuned to this simple temporal aspect of stimulation was explored by May (1999) and May and Tiitinen (2001). The authors considered how a spatial coding of stimulation rate could be achieved through the interaction of excitatory and inhibitory cortical cell populations. The results of May (1999) showed that such a coding can, in principle, be achieved both by neural fields with spatially homogeneous parameter values (e.g., synaptic coupling strengths) and by those where these values depend on field location. In the homogeneous case, adaptation and lateral inhibition allow stimulus events to trigger traveling waves on the neural field that could be used to represent stimulation rate in a topographically organized way. In the non-homogeneous case, where the strength of local feedback inhibition is a spatial variable, each locality of the neural field acts as a temporal bandpass filter, maximally tuned to a specific stimulation rate. The homogeneous and nonhomogeneous models predict that the ending of a train of repetitive stimuli results in sustained activity and multiple stimulus omission responses, respectively. MEG measurements supporting the nonhomogeneous, temporal filter model (May, 1999; May & Tiitinen, 2001), this model is worth considering in more detail.

Figure 3 shows simulations of the temporal filter model exhibiting tuning to stimulation rate and replicating the MMN to sudden decreases in ISI and duration. In this model, interacting excitatory and inhibitory cortical cell populations behave, essentially, as driven harmonic oscillators with damping. Therefore, cells at each neural field location synchronize their activity to periodic stimulation, but act as bandpass filters by responding
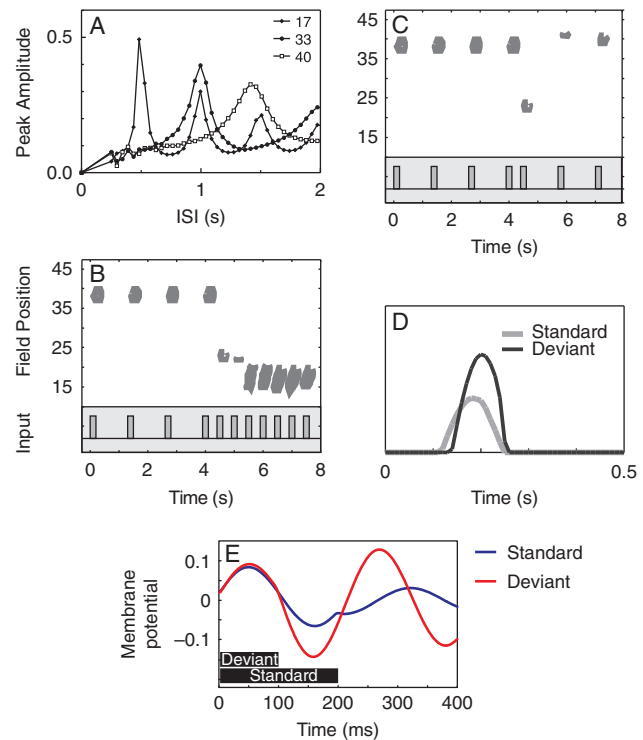

Figure 3. Simulations showing how a topographic mapping of stimulation rate (ISI) can be achieved through a temporal filter mechanism and how this leads to an adaptation-based MMN response for ISI and duration decrements. The model describes a field of locally interacting excitatory and inhibitory cells where all locations receive afferent input. However, because the strength of inhibition varies across field position, each location has a unique resonance frequency, and this directly contributes to each position responding selectively to ISI. A: The ISI tuning curves from three field positions (17, 33, and 40) are shown. Each position is sharply tuned to ISI. B: The model was presented with a series of 100-ms discrete stimuli. At *t* = 4 s the ISI is changed from 650 to 250 ms. As a result, the location of maximal responses (dark gray circumscribed areas) switches from around position 40 to position 20. C: In oddball stimulation, a series of standards with an ISI of 650 ms is interrupted by a 250-ms ISI-decrement deviant at *t* = 4. Again the location of the maximal response is shifted for the deviant and returns back to its original position for the postdeviant standards. D: An MMN response to the ISI decrement is generated by a secondary neural field receiving topographically organized input from the first field. A–D adapted from May (1999). E: An MMN response is elicited by a duration decrement, which disturbs the steady-state oscillation the cells settle into during standard stimulation. The figure shows the averaged activity of a representative cell. Twenty deviants (duration 100 ms) were presented randomly among 180 standards (duration 200 ms). The ISI was 510 ms.

maximally to a particular stimulation rate equivalent to the local neural circuit's resonance frequency. This suggests a straightforward mechanism for stimulus rate representation: If the local parameter values such as interaction weights between the excitatory and inhibitory cell pools of each microcolumn vary across field location (as indirectly indicated by the A1 results of Prieto, Peterson, & Winer, 1994), each location will have its own, unique resonance frequency and therefore respond most strongly to one stimulation rate, or ISI, only. This model lends support to the generality of the adaptation model of MMN by offering an explanation of how a spatial mapping of stimulus rate might be achieved. It also accounts for MMN to duration changes (Figure 3E): Due to the cyclical driving force constituted by the repeated

standard, cortical columns settle into a steady-state oscillatory solution including a response peak at around 100 ms poststimulus latency. The infrequent shortening or lengthening of the stimulus is, in effect, an aberration in the driving force. Crucially, this aberration introduces transient terms into the oscillatory solution, and these can be viewed as transient deviations from the steady-state solution, that is, MMN responses. Thus, cells that "ordinarily" react maximally at the N1 peak latency can be made to discharge at other latencies by complicating the stimulation.

As shown in Figure 4, the temporal filter model predicts that after the ending of a stimulus sequence, damped oscillations continue with angular frequencies proportional to that of the periodic stimulation. Such "rebound" responses were found by May and Tiitinen (2001), who presented 1000-Hz tones at ISIs ranging from 103 to 650 ms and examined the ERF following the ending of the stimulus train. Consistent with the predictions of the model, the N1 response elicited by the final stimulus in the train was followed by two ERF deflections with diminished peak

amplitudes and with latencies proportional to the ISI. Also, in accordance with the model, no differences were found between the source location for the N1 response and those for the rebound responses. Importantly, the rebound responses resemble the omission MMN (Halgren et al., 1995; Yabe et al., 1997, 1998), ERF deflections peaking at around 100 ms after the "onset" of a stimulus omission from a train of identical stimuli presented at a constant ISI. In sum, the temporal filter model accounts for stimulus omission responses observed in experiments and suggests that they are generated by the same cell populations that underlie the N1 response. This model allows for a straightforward explanation of MMN to infrequent increments and decrements in ISI and duration (Figure 3).

In summary, the adaptation model explains the MMN as an enhancement of the N1 response and offers a physiological explanation for the memory trace and comparison process underlying MMN. The memory trace is the spatially distributed suppressive effects of adaptation and lateral inhibition due to
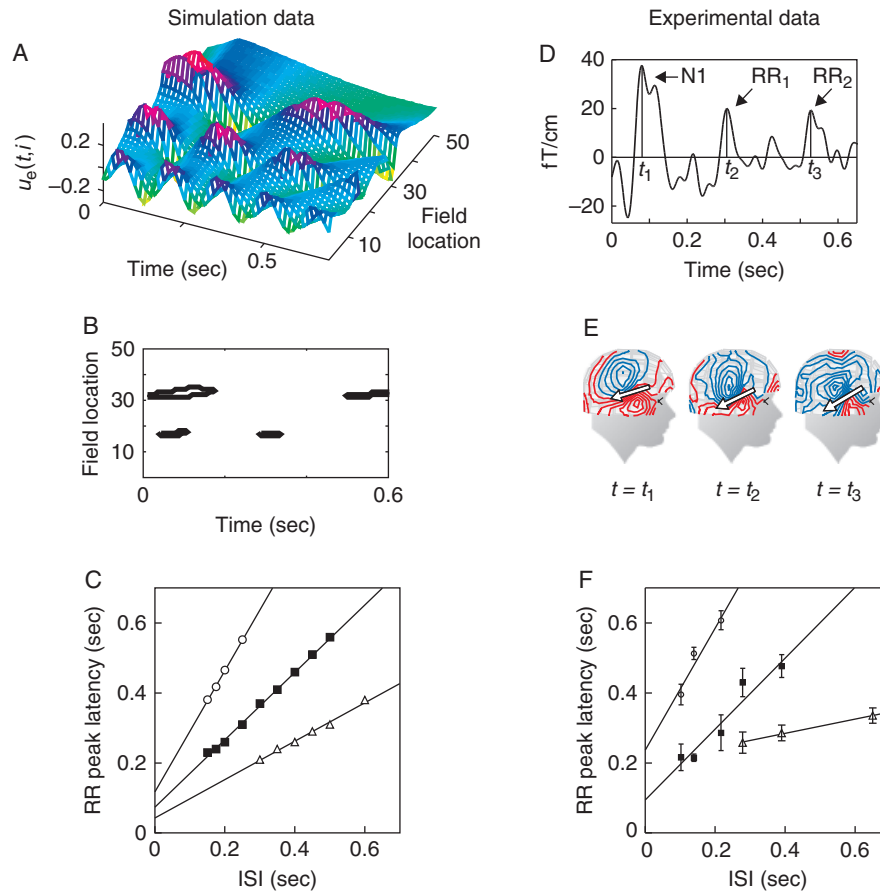

Figure 4. The adaptation model provides an explanation for MMN to stimulus omission. A: Simulations of the temporal filter model showing free oscillations following the ending of a stimulus sequence. Nine discrete stimuli (ISI = 500 ms) were presented, with the last stimulus presented at $t = 0$. The field continues to oscillate in a damped way after the ending of the sequence, thus generating both "N1" responses to the stimuli and "rebound responses" or "omission MMNs" to stimulus omissions. B: These oscillations are demonstrated in the time-location space where activity exceeding a threshold of 0.3 is shown. C: The peak latencies of the omission responses for stimulus sequences of different ISIs. These represent activity at the locations tuned to the ISI as well as $2 \times$ ISI. The latencies were measured in relation to the onset of the last stimulus of the sequence. D: MEG responses of a representative subject measured from a right-hemispheric sensor. The subject was presented with a sequence of stimuli presented at a 279-ms ISI. The last stimulus of the sequence ($t = 0$) elicited a prominent N1, which was followed by two omission responses (RR1 and RR2). E: The ECDs for the N1, RR1, and RR2 responses shown above. F: The peak latencies of the RRs, measured in relation to the onset of the last stimulus of the sequence, plotted against the ISI of the sequence. The peak latencies can be described by three linear ISI–latency relationships, which agree with the prediction of the model (see C). These results indicate that the omission MMN arises from the oscillatory properties of cell populations underlying the N1 response. Adapted from May and Tiitinen (2001). Copyright Lippincott Williams & Wilkins, reprinted with permission.

activation elicited by the standard stimuli. The comparison process arises directly out of the stimulus selectivity of auditory cortical cells. Our previous modeling work shows that the adaptation model can account for the MMN to changes in frequency, ISI, and duration, as well as for the omission MMN. May (1999) suggested that stimulus selectivity combined with adaptation and lateral inhibition could serve as the general mechanism of MMN generation, with the auditory cortex utilizing spatial coding to represent spectral and temporal stimulus features of sound.

5. The Physiological Evidence for the Adaptation Model

The adaptation model (May, 1999; May & Tiitinen, 2001, 2004b; May et al., 1999) as a general explanation of MMN is based on two prerequisites: (a) Adaptation and lateral inhibition are ubiquitous features of auditory cortex. (b) The spectral and temporal stimulus features along which the standard differs from an MMN-eliciting deviant stimulus are represented spatially in auditory cortex. The model requires the existence of stimulus-selective cells but these need not be organized topographically (as in the case of frequency representation). The central prediction of the model is that cell populations underlying the MMN to a particular class of stimulus are also responsive when that stimulus is presented as the standard (see Figure 1). Electrophysiological results strongly support the above building blocks of the adaptation model, although this has been largely overlooked in MMN research.

5.1. Adaptation and Lateral Inhibition in Auditory Cortex

Adaptation, the short-term modification of the responsiveness of neurons by sensory stimulation, is a common feature in cortex (for reviews, see Calford, 2002; Kohn, 2007; Manto, Oulad ben Taib, & Luft, 2006). In auditory cortex, this phenomenon—also known as forward suppression and forward masking—seems to be stimulus specific, as is evident in single-cell recordings in cat A1 using the two-tone paradigm and documented in the classic studies by Brosch and Schreiner (1997, 2000) and Calford and Semple (1995). Here, the effect of a masker tone on the neural response to a probe tone (fixed at the characteristic frequency of the neuron) is examined by parametrically varying the temporal interval (stimulus onset asynchrony, SOA) between the two tones as well as the frequency and intensity of the masker. The results indicate that the frequency range of the masker that induces forward suppression, measured as a reduction of the number of spikes elicited by the probe, is centered at the neuron's excitatory receptive field. Recovery from this forward masking effect depends on the frequency separation between the masker and the probe, with the suppression caused by the masker lasting the longest (53–430 ms) when both the masker and the probe are set at the neuron's characteristic frequency. This stimulus-specificity of adaptation is also seen in measurements using repetitive sounds. Condon and Weinberger (1991) observed receptive field changes in the auditory cortex of guinea pig resulting from several hundred repetitions of a tone. In most of the neurons studied, repetition resulted in a substantial decrease of the response that was highly specific to the repeated frequency. This decrease could not be explained as resulting from simple "fatigue" or "refractoriness" processes but, rather, exhibited complicated characteristics such as long-term effects and incubation (i.e., increase in strength after the cessation of the repetition) that the authors interpreted in terms of frequency-specific habituation caused by synaptic modifications.

Adaptation seems to be largely due to synaptic effects in auditory cortex. Its cortical origin is likely because in subcortical areas masking effects decay rapidly (Brosch & Schreiner, 1997; Schreiner, 1981; Ulanovsky, Las, Farkas, & Nelken, 2004; Wehr & Zador, 2005), because thalamic cells follow amplitude-modulated sounds at much higher rates than cortical cells (Creutzfeldt, Hellweg, & Schreiner, 1980) and because of considerations related to the nonmonotonic masking-level profiles measured in auditory cortex (discussed in Calford & Semple, 1995). As tone-evoked synaptic inhibition contributes to responsiveness up to around 100 ms only, the most likely candidate for the mechanism of longer term adaptation is synaptic depression (Wehr & Zador, 2003, 2005). Also, Ulanovsky et al. (2004) studied the time course of adaptation in cat A1 using various experimental designs that had probabilistic structures spanning different time scales. They found that stimulus-specific adaptation has several concurrent time scales, ranging from a few milliseconds to tens of seconds, and concluded that the time scales of adaptation reflect those present in the stimulation. As pointed out by the authors, these time scales match the several coexisting time constants that best describe the lifetime of synaptic depression of corticocortical synapses (Markram, Wang, & Tsodyks, 1998; Tsodyks & Markram, 1997; Varela et al., 1997).

Evidence for the adaptation model of MMN is provided by single-cell observations in the cat auditory cortex and thalamus. Presenting pure-tone stimuli in the oddball paradigm, Ulanovsky et al. (2003) found that A1 neurons responded more strongly to frequency and intensity deviants than to standards. The resulting difference signal between the responses was in many ways similar to the MMN: Both have similar temporal dynamics as well as amplitudes that are positively correlated with the frequency difference between the standard and the deviant and negatively correlated with the ISI and the probability of the deviant. Adaptation was observed in cortex only, with thalamic cells showing no differential responses according to stimulus type. The authors concluded that these effects were due to stimulus-specific adaptation in auditory cortex and that the "results provide the first direct evidence that neuronal adaptation has the right properties to account for MMN" (Ulanovsky et al., 2003, p. 396).

Lateral inhibition, along with adaptation, is a common feature of the central auditory pathway (for reviews, see Ehret & Merzenich, 1988; Suga, 1995). Evidence for lateral inhibition in primary auditory cortex comes from vertebrate studies using two-tone stimulation in the simultaneous masking paradigm (Sutter & Loftus, 2003; Sutter, Schreiner, McLean, O'Connor, & Loftus, 1999), and two-tone (Brosch & Schreiner, 1997; Calford & Semple, 1995; Shamma & Symmes, 1985) and multifrequency (Valentine & Eggermont, 2004) stimulation in the forward-masking paradigm. These results show that inhibition occurs for masker tones that are outside the receptive field area of the cell responding to the probe tone. In addition, Shamma and Symmes (1985) found that strong lateral inhibition is primarily a feature of A1. Howard et al. (1996) found evidence for lateral inhibition in the human auditory cortex by studying single-cell responses to tones of different frequencies. The majority of the cells demonstrated sharply tuned excitatory best-frequency responses in conjunction with inhibitory sidebands. In these sidebands, the onset of the tone resulted in a decrease of the firing rate of up to 50% in relation to prestimulus, background firing. Recent MEG measurements in humans demonstrate that the N1 is attenuated

both by stimulus-specific adaptation (habituation) and lateral inhibition (Pantev et al., 2004; Okamoto, Kakigi, Gunji, Kubo, & Pantev, 2005; Okamoto, Kakigi, Gunji, Pantev, 2007; Okamoto, Stracke, & Pantev, 2008). This inhibition has a strength that diminishes with ISI and a lifetime of seconds (Okamoto, Ross, Kakigi, Kubo, & Pantev 2004). Although lateral inhibition has been verified in the frequency dimension, it remains unexplored for other stimulus dimensions.

In summary, the evidence is clear that adaptation and lateral inhibition are key modulatory mechanisms of auditory cortical neurons and should therefore be incorporated into any physiologically based model of auditory processing.

5.2. *Representation of Temporal and Complex Sound Features in Auditory Cortex*

The generality of the adaptation model requires that the standard and deviant stimulus elicit different spatial distributions of cortical activity, that is, the difference between the two stimuli is reflected in the sets of cells they activate. Therefore, as MMN seems to be elicited by any kind of audible change in stimulation, the spectrotemporal structure of the auditory environment is represented by the spatial distribution of activity in auditory cortex. This idea is in line with Shamma's (2001) suggestion that, instead of relying on specialized computational machinery (e.g., systematically organized delay lines), auditory cortex uses the same basic computational principle as visual and other sensory areas for processing sensory information. This principle is to transform the activity originating from the periphery into spatial patterns of central activation through the mechanisms of lateral inhibition, multiscale analysis, and temporal and spatial coincidence detection. In the auditory system, these mechanisms are used for forming spatial representations of the spectral and spectrotemporal profile of sounds as well as of periodicity pitch and binaural sound source localization.[2]

Evidence for a spatial decomposition of stimulus features in auditory cortex has been steadily accumulating. Results in animal models show that, apart from being organized tonotopically, cells in auditory cortex respond selectively to multiple sound features, namely, intensity (Heil, Rajan, & Irvine, 1994; Phillips, Semple, Calford, & Kitzes, 1994; Schreiner, Mendelson, & Sutter, 1992; Sutter & Schreiner, 1995), bandwidth (Schreiner & Mendelson, 1990; Schreiner & Sutter, 1992), frequency composition (Sutter & Schreiner, 1991), and binaural information (Clarey, Barone, & Imig, 1994). These selectivities are independent of each other (Recanzone, Schreiner, Sutter, Beitel, & Merzenich, 1999; for a review, see Schreiner, Read, & Sutter, 2000). Further, cells in auditory cortex have been found to respond

selectively to the temporal structure of sound, including stimulus duration (He, Hashikawa, Ojima, & Kinouchi, 1997), the speed and direction of modulation of frequency-modulated sounds (Heil, Rajan, & Irvine, 1992a, 1992b; Mendelson & Cynader, 1985; Mendelson, Schreiner, Sutter, & Grasse, 1993; Shamma, Fleshman, Wiser, & Versnel, 1993; Tian & Rauschecker, 1998, 2004), the frequency of modulation of amplitude-modulated sounds (Bieser & Muller-Preuss, 1996; Schreiner & Urbas, 1986, 1988), and species-specific vocalizations (Rauschecker, Tian, & Hauser, 1995; Wang, Merzenich, Beitel, & Schreiner, 1995). Cells tuned to temporal structure also exhibit adaptation to sound repetition as well as response facilitation if the sound to which they preferentially respond is preceded by another one with a different temporal structure (Bartlett & Wang, 2005). It seems that preferential responding to tones is restricted to primary auditory cortex, with surrounding secondary areas showing selectivity to richer and more complex stimuli (Kaas & Hackett, 2000; Rauschecker, 1998; Rauschecker & Tian, 2004; Rauschecker et al., 1995). These results from animal models are supported by measurements in humans: Tonotopic organization has been verified intracortically (Howard et al., 1996) and with MEG measurements (Pantev et al., 1988, 1994), which also indicate the existence of amplitopic maps (Pantev, Hoke, Lehnertz, & Lütkenhoner, 1989). Also, fMRI results indicate that the frequency of amplitude modulation (i.e., the inverse of ISI) is a feature represented spatially, with primary auditory cortex responding preferentially to sounds amplitude-modulated at 8 Hz and secondary regions at 4–8 Hz (Giraud et al., 2000).

The response properties of auditory cortical cells can be characterized in a unified way by using ripple stimuli (Calhoun & Schreiner, 1998; Klein, Depireux, Simon, & Shamma, 2000; Kowalski, Depireux, & Shamma, 1996a, 1996b; Shamma & Versnel, 1995; Shamma, Versnel, & Kowalski, 1995) and random tone sequences (deCharms, Blake, & Merzenich, 1998). The responses to these reveal the cell's spectrotemporal receptive field (STRF), that is, the time-evolving spectral structure of an auditory stimulus to which the cell responds selectively. For example, in A1, cells display a wide variety of STRFs that is in line with the existence of tuning properties to multiple stimulus features. In this sense, instead of comprising several sequential and overlaid feature maps, the auditory cortex might better be described as a single map consisting of cells with various spectrotemporal response fields.

Thus, in view of the physiological evidence, it is likely that the spectrotemporal structure of the auditory environment is mapped onto the surface of auditory cortex. Supporting the adaptation model of MMN generation, this kind of representational strategy allows for the repetitive standard stimulation in the oddball paradigm to activate a different distribution of cells than the deviant. Therefore, when this mapping ability is coupled with neural adaptation, the result is a differential (MMN) response to the standard and the deviant representing any kind of spectrotemporal stimulus change.

5.3. *The Evidence from Epidural and Intracortical MMN Recordings*

Epidural recordings have been used to measure MMN above auditory cortex in guinea pig (King et al., 1995; Kraus et al., 1994), cat (Csépe, 1995; Csépe, Karmos, & Molnar, 1987; Pincze, Lakatos, Rajkai, Ulbert, & Karmos, 2001, 2002), and monkey (Javitt, Schroeder, Steinschneider, Arezzo, & Vaughan, 1992). These recordings have provided evidence for the MMN being localized to primary or secondary auditory cortex, depending on

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[2]As stimulus-specific adaptation and spatial representation of stimulus features are principles of operation in the visual cortex also, the adaptation model suggests that differential responses to changes in visual stimuli should occur. Indeed, numerous studies employing the oddball paradigm in visual stimulation have established that infrequent deviant stimuli elicit event-related responses that, compared to responses to frequent standard stimuli, are enhanced in the 100–300-ms range (for a review, see Pazo-Alvarez, Cadaveira, & Amenedo, 2003). Curiously, there has been a reluctance to identify these enhancements as MMN responses reflecting automatic, memory-based change detection because their attention independence has been questionable and because it is unclear to what extent they reflect fresh-afferent activation rather than genuine memory-based processing. Thus, although measurements in visual cortex may or may not support the existence of a memory-based visual MMN, they clearly offer corroborating evidence for the adaptation model.

animal type. However, just as in the case of EEG and MEG, epidural electrodes measure the summed activity of multiple sources, where the contribution of each source has to be estimated by using inverse methods such as independent component analysis (e.g., Takahashi, Nakao, & Kaga, 2007). Therefore, the waveforms these electrodes yield are not helpful for directly revealing the underlying mechanisms of MMN generation. This also holds for intracranial MMN recordings in humans (Halgren et al., 1995; Kropotov et al., 1995, 2000; Liasis, Towell, & Boyd, 1999, 2000; Rosburg et al., 2005): Researchers using implanted arrays of electrodes (separated by millimeters) have been able to measure larger responses to deviants than to standards and to identify different areas of peak activity during the N1 to the standard and the MMN to the deviant. Importantly, however, epidural and intracortical recordings in animals and humans have been unable to identify sources producing ''genuine'' memory-based MMNs, that is, specific cell populations remaining unresponsive when a stimulus is presented as a standard stimulus or at long ISIs (i.e., in the ''deviants alone'' condition) and becoming active *only* when that same stimulus appears as a deviant in the context of previous standard stimuli (see also Section 6.10).

Evidence for the adaptation model of MMN can be found in intracortical measurements in monkey. Javitt and colleagues (Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo, 1994; Javitt et al., 1995, 1996) conducted multichannel electrode recordings to reveal the laminar distribution of MMN-related activity in A1. The results showed that the initial thalamocortical activation was similar to both the standard and the deviant stimulus, but that the surface-recorded MMN was associated with increased activation of pyramidal cells within supragranular laminae. Importantly, the measured cell populations responded to both the standards and deviants, but the strength of the response was inversely proportional to the probability of the stimulus. This effect, paralleling that found with single-unit MMN recordings in cat (Ulanovsky et al., 2003, 2004), is entirely consistent with the adaptation model: Responses to standards are diminished compared to those to deviants due to the differential adaptation of the cells responding to the stimuli. Again, the above intracortical recordings revealed no areas where cells respond to a stimulus *only* when it appears as the deviant among standards. This lack of evidence for the memory-based model of MMN was explicitly stated by Javitt et al. (1994): ''Intracortical MMN generation was superimposed upon a pattern of obligatory activity in AI, suggesting that the same local area of cortex contributes simultaneously to the generation of cognitive and obligatory sensory ERP components'' (p. 197). That is, contrasting the interpretation advocated in, for example, Näätänen et al. (2005), the populations that contribute to the MMN elicited by a tone when used as a deviant also take part in the response when that same tone is used as the standard stimulus.

Javitt et al. (1996) studied the neurotransmitter mechanisms of MMN in monkey. They found that NMDA antagonists PCP and MK-801 do not influence the time course and laminar distribution of activation to the standard stimulus whereas the supragranular activity elicited by the deviant can be sufficiently suppressed to abolish the MMN. However, blocking both NMDA and non-NMDA glutamate (excitatory) receptors with kynurenic acid curtailed the generation of standard-induced activity in supragranular layers. In contrast, administering the GABA$_A$ antagonist bicuculline led to the standard stimuli eliciting enhanced activity in all laminae, with the enhancement being particularly large in supragranular laminae. This enhancement,

being reversable by MK-801, was due to current flow through NMDA channels. The authors suggested that these results could be accounted for by a model (much like that of Näätänen, 1984) whereby the repetitive presentation of a stimulus increases the tonic GABA$_A$-mediated inhibition of cells tuned to that stimulus while decreasing it for other cells. However, as pointed out by the authors, this leaves open the question of how GABA$_A$-mediated tonic inhibition could be maintained for the 10–20-s lifetime of the sensory memory trace underlying MMN, given that GABA$_A$ postsynaptic potentials have a duration of tens of milliseconds only. Presumably, the presynaptic interneurons would require tonic excitation, begging the question of where this excitation originates (certainly not locally) and how it is modulated.

As an alternative, one might consider a model based on local recurrent excitation, a central feature of cortical circuitry (Douglas, Koch, Mahowald, Martin, & Suarez, 1995; Douglas & Martin, 1991) included in the adaptation model also (May, 1999; May & Tiitinen, 2001, 2004b; May et al., 1999): As the standard is repeatedly presented, synaptic depression (i.e., adaptation) lower the magnitude of the local recurrent excitation, and, therefore, the depolarization of pyramidal cells falls below the level at which NMDA receptors are kept unblocked. Consequently, the adapted cells respond to the standard through non-NMDA recurrent excitation, and the nonadapted cells tuned to the deviant are able to trigger recurrent excitation that increases the depolarization sufficiently for NMDA channels to become active. Thus, NMDA antagonists suppress the response to the deviant but not to the standard. Upsetting the local balance between excitation and inhibition by introducing a GABA$_A$ antagonist would allow the non-NMDA excitation to depolarize the cells sufficiently to unblock the NMDA channels. This model would require no tonic inhibition, relying instead on known cortical microcircuitry whereby inhibitory interneurons are driven by local pyramidal cells whose activity they, in turn, modulate (Markram et al., 2004).

5.4. Summary: The Physiological Case for the Adaptation Model
In sum, the adaptation model is consistent with knowledge about the physiology of the auditory system. Both adaptation and lateral inhibition are readily found in auditory cortex, and the spectral and temporal structure of the auditory environment seems to be reflected in the spatial distribution of activity in auditory cortex. Also, epidural and intracortical results agree well with the adaptation model, and multi-unit recordings offer direct support. It is therefore conceivable that when the environment is repetitive, a specific set of cells is the most active and becomes adapted. At the same time, neighboring cells are inhibited through lateral interactions. The result is a spatial distribution of supression of activity specific to the repetitive stimulation. Deviations to the repetitive environment activate a set of cells with a different spatial distribution (fresh afferents). Due to these differences in distribution, the standard and deviant activate cells that are differentially suppressed through adaptation and lateral inhibition, the outcome being a larger response to the deviant, which, following subtraction, is generally assumed to be a separate component and is labeled the MMN.

6. The Arguments against the Adaptation Model and the Separability of N1 and MMN

The adaptation model proposes that the subtraction between the response to the deviant and the standard (the technically defined

MMN), although reflecting differential responding to sounds of different informational or novelty value, might not in itself reflect a brain event exclusively representing change detection. Rather, it might be due to N1 generators being under the modifying effects of spatially unevenly distributed sensory memory traces. For this model to have any credibility, one is forced to challenge the phalanx of counterarguments that has become impressively large over the years (e.g., Näätänen, 1990, 1992; Näätänen & Alho, 1995; Näätänen & Winkler, 1999; Näätänen et al., 2005, 2007). Therefore, in the following, we will examine these counterarguments and show that they are based on untenable and/or untested assumptions.

6.1. MMN Occurs Later than the N1

Perhaps the most straightforward and intuitive reason for treating the N1 and MMN as separate "components" arises from the finding that the N1 and MMN behave differently with regard to timing: Not only does the MMN always peak later than the N1 to the standard, but, also, the N1 occurs at a relatively invariant latency whereas the latency of the MMN fluctuates over a wide range. Thus, it is tempting to argue that the two must be generated by separate brain mechanisms. However, this argument presupposes that the N1 is generated by latency-invariant activation patterns in cortex, and this presupposition is then used to deduce that the MMN has a large latency variation and must therefore be a separate entity from the N1. Besides being circular, this argument overlooks the effects of the dynamic state into which the cortex is "driven" by oddball stimulation.

The tardiness of the MMN was originally used by Näätänen et al. (1978) as the grounds for ruling out the adaptation-based explanation of MMN: "It is, however, possible that the initial part of the [MMN] negativity concerned is due to the stimulus activating . . . such fibers that are not activated by the standards. If this were the case it could, naturally, directly account for only that phase of the negative shift which corresponds to the latency of the N1 component" (p. 324). This argument has since been used as one of the standard justifications of the memory-based model of the MMN (Näätänen, 1990, 1992; Näätänen & Alho, 1995; Näätänen, Paavilainen, Alho, et al., 1989; Näätänen et al., 2005). In these accounts, the reasoning is straightforward: Because the peak latency of the MMN varies in the 100–200-ms range according to deviance magnitude (e.g., Näätänen, Paavilainen, & Reinikainen, 1989; Sams, Paavilainen, et al., 1985; Tiitinen et al., 1994), the MMN cannot be equated with the N1, a response with a relatively stable peak latency of around 100 ms. Consequently, legitimation is provided for the subtraction procedure whereby the fixed-latency N1 is removed from the response to the deviant thereby revealing the "genuine" memory-related MMN response.

However, where is the evidence that the N1 latency is fixed, being unaffected by the temporal context of the stimulus by which it is elicited? This question is crucial, because if the assumption regarding the latency invariance of the N1 turns out to be incorrect, the rationale of the subtraction procedure would be undermined. Consequently, the subtraction would, at the very least, introduce artifactual latency and amplitude changes to the MMN, thus limiting the usefulness of the MMN in both basic and applied research. It might even be possible that all of the latency variations found in the response to the deviant can already be accounted for by changes in the latency of the N1.

As noted in Sections 3 and 4, the fixed, invariant nature of the latency of the N1 is doubtful on multiple grounds. First, the peak latency of the N1 elicited by repetitive stimuli varies tens of milliseconds already according to the frequency of the stimulus (Mäkelä et al., 2002; May et al., 1999; Stelmack et al., 1977) and can be as late as 153 ms (Roberts & Poeppel, 1996). Second, the computational modeling results of May et al. (1999) suggest that both adaptation and lateral inhibition lead to the N1 latency becoming sensitive to the magnitude of deviance in the oddball paradigm and that, with lateral inhibition, the responses to deviants become more delayed than the N1 to the standard (Figure 2). This model correctly predicted the nonmonotonic shape of N1 latency as a function of magnitude of deviance. Direct evidence for these latency delays in the oddball paradigm comes from the single-cell measurements carried out by Ulanovsky et al. (2003), who, in effect, advocated the adaptation model of MMN. These authors, measuring the responses of "afferent" A1 neurons to sinusoidal tones with varying probability of occurrence (i.e., when they were presented either as frequent standards or infrequent deviants), found that the latency of the difference signal (DS) between the responses to the standard and deviant stimuli increased as the frequency difference between these two types of stimuli was decreased. They also found that for small frequency differences, the DS was of a longer latency than the response to the standard, which lends further verification to the predictions of the May et al. (1999) modeling work.

Further evidence of delays of cortical fresh-afferents activation comes from intracortical recordings using the two-tone masking paradigm. Measuring single-cell activity in the primary auditory cortex of cat, Brosch and Schreiner (1997) demonstrated that a preceding masker tone can delay the latency of the initial spike to the probe tone. A similar effect was found by Calford and Semple (1995), who also showed that the delay due to masking is proportional to the reduction in the strength of the response (i.e., the total number of spikes). These delaying effects of up to 7 ms may seem rather small, but they are sizable, given the approximately 15-ms delay between the peak latencies of the N1 and MMN measured in cat (in the 45–60- and 60–75-ms ranges, respectively; Pincze et al., 2001, 2002). Taken together, these results indicate that, in the primary auditory cortex, the adaptation and lateral inhibition caused by one stimulus delays the responses to a subsequent stimulus.

A further source of N1 latency delays can be identified through considering the neuroanatomical origins of this response, which is generated in secondary and association areas (i.e., outside the primary areas) of auditory cortex. The auditory cortex of the primate contains not only parallel processing streams but is organized serially (for reviews, see Eggermont & Ponton, 2002; Kaas & Hackett, 2000; Pandya, 1995). The core areas, receiving afferent input via the thalamus, consist of at least three fields with sharply tuned, tonotopically organized cells and are surrounded by eight interconnected belt areas comprising several tonotopic fields that are driven by the core. Belt areas, in turn, drive surrounding parabelt areas, which lack direct input from the core. Thus, auditory cortex contains several parallel processing streams, each progressing serially through the core, belt, and parabelt. A similar organization has been identified in humans, with the primary auditory cortex comprising three tonotopic fields situated in the postero-medial part of Heschl's gyrus (HG) and surrounded by belt areas on the lateral part of HG and along the planum temporale (PT) and the superior temporal gyrus (STG; Galaburda & Sanides, 1980; Morosan et al., 2001; Rivier & Clarke, 1997; Sweet, Dorph-Petersen, & Lewis, 2005). Serial activation of primary and secondary areas

along the medio-lateral and posterior-anterior directions, probably reflecting the core–belt–parabelt structure, is evident in intracortical measurements in human auditory cortex (Gourévitch, Le Bouquin Jeannès, Faucon, & Liégeois-Chauvel, 2008; Guéguin et al., 2007; Liégeois-Chauvel et al., 1994; Yvert et al., 2005). Recently, Inui et al. (2006), using multiple source analysis of MEG, demonstrated that activation spreads medio-laterally in parallel streams in at least three distinct stages, from the primary areas on the most medial part of HG (core areas, with onset latencies at around 15 ms) to the lateral part of HG (belt areas) and from there to PT (with onsets at around 40 ms) and also to the STG and the posterior parietal cortex. Whereas the middle-latency evoked responses are due to activation of HG (Liégeois-Chauvel et al., 1991, 1994), the N1 is associated primarily with activation of PT (Inui et al. 2006; Liégeois-Chauvel et al., 1994; Lütkenhöner & Steinsträter, 1998), although lateral parts of the HG and the STG have also been shown to contribute (Jääskeläinen et al., 2004; Yvert et al., 2005). Thus, with parabelt areas in humans being largely located on PT (Sweet et al., 2005), the N1 seems to be generated by the final stages of feedforward activation in human auditory cortex (see also Section 4).

Notably for the current discussion, if delays in onset latencies are brought about through suppression at each link of this core–belt–parabelt chain, the total delay in activation of the parabelt could become sizable. For example, already a 30-ms delay at each stage would contribute to the N1 being postponed by around 100 ms. Apart from lateral inhibition, a further source of delay could arise from the activation at each stage requiring that a threshold (e.g., for firing or for the opening of NMDA channels of pyramidal cells) be exceeded and from adaptation-attenuated responses of the previous stage taking longer to drive the activity to this threshold. These delays in the core–belt–parabelt activation chain are supported by the combined fMRI and MEG results of Jääskeläinen et al. (2004), who showed that the anterior STG that is active during the MMN peak latency ($\sim$170 ms) is active during the N1 ($\sim$110 ms) elicited by the deviant in the "deviants alone" condition. Interestingly, they are directly supported by the intracranial measurements carried out by Kropotov et al. (2000) in area 22 in human cortex. In this parabelt area (see Hackett, Stepniewska, & Kaas, 1998), the response to a deviant tone presented in the oddball paradigm resembles that elicited by a rare tone presented at the interdeviant interval but without the intervening standards (i.e., both consist of an initial negative deflection followed by a large-amplitude positive deflection). Importantly, however, the oddball response is delayed by some 100 ms. A similar delay is evident when the deviant response is compared to that elicited by the standard.

The above mechanisms for N1 delay in the oddball paradigm are demonstrated in simulations shown in Figure 5. As detailed in the Appendix, we constructed a simplified model of auditory cortex containing tonotopically organized core, belt, and parabelt areas including adaptation and lateral inhibition as in the model originally proposed by May et al. (1999). In addition, the present model included broadly tuned cells (e.g., Irvine & Huebner, 1979; Merzenich & Brugge, 1973) driven by afferent input from the thalamus (as suggested by the study of Kajikawa, de La Mothe, Blumell, & Hackett, 2005). This model, when presented with oddball stimulation, produced an N1 to the standard (peaking at around 100 ms) and a considerably delayed MMN (peaking at 180 ms for small frequency differences between the standard and the deviant). These simulations of the adaptation model show that the emergence and latency variation of the MMN can be accounted for by the variable delays in the onset latencies of neural areas generating the auditory N1 response, with sharply tuned populations showing larger delays than broadly tuned populations.

In sum, the argument that the MMN is elicited later than the N1 cannot be used to support the memory-based interpretation. The experimental evidence clearly shows that the activation of auditory cortex is delayed by previous stimulation. Due to the serial element of auditory processing, delays in primary areas are not only carried over to activations of secondary auditory areas generating the N1 but may, in fact, be magnified in these subsequent stages of processing. The claim that the N1 has an invariant latency is not an experimentally verified fact but, rather, an assumption contradicted by experimental findings.

6.2. MMN and N1 Have Different Generator Locations

A number of MEG studies have reported 7–10-mm differences in the generator locations of the N1 to the standard and the MMN to the deviant (Csépe, Pantev, Hoke, Hampson, & Ross, 1992; Hari et al., 1984; Sams, Kaukoranta, Hämäläinen, & Näätänen, 1991; Tiitinen et al., 1993). Not surprisingly, these results have been taken as strong evidence for the memory-based interpretation of MMN (Näätänen & Alho, 1995; Näätänen & Winkler, 1999; Näätänen et al., 2007; Winkler & Cowan, 2005): If the MMN is generated in a cortical area distinct from that generating the N1, it can hardly be due to delayed responding of N1 generators, and therefore the N1 and MMN must be separate "components" generated by separate cortical mechanisms.

However, the above localization results should not be interpreted at face value, as they were all achieved through fitting a single equivalent dipole (ECD) to the ERFs. Namely, a successful ECD fit to the peak of an ERF response in no way implies that a single source was active at that particular time (Lütkenhöner & Steinsträter, 1998), with activation of the auditory cortex involving multiple parallel areas in the Sylvian fissure and STG (e.g., Yvert et al., 2005). To account for the localization differences between the N1 and MMN in the framework of the adaptation model, May (1999) and May and Tiitinen (2004b) suggested that although the same cortical areas produce the response to both the standard and the deviant, organizational differences between areas of auditory cortex would account for the differences in ECD location. Thus, in the case of the frequency MMN, tonotopically organized areas with sharp tuning curves respond differently to the standard and the deviant, whereas nonspecific areas (i.e., those whose cells have broad tuning curves) elicit similar responses regardless of tone frequency. When a single ECD is used to model the magnetic field, the response to the deviant, and therefore the MMN, is weighted toward the tonotopically organized field. This principle is demonstrated in Figure 6, where the forward solutions of two active cortical areas were calculated with the assumption that one contains broadly tuned afferent cells and the other sharply tuned cells. The resulting activations during oddball stimulation resulted in ECD location differences between the N1 and MMN strikingly similar to those found experimentally. May (1999) suggested that, based on MEG results (Hari et al., 1984; Sams et al., 1991; Tiitinen et al., 1993), frequency-nonspecific areas are posterior to tonotopically organized areas in human auditory cortex. This would be consistent with results from the monkey showing that a field of broadly tuned units whose CFs are difficult to specify is situated caudomedially in relation to tonotopically
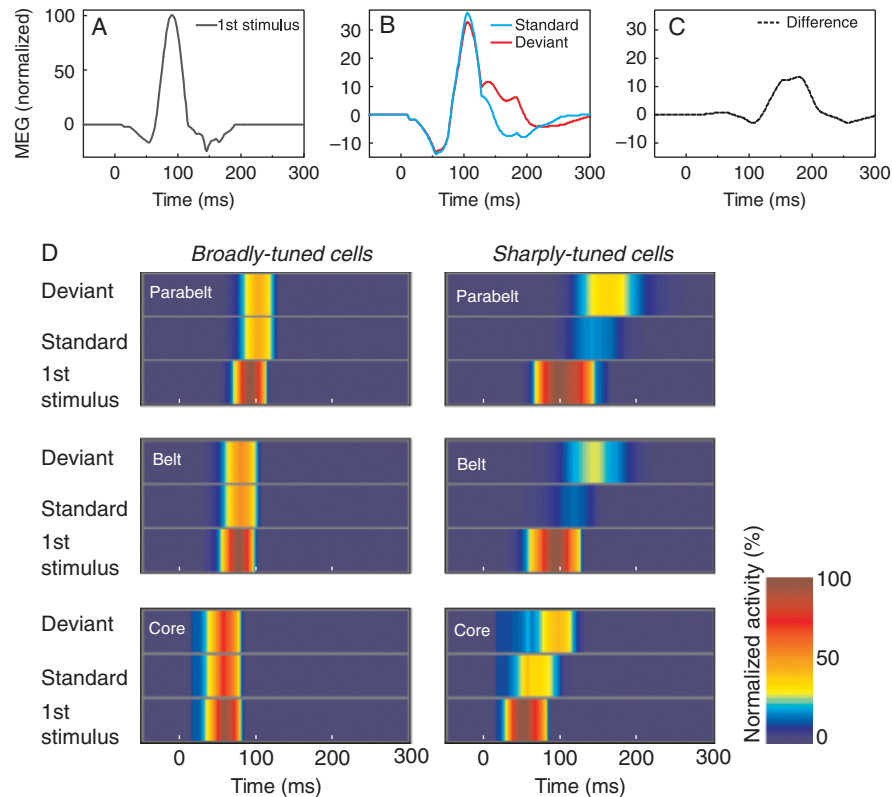
Figure 5. Simulations of the adaptation model showing the origin of the latency differences between the N1 and MMN. As detailed in the Appendix, the model contained serially connected core, belt, and parabelt areas, each comprising broadly tuned cell populations and sharply tuned, tonotopically organized populations. A: The model, when stimulated at rest by a transient tone (i.e., by the first stimulus in a series following a long silence), produced a prominent N1 response peaking at around 100 ms. B: The model was presented with oddball stimulation where frequent tones of one frequency (standards) were infrequently interspersed with tones of a second frequency (deviants). This resulted in the standards and deviants eliciting similar N1 responses peaking at around 100 ms. In the 120–220-ms latency range, the response to the deviant was enhanced compared to that elicited by the standard. C: The difference curve obtained by subtracting the standard response from the deviant one revealed an MMN response peaking at around 180 ms. D: A breakdown of the activities in the core, belt, and parabelt areas is shown (normalization per area according to maximum activity elicited by the first stimulus). For both the broadly tuned and sharply tuned cells, poststimulus activity commences at 10 ms latency. In the case of the broadly tuned cells, activity propagates from the core to the parabelt, where the activity peaks at around 100 ms at an amplitude that is the same for both the standard and the deviant and thus leads to an apparently invariant N1 response. In contrast, for the sharply tuned cells, the activation by the deviant is delayed and stronger compared to that elicited by the standard. In the parabelt area, the deviant response peaks at 170 ms, a poststimulus latency at which the weak response to the standard has almost died away, the result being the MMN. In sum, the latency difference between the N1 and MMN is usually taken as evidence for the memory-based model of MMN, but the current simulations show that it can arise out of the adaptation/fresh-afferents mechanism. That is, no dedicated MMN generator, activated only at the MMN latency, need be postulated. Instead, the N1–MMN asynchrony could be accounted for by delays in the activation latencies of neural areas generating the N1 response. *Stimulus material:* Stimuli were transient 50-ms tones (5 ms linear onset/offset slopes) presented at a 1-s ISI. The frequencies of the standard and deviant tones were 1000 and 1032 Hz, respectively. The stimulus block consisted of 100 deviants ($p = .2$) presented randomly among 400 standards ($p = .8$). Responses averaged across the stimulus block are shown.

organized A1 fields (Irvine & Huebner, 1979; Kajikawa et al., 2005; Merzenich & Brugge, 1973).

The above adaptation-based explanation of N1 and MMN localization differences was recently given support by Jääskeläinen et al. (2004), who, using combined fMRI and MEG measurements in humans, showed that activity elicited by the frequency deviant can, essentially, be described in terms of posterior areas with broad tuning curves producing an "N1p" response that is diminished by a wide range of differences between the standard and deviant whereas anterior areas with sharp tuning curves generate an "N1a" response that is less affected by this difference. Furthermore, the adaptation-based account predicts that when single-ECD modeling is used, comparisons between the N1 to the standard and the MMN *and* between the tone-alone response to the deviant and the MMN should reveal similar posterior–anterior shifts in source location: Compared to that of

the MMN, the center of gravity of the tone-alone response is, of course, pulled toward the posterior nonspecific areas (which respond more strongly to the tone-alone stimulus than to the deviant). This prediction is directly verified by the results of Korzyukov et al. (1999), despite the memory-based interpretation offered by these authors. Also, based on the results of Sams et al. (1991), showing that the ECD for the N1 elicited by the standards and deviants is posterior to that fitted to the MMN elicited by frequency, intensity, and duration deviants, the adaptation model predicts that tuning to intensity and duration can be found predominantly in anterior areas of auditory cortex.

In sum, localization differences between the N1 and MMN based on ECD modeling have been overinterpreted in favor of the memory-based explanation of the MMN: They do not, in fact, provide positive evidence that N1 and MMN are generated by different auditory areas. In contrast to the memory-based
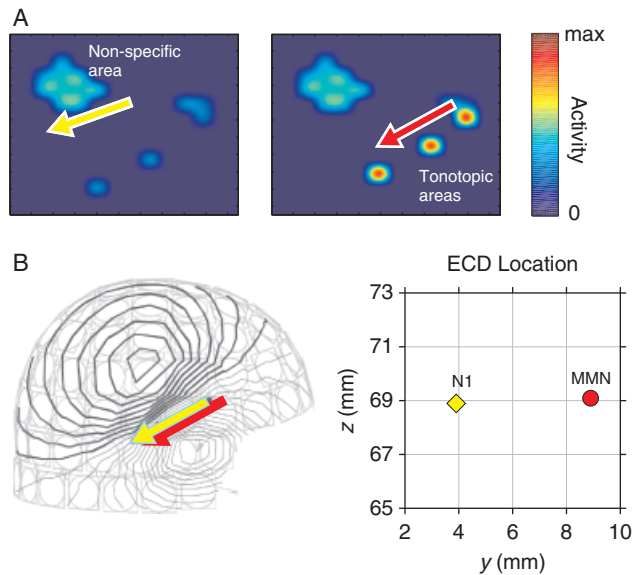
Figure 6. The origin of the differences in ECD location between the N1 and MMN as explained by the adaptation model. A: The schematic illustration shows the activation of four auditory areas, one which is frequency nonspecific and three that are tonotopically organized. When the standard stimulus is repeated (left), all the areas generate an attenuated response and the "center of gravity" of the activation described by an ECD fit is located between the nonspecific and tonotopic areas (yellow arrow). In contrast, the frequency deviant leads to much stronger activation of the tonotopic areas (right) toward which the center of gravity shifts (red arrow). B: Computational results demonstrate how the ECD for the MMN becomes anteriorly shifted. In forward modeling, current dipoles were used to describe the activity of an anteriorly located, tonotopically organized area and a posterior nonspecific area (displacement = 1 cm). Due to adaptation, the standard stimulus was assumed to activate weakly both areas (5 nAm). However, because of the differences in tuning sharpness, the deviant was assumed to activate strongly the tonotopic area (30 nAm) and weakly the nonspecific area (5 nAm). The forward problems for the standard and deviant responses were solved in a spherical head model, and unconstrained ECDs were fit to the "N1" response to the standard (yellow arrow) and the "MMN" derived through subtracting the N1 from the response to the deviant (red arrow). The resulting ECDs for the N1 and MMN had a 5-mm displacement along the anterior–posterior (y) axis. This result demonstrates that differences between the ECD locations of the N1 and MMN do not imply the existence of a separate generator exclusive to the MMN, but, rather, can arise when the MMN is due to activity of the N1 generators. Adapted from May and Tiitinen (2004b).

interpretation, the adaptation model takes into account the distributed nature of cortical activation and, in so doing, offers a plausible explanation of MEG localization results relating to the source locations of the N1 and MMN.

6.3. Variations on the N1/MMN Generator Loci Theme
The argument for the memory-based interpretation of the MMN based on generator locations was expanded on by Näätänen et al. (2005), who noted several differences between the N1 and MMN in terms of generator loci and scalp distributions. First, the N1 and MMN have different interhemispheric distributions: The N1 is always larger in the hemisphere contralateral to the stimulated ear (Näätänen & Picton, 1987) whereas the MMN is predominantly right-hemispheric irrespective of the ear of presentation when pure tones are used (Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991) and left-hemispheric when binaural vowel

stimulation is used (e.g., Näätänen et al., 1997; Shestakova et al., 2002). Second, different types of deviants (e.g., along the frequency, duration, or intensity axes; simple vs. complex stimulation) lead to different scalp distributions of electric potential and magnetic field (Alho et al., 1996; Giard et al., 1995; Levänen, Ahonen, Hari, McEvoy, & Sams, 1996; Rosburg, 2003). Third, the MMN has a frontal generator (for a review, see Alho, 1995), unlike the N1 generated in anterior auditory cortex (Jääskeläinen et al. 2004). Fourth, the dipole locations of the N1 shifts along a trajectory different from that taken by the ECD fitted to the MMN (Rosburg, Haueisen, & Kreitschmann-Andemahr, 2004). Thus, according to the memory-based interpretation of MMN, as the N1 can be distinguished from the MMN in terms of its dipole location and scalp distribution, the N1 and MMN responses cannot be generated by the same neural generators.

Although consistent with the memory-based model of MMN generation, the above results do not provide evidence against the adaptation model proposed by May and colleagues (May, 1999; May & Tiitinen, 2001, 2004b; May et al., 1999). This follows from the fact that the adaptation model, although suggesting that the MMN is due to a delayed and amplitude-modulated N1, does *not* predict that the response to the deviant has the same scalp distribution as the response to the standard (see Section 4). As auditory cortex comprises a variety of cells, some of which are sharply tuned to the feature separating the standard from the deviant whereas others exhibit broader tuning to this feature (see Section 5.2), it is to be *expected* that the response to the standard has a different scalp distribution than the response to the deviant. That is, a deviant will activate a population of broadly tuned cells in much the same way as the standard, whereas an area with sharply tuned cells will produce a stronger response to the deviant than to the standard. Therefore, when considering all of auditory cortex, the standard elicits a constellation of activity that differs from that elicited by the deviant. When this distinction is kept in mind, one can arrive at rather interesting interpretations of the above observations referred to by Näätänen et al. (2005).

First, in the framework of the adaptation model, the right-hemispheric predominance of the MMN (Paavilainen et al., 1991) implies sharper tuning to frequency, duration, and intensity in the right hemisphere than in the left. Indeed, this is consistent with intracortical results in humans demonstrating that cells of the auditory cortex of the right hemisphere are more sharply tuned to frequency than those in the left hemisphere (Liégeois-Chauvel, Giraud, Badier, Marquis, & Chauvel, 2001). Conversely, the larger left-hemispheric MMN to vowel stimulation (e.g., Näätänen et al., 1997; Shestakova et al., 2002) could be explained by cells in the auditory cortex of the left hemisphere being more selective to vowel identity than auditory cells in the right hemisphere. Second, in view of the studies showing variations in the scalp distribution and ECD location of the MMN according to the deviant type (Alho et al., 1996; Giard et al., 1995; Levänen et al., 1996; Rosburg et al., 2004), it seems probable that the areas of auditory cortex exhibit differential tuning to frequency, duration, and intensity as well as to simple and complex sound structure. This is not surprising, given, for example, that cells tuned to complex sounds are found in the lateral belt areas whereas responsiveness to pure tones is predominantly a feature of core areas (Kaas & Hackett, 2000; Rauschecker, 1998; Rauschecker & Tian, 2004; Rauschecker et al., 1995). Third, the existence of a frontal MMN generator can hardly be seen as evidence against the adaptation model for MMN generation, given that the N1 also has generators in frontal cortex (for a

review, see Näätänen & Picton, 1987). Fourth, just as differences in ECD locations between the standard and deviant response may arise out of differences in tuning widths between auditory areas (see Section 6.2), the spatial route taken by these ECDs during the respective responses will also differ.

Thus, observations on the dependence of ECD location and scalp distribution do not serve as evidence for the memory-based model: Due to variations in stimulus selectivity of cortical cells, the spatial distribution of the responses elicited by the standard and deviant will differ without implying the existence of a
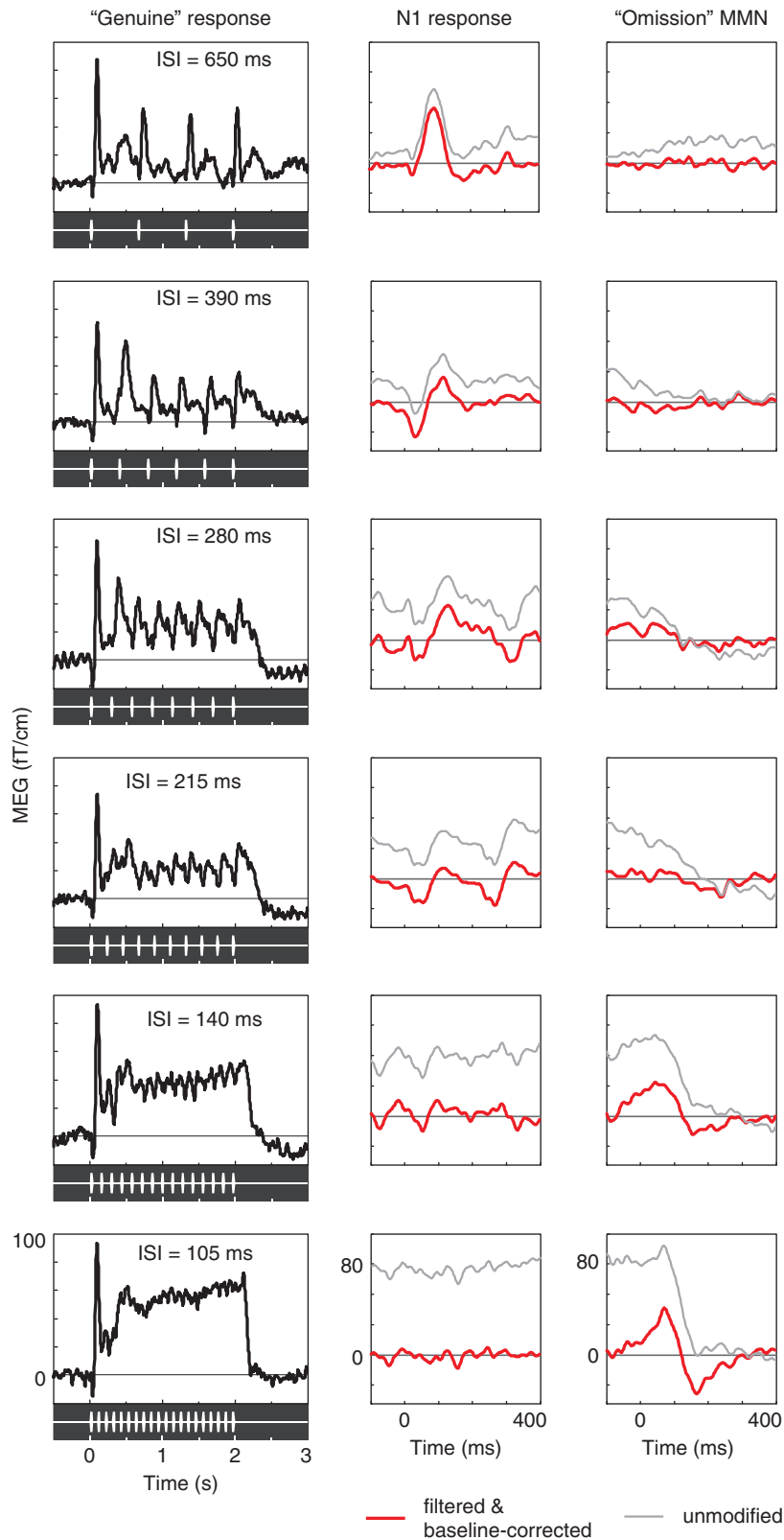
separate MMN generator. Again, the adaptation framework does not dispute the observations upon which Näätänen et al. (2005) base their defense of the memory-based interpretation. Rather, it offers alternatives for interpreting these results in terms of the mapping of auditory stimulus features in cortex. Instead of being rejected outright, these interpretations based on the adaptation model could be treated as clear-cut predictions to be tested in future experimental work.

6.4. MMN Is Elicited by Stimulus Omissions

When the deviant event is an occasional doubling of the ISI (i.e., an omission of the standard stimulus) in a sequence of identical stimuli presented at a constant ISI, the result is a transient enhancement of the ERP/ERF that is labeled as omission MMN (Fisher et al., 2006; Rüsseler, Altenmüller, Nager, Kohlmetz, & Münte, 2001; Yabe et al., 1997, 1998, 2001, 2005; see also Oceák, Winkler, Sussman, & Alho, 2006; Shinozaki et al., 2003; Tervaniemi, Saarinen, Paavilainen, Danilova, & Näätänen, 1994). Näätänen et al. (2005) stated that the omission MMN is compelling evidence for the memory-based MMN. According to this argument, the stimulus omission is an auditory event that cannot activate the afferent neurons generating the N1, and, consequently, the omission MMN must result from the activity of some other neural population: "The MMN elicitation by stimulus omission, . . . in itself, provides strong evidence for the memory trace hypothesis because, obviously, no afferent neurones could be activated by the physically absent stimulus" (Yabe et al., 1997, p. 1974).

However, the above point of view seems to be based on the intuitive assumption that the cortical areas receiving afferent input constitute a rigid stimulus–response machine rather than belong to a system that displays dynamic, possibly even counterintuitive behavior (see Section 4). Indeed, the mechanism by which an omission response can emerge through the activity of cells producing the N1 was demonstrated by the temporal filter model of May and Tiitinen (2001) described in Figure 4: The tuning to stimulation rate emerging from the interaction of excitation and inhibition in cortex also produces multiple omission (rebound) responses. Although one is free to label these responses as "omission MMNs," this does not serve as conclusive proof of a genuine memory-based MMN. The relatively uncomplicated oscillation mechanism of these omission responses would seem to indicate that they should emerge in other parts of the nervous system also. Indeed, similar stimulus omission responses can be found in, for example, the nervous system of the ray (Bullock, Hofmann, Nahm, New, & Prechtl, 1990; Bullock, Karamursel, & Hoffmann, 1993) and turtle (Prechtl & Bullock, 1994), that is, in phylogenetically far simpler systems than the

auditory cortex. Clearly, an explanation of the emergence of the omission MMN does not require the postulation of a "higher order" cognitive cortical system.

There is an interesting variety of omission responses found in humans. Tervaniemi, Saarinen, et al. (1994) measured MMNs to omissions of the second tone of a repetitively presented tone pair when the intertone interval was very short (40 and 140 ms). This result could be a reflection of a temporal integration mechanism that has been suggested to underlie the functioning of duration-sensitive neurons in auditory cortex (He, 1998; He et al., 1997) and may therefore suggest that the length of stimulus sequence is one of the many aspects to which cells in auditory cortex are selective. Further, May and Tiitinen (2001) were able to measure omission MMNs in sequences of repetitive tones with ISIs ranging from 103 to 650 ms, and Halgren et al. (1995) found omission responses with an ISI of 800 ms. In contrast, Yabe et al. (1997, 1998), interpreting their results in terms of a 200-ms "temporal window of integration," were able to observe omission MMNs only with ISIs smaller than 150 ms, at which the N1 responses to the stimuli were hardly discernible. To shed further light on this topic, we reanalyzed the MEG data from a previous study of ours (May & Tiitinen, 2004a). Figure 7 shows the activity elicited by sequences of 50-ms tones, that is, transient stimuli, presented at ISIs of 50–1950 ms during a 2-s window that was followed by a 10-s intersequence silent period. Brain activity was recorded with whole-head MEG with a low-pass filter of 30 Hz, allowing the monitoring of both transient and sustained activity. For ISIs above 300 ms, the stimuli elicited N1 responses that were attenuated for the second and subsequent stimuli in the sequence. At very short ISIs, below 300 ms, the N1 activity elicited by the transient tones appeared to overlap, with the result being a sustained response (SR). The magnitude of this SR was proportional to ISI, reaching maximum for transient stimuli presented at 100- and 50-ms ISIs. The elicitation of an SR with short, 50-ms stimuli is interesting in itself and has consequences for understanding the generation of the omission MMN.

First, the responsiveness of auditory cortex is not abolished by short ISIs (contrary to the general assumption arising from the "disappearance" of the N1 response with short ISIs), but, rather, the activity elicited by previous stimuli is maintained during the short ISI in the form of sustained activity. This, obviously, extends the range of stimulation that can elicit the SR. Previous studies have indicated that an SR can only be observed when long-duration continuous stimuli (of several hundred milliseconds) exceeding the duration of the N1-P2 onset responses are used (Picton, Woods, & Proulx, 1978a; Scherg, Vajsar, & Picton, 1989). The data presented in Figure 7 demonstrate, in essence, that the amplitude-diminished N1 measured at very

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Figure 7. The MMN to stimulus omission revisited. In the left column, MEG responses grand-averaged over 10 subjects to 2-s sequences of 50-ms tones are shown from the gradiometer exhibiting the largest N1 response. The number of tones presented in the 2-s window was increased from 2 to 20, with a corresponding decrease of the ISI from 650 ms to 105 ms (black panels). With long ISIs, the tones elicited transient N1 responses; at ISIs <280 ms, the tone sequences elicited a sustained response (SR) that increased in amplitude as ISI was decreased. At the shortest ISIs (105 and 140 ms), individual N1s are hardly discernible, and the response resembles closely the "classical" SR. The middle column shows the N1 responses measured for tones occurring midsequence (i.e., first stimulus with an onset >1 s). The responses from each channel were 1–30-Hz passband filtered (zero-phase fourth-order Butterworth, 24 dB/octave roll-off, 48 dB attenuation in stop band) and corrected using a 100-ms prestimulus baseline (red curve), which eliminates the SR (i.e., the unmodified response; gray curve) from observation. Thus, the MEG response appears steadily to decrease from a prominent N1 response to near-zero level as ISI is decreased from 650 to 105 ms. In the right column, the response to the first tone "omission" following the ending of the sequence is shown (e.g., in the 650-ms condition $t = 0$ at the onset of the fifth, "missing" tone). Measurements were made with respect to a 100-ms preomission baseline, and the responses were 1–30 Hz passband filtered (red curve). Omission MMNs were now obtained in the conditions using the shortest ISIs (<200 ms). Crucially, these omission MMNs are largely due to filtering transforming the ending of the sustained response and the rapid return to baseline (gray curve) into a transient response following stimulus omission. Data from May and Tiitinen (2004a).

short ISIs against a baseline ending at stimulus presentation drastically underestimates the strength of cortical activation. That is, at rapid stimulus presentation rates, even though no transient (N1-like) activation may be observable (e.g., for the standard stimuli preceding stimulus omission), the auditory cortex is driven to a state of high-level, continuous activation of a magnitude comparable to that of the peak amplitude of the N1 elicited by stimuli presented with long ISIs. Second, with very short ISIs, the ending of the stimulus series, that is, omitting the stimuli the auditory system has grown "accustomed" to, results in a sudden decrease in the sustained activity that may even be accompanied by a response that closely resembles the offset response typically following the ending of a long-duration stimulus (Picton et al. 1978a, 1978b; Scherg et al., 1989). Crucially, when this decrease is passed through a high-pass filter, the end result can be a transient response with the same polarity as the N1 and which closely resembles the omission MMN reported in studies using the oddball paradigm. The severity of this filtering artifact depends, of course, on the filter settings. Figure 7 shows the effect of using a 1-Hz high-pass limit (as utilized in Fisher et al., 2006; Yabe et al., 1998, 2001, 2005). Also affecting the size of the artifact is the rapidity with which brain activity, presumably, regains the sustained level as the stimulation recommences after the omission.

In sum, the oscillatory properties of cortical cell populations provide a natural explanation to the omission MMN that is consistent with the adaptation model, as explained in Section 4. In addition, with the emergence of a sustained response at very fast stimulation rates, the omission MMN may be equivalent to the offset response, that is, the N1-like response to the ending of stimulation. A further contributor to the omission MMN is high-pass filtering that transforms the sudden, omission-related drop in the sustained response into an N1-like deflection. Based on the observations presented above, the omission MMN indexing an assumed "temporal window of integration" is, putatively, not due to a transient *increase* in the ERP/ERF caused by an occasional stimulus omission in a series of tones that themselves elicit minute-amplitude N1s; rather, it may arise out of high-pass filtering applied to the sudden *decrease* in sustained brain activity when a series of stimuli presented at ISIs below 300 ms is interrupted. This ISI limit could, in a sense, be claimed to represent the width of the "temporal window of integration" as revealed by the N1 response.

6.5. MMN Is Elicited by "Abstract" Changes

MMN can be measured for deviants when the repetitiveness of auditory stimulation is defined through some spectrotemporally "abstract" rule, for example, in cases where tones steadily ascend or descend in frequency (Tervaniemi, Maury, & Näätänen, 1994), the frequency ratio between the two tones of a tone pair is constant (Korzyukov, Winkler, Gumenyuk, & Alho, 2003; Paavilainen, Saarinen, Tervaniemi, & Näätänen, 1995; Saarinen, Paavilainen, Schöger, Tervaniemi, & Näätänen, 1992), or the intensity of a tone depends monotonically on its frequency (Paavilainen, Simola, Jaramillo, Näätänen, & Winkler, 2001). MMN responses to violations of these rules have been taken as evidence for "primitive intelligence" mechanisms (Näätänen, 1995; Näätänen et al., 2001) that cannot be accounted for by N1 adaptation because the "standard" environment is not constituted by the repetition of one spectral feature and, therefore, feature-specific adaptation cannot occur (Näätänen et al., 2005).

This argument works, of course, if one assumes that auditory cells are selective to spectral features only, that is, that the only

kinds of feature maps in auditory cortex are the tonotopic and amplitopic ones. However, as reviewed above (Section 5.2), cells in auditory cortex are differentially selective to a multitude of auditory features, both spectral and temporal, and the transformation of the continually evolving soundscape into spatial representations is a likely candidate for the general principle of the functioning of auditory cortex (Shamma, 2001). The "abstract" rules in the above MMN experiments could well be expressed in the large variety of response properties found even in the cells of primary auditory cortex.

Ascending and descending tone pairs being a form of frequency modulation, the MMN to frequency direction violations (Korzyukov et al., 2003; Paavilainen et al., 1995; Saarinen et al., 1992; Tervaniemi, Maury, et al., 1994) could be accounted for by the adaptation of cells of auditory cortex tuned to the direction of modulation of FM sounds (Godey, Atencio, Bonham, Schreiner, & Cheung, 2005; Heil et al., 1992a, 1992b; Kowalski, Versnel, & Shamma, 1995; Mendelson & Cynader, 1985; Mendelson & Grasse, 1992; Mendelson et al., 1993; Phillips, Mendelson, Cynader, & Douglas, 1985; Shamma et al., 1993; Tian & Rauschecker, 1994, 1998, 2004; Whitfield & Evans, 1965). Specifically, Suga (1965a, 1965b) suggested that FM direction selectivity arises out of frequency-tuned cells having asymmetric inhibitory sidebands. This mechanism enjoys extensive experimental support (Gordon & O'Neill, 1998; Heil et al., 1992a, 1992b; Razak & Fuzessery, 2006; Shamma et al., 1993; Suga, 1965a, 1965b; Zhang, Tan, Schreiner, & Merzenich, 2003) and could readily explain frequency-direction MMN in the context of the adaptation model. For example, when ascending and descending tone pairs are designated as the standard and deviant stimuli, respectively, and where the frequency levels of these randomly vary (Korzyukov et al., 2003; Paavilainen et al., 1995; Saarinen et al., 1992), frequency-tuned cells that are asymmetrically inhibited by lower frequencies only will fail to respond to the second tone in the standard tone pair. In contrast, they will remain responsive to the second, descending tone in the deviant pair. Meanwhile, cells inhibited exclusively by higher frequencies will fail to respond to the second tone in the deviant pair but, due to the adaptation brought about by the frequent presentation of the standards, will also respond in an attenuated way to the second tone in the standard pair. Therefore, on average, the spatially summed responses to the deviants (i.e., the responses obtained in EEG/MEG recordings) will be enhanced compared to those elicited by the standard tone pairs. Consequently, the auditory cortex reacts to the "abstract" feature of the second tone being either of a higher or lower frequency than the first. This setup would also explain why infrequent stimulus repetitions in a sequence of tones steadily descending in frequency elicit an MMN (Tervaniemi, Maury, et al., 1994): Again, cells inhibited only by lower frequencies will become adapted, but cells asymmetrically inhibited by higher frequencies will produce responses of variable strength depending on the degree to which the previous response was, in its turn, inhibited. In this framework, stimulus repetition equates with a doubling of the period in which the lateral inhibition from the higher frequencies decays, which allows for enhanced responses on average. The emergence of the MMN is yet again explained by an adaptation-based setup: Adaptation and lateral inhibition contribute to the differential responses to the standard and deviant, and cells that generate the N1 also produce the MMN.

Finally, wielding Occam's razor once more, the "primitive intelligence" MMN to violations in frequency-intensity rules

(Paavilainen et al., 2001) can be accounted for already by the intensity selectivity of cells in auditory cortex. Intracortical measurements have demonstrated the presence of cells tuned to intensity in the auditory cortex of cat (Phillips & Irvine, 1981; Schreiner et al., 1992; Sutter & Schreiner, 1995) and monkey (Brugge & Merzenich, 1973; Pfingst & O'Connor, 1981). Of particular interest in the context of the results of Paavilainen et al. (2001) are two studies focusing on intensity representation in cat A1. Heil et al. (1994) found that several neuronal properties related to intensity coding are represented topographically along the isofrequency axis of A1. Especially for medium and high intensities (>30 db SPL), the spatial pattern of the activated cells on the isofrequency strip changes according to stimulus intensity whereas the average activity remains unchanged. Further, Phillips et al. (1994) used tonal stimulation with a wide range of intensity–frequency combinations and constructed spatial maps of the areas activated by each tone. These authors found that each frequency–intensity combination resulted in a unique spatial pattern of activation. The above results allow for a parsimonious explanation

of "primitive intelligence" in terms of the adaptation model. In this instance, the frequency-intensity "standard" combinations activate particular spatial distributions of cortical cells that, due to the frequent stimulus presentation, become adapted. The infrequent deviant frequency–intensity combinations activate cells that are, on average, less suppressed and therefore produce larger responses. The abstract "rule" that is being broken by the deviants needs no complicated higher-order cognitive analysis but, rather, is expressed as the combined spatial distribution of cells responsive to the tones that happen to be designated as the standards by the experimenter. Indeed, a prediction of the adaptation model is that *any* arbitrary or random rule for combining stimulus features (e.g., any division of the set of frequency–intensity combinations used by Paavilainen et al., 2001) will produce MMN-like responses when broken, so long as the stimulus feature combinations are spatially represented. This principle is demonstrated in simulations in Figure 8: random rules were applied to the auditory cortex model, and in each case the stimuli breaking the rule elicited more prominent responses than those adhering to the rule.
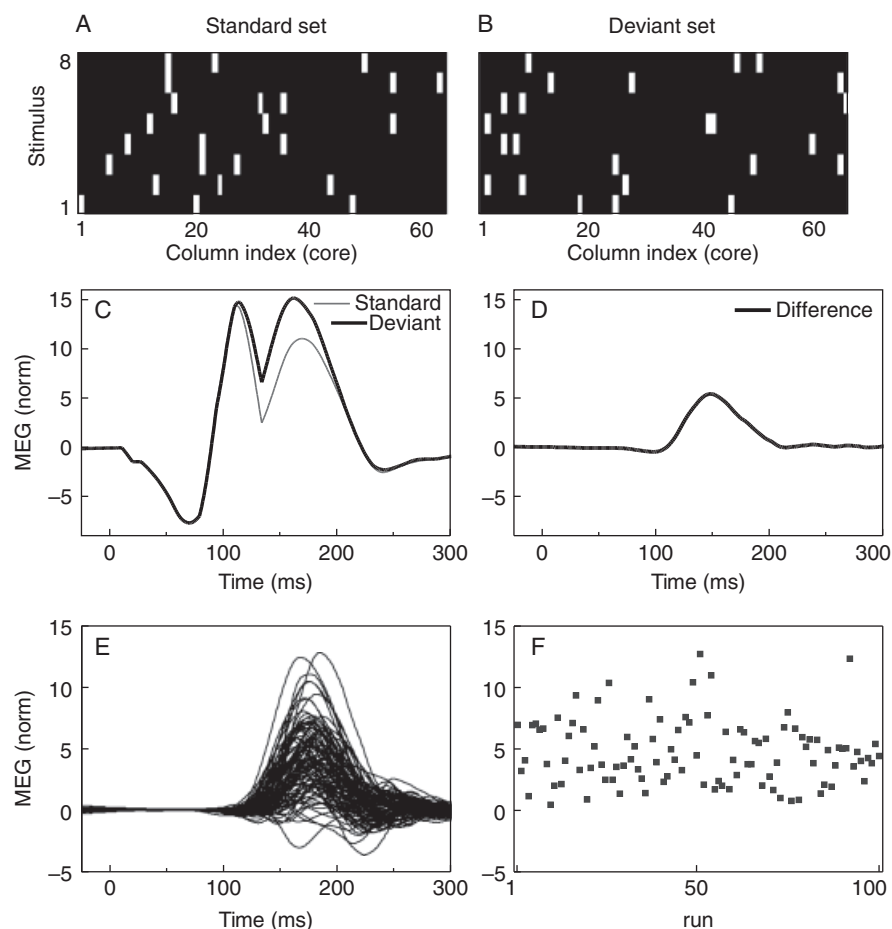

Figure 8. Simulations showing how the adaptation model is able to account for MMN to changes in any random "rule" in afferent stimulation. In each simulation run, the standards ($p = .875$) were equiprobably taken from a set of eight random stimuli, each activating a unique distribution of columns ($N = 3$) in the core area. Similarly, the deviants ($p = .125$) adhered to the rule of belonging to a second set of eight random stimuli. A: An example from one simulation run, showing a set of eight standard stimuli. The white rectangles indicate the columns activated by each stimulus. B: The set of deviant stimuli from the same stimulation run. C: Compared to the averaged response to the standards, the deviants elicited a response that was enhanced in the 100–200-ms latency range. D: The deviantstandard difference curve revealed an "abstract rule" MMN peaking at around 150 ms. E: The difference curves from 100 simulation runs are shown, each with unique standard and deviant sets. In all cases, an "abstract rule" MMN was elicited. F: The peak amplitudes of the MMNs from the different simulation runs again demonstrate that the MMN is robustly elicited by changes in any random "rule." *Stimulus material:* Stimuli were transient 100-ms tones (10-ms linear onset/offset slopes) presented at an 400-ms ISI. In each simulation run, 50 deviants and 350 standards were presented.

In sum, it is quite conceivable that adaptation, coupled with the sensitivity of certain cortical cells to FM stimulation and intensity, endows auditory cortex with "primitive intelligence" and that MMN to abstract changes can be explained in terms of the adaptation model without invoking higher-order cognitive ghosts in the machine.

6.6. Control Measurements for Refractoriness Reveal a Genuine MMN

Schröger and Wolff (1996) and Schröger (1997) advocated a paradigm for separating memory-related processing from the effects due to adaptation (refractoriness) of fresh-afferent activity (see also Näätänen & Alho, 1997). In this paradigm, the stimulus used as the deviant in the oddball paradigm is presented in a control block as one among many equiprobable stimuli differing from each other along the feature axis separating the standard and the deviant. When the separation between the deviant stimulus and the other equiprobable stimuli is, on average, larger than the separation between the standard and the deviant, the refractory state of the afferent neurons responding to the deviant can be no larger in the control than in the oddball block. Therefore, when comparisons are made between the responses to the stimulus in the two conditions, a larger response measured in the control condition would be in line with the adaptation hypothesis of MMN generation, but, importantly, a larger response in the oddball condition would indicate the presence of a "genuine" memory-based MMN response. Based on such reasoning, this method has yielded evidence that a genuine MMN response is elicited by changes in tone frequency (Campbell et al., 2007; Horváth et al., 2008; Jacobsen & Schröger, 2001; Jacobsen, Schröger, et al., 2003; Maess et al., 2007), intensity (Jacobsen, Horenkamp, et al., 2003), duration (Jacobsen & Schröger, 2003), complex tone structure (Jacobsen, Schröger, & Sussman, 2004), and vowel identity (Jacobsen, Schröger, & Alter, 2004).

Although not stated explicitly by the above authors, this method, unfortunately, rests on the assumption that the response latencies of the cortical cells producing the "afferent" N1 response are fixed, unaffected by whether stimuli are presented in the oddball or control condition. This assumption is refuted by the same considerations as those concerning the latency differences between the N1 and MMN (see Section 6.1). Essentially, lateral inhibition of the cells mapping the deviant is arguably stronger in the oddball than control condition. This is because in the oddball condition most of the stimuli (i.e., the standards) are mapped to a location close to that representing the deviant, whereas in the control condition most of the stimuli (i.e., the equiprobable stimuli) activate locations further away. Lateral inhibition having a delaying effect on cortical activation (see Section 6.1), one might expect responses originating from the different stages of the core–belt–parabelt stream to be "strung out" in time in the oddball condition and to be more "bunched up" in the control condition. This effect is demonstrated in simulations of the adaptation model shown in Figure 9. As a result of the delaying effect of lateral inhibition, the responses in the 100-ms range are larger in the control condition, and subsequent responses (in the MMN latency range) are larger in the oddball condition. Therefore, subtracting the control from the oddball response leaves much of the oddball response intact in the MMN latency range. Indeed, this pattern of increased activity in the N1 and MMN latency ranges in the control and oddball conditions, respectively, is evident in the results of the experiments designed to reveal a "genuine" MMN response (Jacobsen, Horenkamp,

et al., 2003; Jacobsen & Schröger, 2001, 2003; Jacobsen, Schröger, et al., 2003; Schröger & Wolff, 1996). Thus, the evidence from these experiments supposedly supporting a genuine memory-based MMN is, in fact, perfectly in line with the adaptation model.

Further, an implicit assumption underlying the genuine-MMN hypothesis is that the receptive fields of the cortical cells generating the N1 are unaffected by the experimental condition (see also Section 6.8). However, this assumption is contradicted by evidence from animal models and cortical cell cultures pointing to the presence of stimulation-induced synaptic plasticity in sensory processing. In auditory cortex, rapid receptive field changes can be achieved through pure-tone stimulation (Calford, 2002; Calford, Rajan, & Irvine, 1993), simultaneous acoustic input and intracortical stimulation (Cruikshank & Weinberger, 1996; see also Maldonado & Gerstein, 1996) and conditioned learning (for a review, see Weinberger, 1993; see Section 7.3). Thus, a fundamental feature of auditory cortex is its dynamic nature and rapid modifiability, and it is therefore likely that the receptive fields of auditory cells during the oddball condition differ from those during the control condition proposed by Schröger and Wolff (1996). For example, the repeated presentation of the standard stimulus could lead to Hebbian strengthening (as indicated by the results of Cruikshank & Weinberger, 1996; Maldonado & Gerstein, 1996) of connections between the cells in the projective field of the standard. This could lead to an enhanced response to the deviant in the oddball as opposed to the control condition if the two stimuli have overlapping projective fields.

Stimulation-dependent plasticity during oddball stimulation was demonstrated in the study of Eytan, Brenner, and Marom (2003), who performed recordings in a network of cortical neurons cultured ex vivo and stimulated frequently at one site and infrequently at another. Most of the neurons responded to the initial stimulation (regardless of stimulated site), but after 15 min of continued oddball stimulation, neurons exhibited attenuated responses to the frequent stimulus and, interestingly, amplified responses to the rare stimulation. This two-way adaptation was found to be due to activity-dependent synaptic depression in (a) the excitatory pathways specifically activated by each stimulus type and (b) a highly connected inhibitory network providing a common inhibitory resource to the excitatory pathways. Therefore the authors concluded that "because most of the synapses comprising the excitatory pathway from the rarely stimulated site are not depressed whereas the overall inhibitory resources are, the response to the rare stimulation source [i.e., the deviant] is increased on average" (pp. 9354–9355).[3] The cortex contains electrically coupled networks of interneurons that strongly synchronize inhibition within a span of around 100 μm (Beierlein, Gibson, & Connors, 2000) and that, as pointed out by Eytan et al. (2003), are similar to the inhibitory network in the cultured cell population. In the auditory cortex, the conditions present in

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[3]This explanation should not be confused with the proposal by Näätänen (1984) that repetitions of the standard leads to a release from tonic inhibition of cells tuned to the deviant in the MMN generator, thereby allowing the elicitation of the MMN: In the study of Eytan et al. (2003), the cultured network of cortical cells was not under tonic inhibition before the presentation of the standards and, thus, contrary to the Näätänen model, responded to the deviant when this was presented alone. Further, the suppression of inhibition in the cortical-cell network took several minutes of continued oddball stimulation to develop, whereas the Näätänen model requires that it develop rapidly, presumably after just two presentations of the standard.

the cultured network might therefore be reproduced if the standard and deviant have overlapping projective fields (i.e., when they are close to each other in terms of their physical features). This would imply that when oddball stimulation is applied for several minutes—as is the case in MMN measurements—the "fresh-afferent" neurons responding to the deviant increase their responsiveness. Thus, the above results on plasticity being taken together, it is entirely feasible, even in the framework of the adaptation model, that a deviant stimulus elicits a larger response in the oddball condition than in the control condition proposed by Schröger and Wolff (1996). Even in cases where the larger oddball and smaller control responses overlap in the N1 range (Campbell et al., 2007; Horváth et al., 2008; Jacobsen, Schröger, & Alter, 2004; Jacobsen, Schröger, & Sussman, 2004)—when the difference wave between the two cannot solely be explained in
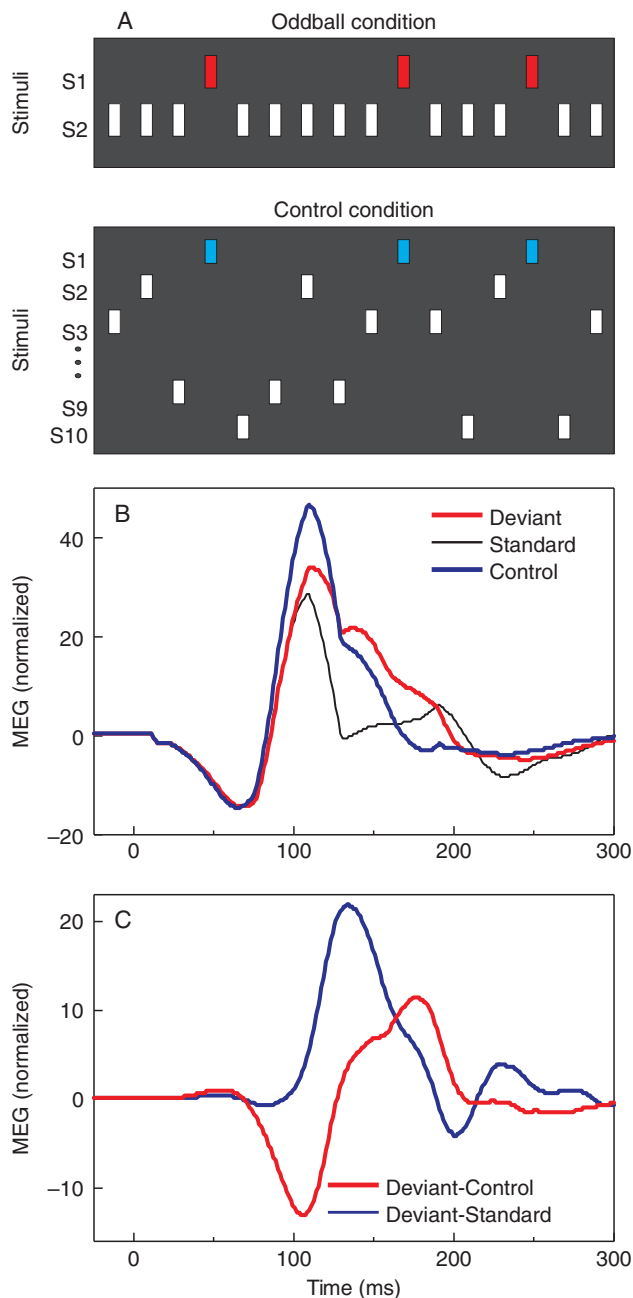
terms of latency delays discussed above—there are no grounds for ruling out the adaptation model.

In sum, inherent in the adaptation model are the latency variations of activations in auditory cortex. These variations combined with electrophysiological results on synaptic plasticity offer a more plausible explanation than the memory-based interpretation of MMN for results obtained by using the control condition suggested by Schröger and Wolff (1996).

6.7. MMN Is Not Elicited by Any Stimulus Per Se

According to the memory-based interpretation, the N1 and MMN cannot be generated by the same neural populations because no MMN is elicited when the ISI is long enough and because MMN is not elicited by the first stimulus of a series—that is, MMN is not elicited by any stimulus per se (Mäntysalo & Näätänen, 1987; Näätänen & Alho, 1995; Näätänen, Paavilainen, Alho, et al., 1989; Sams, Hämäläinen, et al., 1985). Increasing the ISI leads to the N1 elicited by the standard to become more prominent while the difference wave between the response to the standard and that to the deviant diminishes until disappearing for ISIs in the range of 5–10 s (Böttcher-Gandor & Ullsperger, 1992; Mäntysalo & Näätänen, 1987). With regard to the lack of MMN for the first stimulus in a tone sequence, Cowan et al. (1993) presented subjects with sequences of nine stimuli, eight standards and one deviant, with an intersequence interval of 11–15 s. The frequency deviant was presented in serial position 1, 2, 4, or 6, and the MMN was determined by subtracting the responses across serial position. Crucially, the response to the deviant presented in position 1 did not differ significantly from that to the first standard, and therefore the authors concluded that no MMN was elicited by the first stimulus following a long silence. In sum, MMN and N1 behave in diametrically opposed

Figure 9. Simulations demonstrating that the adaptation model accounts for the results apparently showing a "genuine" memory-based MMN. A: In the oddball stimulation condition, the deviant (stimulus S1, red) is a rare stimulus among the repetitive standards (S2, white). In the control condition, the standard stimuli have been replaced by multiple stimuli (S2 ... S10), and the deviant (S1, blue) becomes one among several equiprobable stimuli and is considered to be the control stimulus with which the contribution of fresh-afferent activity can be controlled for (see text for details). B: In simulations of the adaptation model, the deviant (red curve) elicits a larger response than the standard (black curve) in the 100–200-ms range. Importantly, compared to the response to the deviant in the oddball condition, the control stimulus (blue curve) elicits a response that is enhanced around 100 ms and diminished in the 120–200-ms range. C: The subtraction curves resemble those generally shown in studies attempting to demonstrate a "genuine" MMN. The deviant-control subtraction (red curve) has a negative deflection in the N1 latency range and a positive one in the MMN latency range. This latter positivity is usually taken as unequivocal proof of a genuine memory-based MMN. However, the current results demonstrate that these findings are more properly accounted for by the adaptation model: In the oddball condition, strong lateral inhibition spreads out the response in time, whereas in the control condition, the weaker lateral inhibition leads to activity being more concentrated around the 100-ms range. *Stimulus material:* Stimuli were transient 100-ms tones (5-ms linear onset/offset slopes) presented at a 500-ms ISI. In the oddball condition, the frequency of the standard ($p = .9$) and deviant ($p = .1$) was 550 and 500 Hz, respectively. In the control condition, the control tone had a frequency of 500 Hz ($p = .1$), and the other nine equiprobable tones had respective frequencies 550, 605, 666, 732, 805, 886, 974, 1072, and 1179 Hz ($p = .1$ each). For both the deviant and control tone, 100 responses were obtained for averaging.

ways: MMN grows and N1 diminishes as ISI is shortened; the first stimulus elicits no MMN but gives rise to the largest ("non-refractory") N1 response in the stimulus series. Consequently, according to the memory-based interpretation, the N1 and MMN must be due to different neural mechanisms.

This rather curious argument can be challenged on a variety of levels. According to the memory-based interpretation, the MMN is a response to a change in repetitive auditory stimulation. That is, as the MMN is the difference between the response to the deviant and those to the preceding standard stimuli, it is ill-defined in the case where the deviant is presented alone, because there are no preceding standards. The technical definition of the MMN in itself precludes the possibility of measuring an MMN to the first stimulus in a sequence—although everyday experience shows that already one stimulus is enough for sensing and perceiving acoustic change in the environment and for forming a memory trace. Further, the argument is circular in that it already *assumes* that the subtraction between the response to the deviant and the standard is a necessary indication that the purported change-detection cells generating a genuine memory-based MMN have responded. This premise is then used in interpreting the experimental result: Large-amplitude N1 responses coupled with a lack of MMN (e.g., with long ISIs and the first stimulus in a series) becomes proof that the N1 cells were activated whereas the MMN cells were not. Consequently, the somewhat bewildering conclusion is reached whereby the MMN and N1 cannot be generated by the same neuronal mechanism because they behave in diametrically opposing ways.

Perhaps the clearest way to counter this argument is to illustrate, by counterexample, that the experimental results can be accounted for by the adaptation model (Figure 10): With long ISIs, the adaptation and lateral inhibition caused by each standard stimulus decays before the following stimulus—standard or deviant—is presented. Therefore, the standard and the deviant elicit interchangeable responses—assuming, of course, that their difference is small enough to avoid stimulus-specific effects on the N1 (see Section 3). Similarly, the first stimulus in a series does not produce an MMN because the neural populations responding to the standard and the deviant are unadapted (i.e., in a nonrefractory state). Therefore, the lack of MMN need not be explained in terms of a change detector specialized in reacting to change in a nonsilent environment but, rather, arises out of the N1-generating "fresh-afferent" neurons responding to the standard and deviant being under the influence of similar levels of adaption.

6.8. The MMN and N1 Do Not Share Their Sensitivity to Experimental Manipulations

As pointed out by Näätänen (1992) and Näätänen et al. (2005), the behavior of the MMN and the N1 to the standard are differentially affected by experimental manipulations. For example, NMDA-receptor antagonists (Javitt et al., 1996; Umbricht et al., 2000) and frontal lesions (Alho, Woods, Algazi, Knight, & Näätänen, 1994) diminish or abolish the MMN while leaving the N1 unaffected; subjects training to perform a difficult discrimination task exhibit an MMN that increases in amplitude as the task is learned while the N1 remains unaffected (Atienza, Cantero, & Dominguez-Marin, 2002; Näätänen, Schröger, Karakas, Tervaniemi, & Paavilainen, 1993); also, subjects with high musical aptitude exhibit larger MMN responses to violations in musical sequences than do nonmusical subjects (Lopez et al., 2003). These results indicate that the N1 behaves differently from
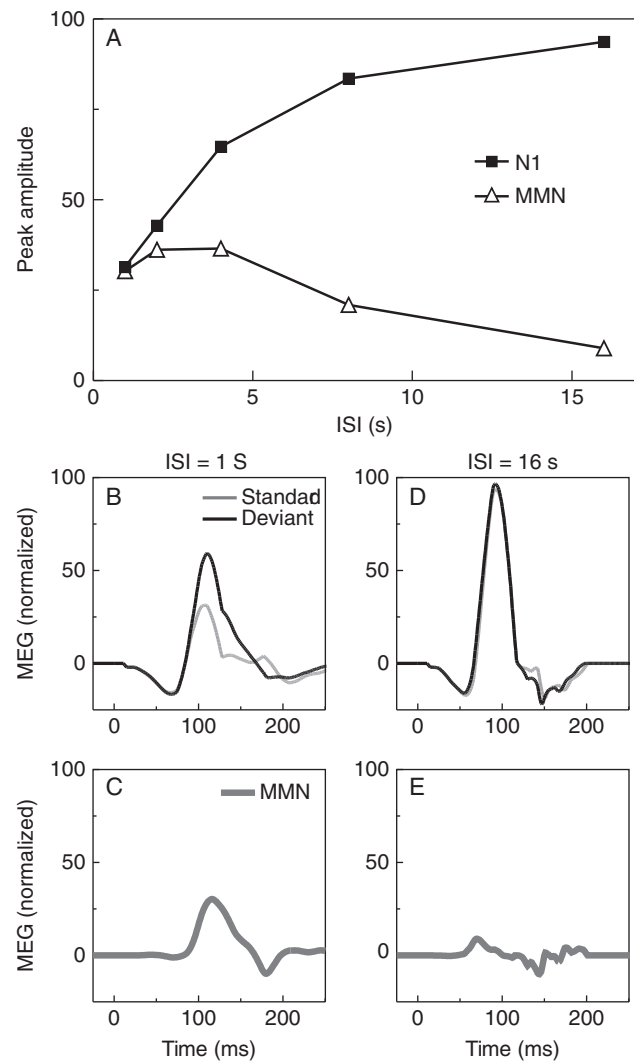

Figure 10. Simulations demonstrating that the adaptation model is able to account for the divergent behavior of the N1 and MMN as ISI is varied. A: At short ISIs (1 and 2 s), the peak amplitude of the MMN is close to that of the N1 obtained for the standard stimulus. As ISI is increased toward 16 s, the N1 grows toward its maximum amplitude of 100 while the MMN decreases toward 0. B,C: The averaged responses to the standard and deviant as well as the MMN subtraction curve are demonstrated in the case of the 1-s ISI. The standard elicits an N1 that has approximately the same amplitude as the MMN. D,E: In the case of the 16-s ISI, the standard elicits a response that has a amplitude similar to that of the response to the deviant. Consequently, the MMN is minute. These results obtained with the adaptation model show that differences between the behavior of the N1 and MMN, as well as the observation that the MMN is not elicited by any stimulus per se, can hardly be used as evidence for a genuine memory-based MMN. *Stimulus material:* Stimuli (100-ms duration; 5-ms linear onset/offset ramps) were presented in separate conditions at ISI of 1, 2, 4, 8, or 16 s. The frequency of the standard ($p = .8$) and deviant ($p = .2$) was 1000 and 1032 Hz, respectively. In each condition, the stimulus block consisted of 500 stimuli. For further details, see Appendix.

the MMN, and it is therefore tempting to conclude that these responses must be generated by separate brain processes.

The above argument fails to take into account the basic principle of the adaptation model: Although the same auditory areas produce both the response to the standard and the deviant, the

set of cells activated by these two types of stimuli, although possibly overlapping, are not identical (essentially due to the spatial representation of sound structure). The main *variables* shaping the activation of these cells are the poststimulus suppressive effects of adaptation and lateral inhibition. These can be assumed to vary both as a function of cortical location and time, and they mediate the effect of previous stimulation, thereby making the responses of cells in auditory cortex sensitive to context. The spatial pattern of poststimulus suppression reflects, at any one time, the past auditory stimulation and is determined by several structural and functional parameters: the width of tuning of individual cells, the spatial extent of lateral inhibition, the strength of local feedback connections, and the rate of decay of inhibitory and adaptation effects (see Sections 5.1 and 5.2). Importantly for the current discussion, a location-specific change to any *one* of these parameters through, for example, experimental manipulation can allow the pattern of poststimulus inhibition to change so that the responses to the standard and the deviant are modified differently from one another.

For example, the experimental results on the effect of NMDA antagonists on the MMN (Javitt et al., 1996; Umbricht et al., 2000) may be explained through adaptation-related changes in the strength of recurrent excitation mediated through NMDA channels (see Section 5.3). A similar phenomenon may underlie the attenuated MMN in frontal lobe patients (Alho, Woods, Algazi, Knight, et al., 1994), with NMDA synapses mediating the effect on auditory cortex activation that is affected by the frontal lesion. Further, the enhancement of the MMN as the subject is engaged in learning to discriminate the deviance in a complex sound (Atienza et al., 2002; Näätänen, Schröger, et al., 1993) could be explained through modifications in the shape of the STRFs of the responding cells. Such changes occurring during perceptual learning are supported by single- and multi-unit measurements in the primary auditory cortex of animal models: When animals learn to perform discrimination tasks, the cells selective to the target stimuli produce stronger responses (e.g., Blake, Strata, Churchland, & Merzenich, 2002) and can increase in number through recruitment on topographic feature maps (e.g., Polley, Steinberg, & Merzenich, 2006; for reviews, see Weinberger, 1993, 2004; see Section 7.3). Thus, as a result of the learning task, the response elicited by the deviant (i.e., the target) becomes stronger, whereas the response to the standard (i.e., the nontarget) remains unchanged. Therefore an enhancement of the MMN is observed whereas the N1 remains unaffected. A similar explanation in terms of neural plasticity associated with perceptual learning may apply to the results of Lopez et al. (2003) showing larger MMN responses in musical than nonmusical subjects.

In sum, viewing the auditory cortex as a dynamical system, experimental manipulation may change one or more parameter values of the system. This change leads to different effects at different locations, for example, at those mapping the standard and deviant stimulus. Because of this changeable nature of auditory cortex, it only makes sense that the N1 and MMN can be made to behave differently through experimental manipulations. Thus, the observations cited by Näätänen et al. (2005) and other similar results, instead of providing evidence that the MMN is to be regarded as an independent component generated separately from the N1, are, in fact, consistent with the adaptation model.

6.9. MMN Is Elicited When No N1 Is Elicited
Näätänen et al. (2005) pointed out that there are conditions other than stimulus omission where the MMN can be elicited in the

absence of the N1. This can occur when ERPs are measured in newborns (e.g., Alho, Sainio, Sajaniemi, Reinikainen, & Näätänen, 1990; Ruusuvirta, Huotilainen, Fellman, & Näätänen, 2003; Winkler et al., 2003) and during REM sleep in adults (Atienza & Cantero, 2001). Therefore, goes the argument, the MMN cannot be a delayed or amplitude-modulated N1 and hence must be generated by some other mechanism than that underlying the N1.

However, an N1 response *can* usually be measured in REM sleep (Armitage, Bell, Campbell, & Stelmack, 1990; Atienza, Cantero, & Gómez, 2001; Campbell, Michaud, Keith, Muller-Gass, & Wiebe, 2005; Loewy, Campbell, & Bastien, 1996; Nordby, Hugdahl, Stickgold, Bronnick, & Hobson, 1996; for a review, see Atienza, Cantero, & Escera, 2001). Indeed, Loewy, Campbell, de Lugt, Elton, and Kok (2000) measured a small N1-P2 complex for standards and deviants during REM sleep, but no identifiable MMN response. In the study of Atienza and Cantero (2001) referred to by Näätänen et al. (2005), the negative-going peak at the N1 latency, although remaining positive throughout, closely resembles the N1 measured in the other conditions in the experiment (e.g., when the subjects were awake). Interestingly, the P1 measured during REM more than doubled its amplitude and may therefore have contributed to this "abolishing" of the N1. Were one to quantify the N1 as the trough-to-peak difference (as was done by, e.g., Atienza, Cantero, & Gómez, 2001), it would clearly be of the same order of magnitude as in awake conditions.

In the neonate cortex, the state of cytoarchitectural and axonal maturity results in the general lack of sharp, large-amplitude auditory event-related responses (Eggermont & Ponton, 2003). Indeed, the response to the standard is characterized by a broad, large-amplitude response (with a positive polarity in EEG) peaking in the 200–300-ms range and, clearly, lacks the well-defined P1-N1-P2 waves found in adults (Kurtzberg, Hilpert, Kreuzer, & Vaughan, 1984; Kushnerenko et al., 2002; Lengle, Chen, & Wakai, 2001; Shibasaki & Miyazaki, 1992). However, by the same token, the MMN measured in neonates is unlike that measured in adults: It is unusually broad, with a duration of several hundred milliseconds, and its peak amplitude is very late, in the range of 200–500 ms (Alho et al., 1990; Cheour, Kushnerenko, Ceponiené, Fellman, & Näätänen, 2002; Cheour-Luhtanen et al., 1995; Cheour, Martynova, et al., 2002; Cheour et al., 1998; Draganova, Eswaran, Murphy, Lowery, & Preissl, 2007; Draganova et al., 2005; Huotilainen et al., 2003; Novitski, Huotilainen, Tervaniemi, Näätänen, & Fellman, 2007) or even 500-600 ms (Tanaka, Okubo, Fuchigami, & Harada, 2001), although on occasion an adult-like MMN can be obtained with a peak latency under 200 ms (Kushnerenko et al., 2001; Martynova, Kirjavainen, & Cheour, 2003); in many cases, the MMN is not even a negativity but, rather, a broad *positive-going* deflection in the EEG (Ceponiené et al., 2002; Cheour, Ceponiené, et al., 2002; Kushnerenko et al., 2007; Novitski et al., 2007; Winkler et al., 2003) with a field pattern in the MEG consistent with a positive EEG response (Sambeth, Huotilainen, Kushnerenko, Fellman, & Pihko, 2006). In some cases (Leppänen et al., 2004; Ruusuvirta et al., 2003), the MMN could best be described as a positive shift, resembling a sustained response, bearing no resemblance to the MMN measured in adults. Thus, it seems that any kind of differential response generated by the newborn brain is accepted as an MMN, regardless of latency, morphology, and even polarity. However, if one chooses to argue that the newborn ERP lacks the N1—because no sharp, negative deflection ap-

pears at around the 100-ms latency—one should, for consistency, also argue that it lacks the MMN, a negative differential wave peaking in the 100–200-ms range.

Interestingly, a number of studies show that an MMN can reliably be measured in children above the age of 7 years in conditions where no N1 response to the standard is evident (e.g., Ceponiené, Cheour, & Näätänen, 1998; Ponton et al., 2000). One may therefore ask whether these results militate against the adaptation model. However, the N1 amplitude is exceptionally rate sensitive in children, becoming indistinguishably small at ISIs that are longer for children than for adults (for a review, see Wunderlich & Cone-Wesson, 2006). Therefore, it makes sense that the response to fast-rate standards in children contains no N1. If the MMN is indeed an expression of the N1, comparisons should be made between the response to the deviant in the oddball condition and the response elicited by the deviant in the deviants-alone control condition (using, of course, an ISI equal to the average deviant-to-deviant interval of the oddball condition). Such a comparison failing to show a negative deflection at a latency preceding or coinciding with the MMN would disagree with the adaptation model. However, the required test has already been performed by Ceponiené et al. (1998), who found a distinct MMN peaking at 220 ms but no N1 to the standard when the ISI was 350 ms. Crucially, in the deviants-alone condition (ISI = 4393 ms), the response to the deviant showed a prominent N1-like response that peaked at 160 ms and that the authors concluded was a correlate of the adult N1. Thus, the response patterns found in children are consistent with the adaptation model. One might note that the deviants-alone condition could be used in this way also to test the adaptation model in the case of MMN elicited during sleep and in newborns.

In summary, the argument put forth by Näätänen et al. (2005) rests on a rather selective approach to the evidence coupled with liberal and stringent sets of criteria for what constitutes the MMN and N1, respectively. This argument also seems to mistake the MMN-N1 relationship proposed by the adaptation model to be a premise of the model, rather than a consequence. That is, if stimulus-specific adaptation explains MMN, it does not follow that the N1 should therefore universally occur (see also Section 6.4). The above results on the N1 and MMN indicate that although sleep stage and developmental stage may affect the pathways of activation and the pattern of peaks and troughs in the event-related response, stimulus-specific adaptation is a feature that continues to operate at different levels of consciousness and that can be found already in the newborn brain.

6.10. Intracortical Measurements in Humans Provide Direct Evidence for the Separability of the N1 and MMN

As discussed in Section 5.3, the MMN can be measured intracortically, but these results usually show that cell populations responding to a tone when used as the deviant also respond to this same tone when it is used as the standard. Therefore, they do not provide direct and conclusive validation for the memory-based interpretation of MMN. In contrast, Kropotov et al. (2000) seem to have found just such validation in intracortical ERP measurements in human neurological patients. Näätänen et al. (2005) emphasized the importance of these results for refuting the adaptation model by stating that they constitute "particularly compelling evidence for the separate generator mechanisms for the N1 and MMN" (p. 6).

Acknowledging that the MMN could be explained as arising either from the frequency or ISI dependence of the N1 (as suggested by the adaptation model), Kropotov et al. (2000) attempted to control for these effects. They presented tones to their subjects in three conditions: In the oddball condition, 1300-Hz frequency deviants were presented among 1000-Hz standards; in the frequent–rare condition, 1000-Hz tones were presented in two separate sequences with an ISI equivalent to either the interstandard or interdeviant interval of the oddball condition; in the frequent–frequent condition 1000- and 1300-Hz tones were presented at the fast ISI in separate stimulus blocks. The authors observed that the responses generated in areas 41 and 42 depended on pitch and ISI, respectively. Importantly, they claimed to have found a genuine memory-based MMN response in auditory association cortex (TC 22). In the oddball condition, the standard elicited a positive wave peaking at 140 ms and the deviant elicited an "additional" negative wave at the same latency. When these measurements were compared to the responses obtained in the frequent–rare and frequent–frequent conditions at the MMN peak latency, there was no significant difference between the responses to the frequent and rare 1000-Hz tones in the frequent–rare condition or between the responses elicited by the 1000- and 1300-Hz tones presented at a fast rate in the frequent–frequent condition. Therefore, at the peak latency of the MMN, cells in TC 22 appear to be insensitive to ISI and frequency, and consequently the MMN cannot be explained by the dependence of the response on ISI (i.e., on "fresh afferents") or frequency.

However, there are problems with the memory-based interpretation of the Kropotov et al. (2000) results. To begin, one should note that area 22 produces prominent responses when a rare stimulus is presented alone, without the intervening standards. Therefore, this area in no way fulfills the requirements for a genuine MMN generator posed by the memory-based interpretation. Further, when the response to the rare stimulus in the frequent–rare condition and that elicited by the deviant in the oddball condition are compared, both are prominent but the response to the deviant is somewhat smaller and delayed by approximately 100 ms. This result is, again, in line with the adaptation model, according to which a rare tone (in the tone-alone condition) results in earlier and enhanced responses than when that same tone is presented as a deviant in the oddball condition (May et al., 1999). Furthermore, the data interpretation of Kropotov et al. (2000) is problematic because it rests on selective comparison of responses at one time point only: the peak latency of the MMN. The results show that, indeed, in area TC 22 around this one particular time point the responses to the frequent and rare tone in the frequent–rare condition cross each other, yielding a zero difference. However, the whole time window of measurement reveals something quite different: The responses to the rarely and frequently presented 1000-Hz tones in the frequent–rare condition, in fact, dramatically differ from each other; their point of intersection (at the MMN peak latency) is preceded by the rare stimulus producing a much larger negative deflection than the frequent stimulus (peaking around 100 ms); it is followed by a large positive difference wave (peaking after 200 ms). That is, the rare stimulus simply results in larger responses than the frequent one, which again agrees with the adaptation model.

In sum, the pattern of responses measured intracranially in humans (Kropotov et al., 2000) is consistent with those predicted by the adaptation model. The memory-based interpretation made by these authors rests on the implicit assumption that, in

the framework of the adaptation model, the latency of the response to the deviant cannot be affected by the presence of the standard stimuli. This piece of evidence against the adaptation model is refuted by considering the latency argument of the memory-based model of MMN (see Section 6.1).

6.11. Masking Effects Show That Adaptation Cannot Explain MMN

The appeal on behalf of the memory-based interpretation of MMN (Näätänen, 1992; Näätänen & Winkler, 1999; Näätänen et al., 2005; Winkler, 1993) cites the results of Winkler, Reinikainen, and Näätänen (1993), who found that the amplitude of the MMN correlates with behaviorally tested backward masking of auditory recognition. These authors presented subjects with tone pairs where one of the tones was a 1000-Hz "masker" and the other, "test" tone was either a 600-Hz standard or a 700-Hz deviant. In the backward masking condition, the test tone preceded the masker by an intertone interval (ITI) that was varied across stimulus blocks in the 20–400-ms range. The authors found that MMN amplitude depended on the ITI and that the response was abolished with the shortest ITIs (20 and 50 ms). This finding apparently rules out the adaptation explanation of MMN, thereby lending support to the memory-based interpretation (Näätänen, 1992; Näätänen et al., 2005). According to this argument (Winkler, 1993), the adaptation model dictates that most of the afferent cells responding to the deviant but not to the standard tone should also have been responsive to the masker, as otherwise the ITI would not have affected the MMN. However, the separation between the deviant and the masker was smaller than that between the standard and the masker. Most of the elements responding to the deviant but not to the standard should have been responding only to a narrow range of frequencies. Consequently, these elements could not have been affected by the mask tone, and thus the effect of ITI on the amplitude of the MMN cannot be accounted for by the adaptation model.

However, it is unclear why cells responding to the deviant but not to the standard should respond to a narrow range of frequencies not including the frequency of the masker and how this can be concluded from the relative separations in frequency between the three stimulus types. Indeed, this assumption is invalid if the respective patches of the map activated by the standard, deviant, and masker tones all overlap with each other. This overlap would make sense given that the amplitude of the N1 elicited by the standard also depends on the ITI, as evident in the Winkler et al. (1993) study. Furthermore, this study used an experimental setup that was in many ways similar (i.e., in terms of interpair ISI, ITI, deviant p, and the standard/deviant frequency ratio) to that used by Tervaniemi, Maury, et al. (1994). Interestingly, Tervaniemi and colleagues—studying the integration of information about closely spaced stimuli into unitary events—recorded prominent MMN responses at a 40-ms ITI. In contrast, Winkler and colleagues—studying masking—were unable to measure the MMN at the 20- and 50-ms ITIs. Thus, it seems that the results pertaining to the masking of MMN may be in need of replication.

An explanation of the MMN masking results can be formulated in terms of the adaptation model containing lateral inhibitory effects as suggested by May (1999) and May et al. (1999). The ITI dependence of the N1 to the standard implies that the presentation of the masker tone affected at least some of the cells responsive to the standard. This could come about through the projective field of the standard overlapping with that of the masker (so that the adaptation of the cells in the overlapping area is due to both stimulus types), or, alternatively, through sharply tuned cells responding to the standard and masker interacting through lateral inhibitory connections. In both cases, diminishing the ITI between the standard and the masker, first, attenuates the response to the masker and, second, extends the silent interval preceding each standard, thereby allowing for a longer period in which the attenuating effect of the masker on the response to the standard decays. Therefore, the response to the standard should increase as ITI is decreased. The situation becomes more complicated when the response to the deviant is considered. As with the standard tone, the direct effect of the masker, be it through overlapping projective fields or lateral inhibition, is to attenuate the response to the deviant as a function of ITI. However, in the case of lateral inhibition, this direct effect on the cells responding to the deviant is complemented by an indirect one. Namely, as ITI is decreased, the response to the standard is increased and, consequently, the lateral inhibition originating from the cells responding to the standard is enhanced, leading to reinforced suppression of the cells tuned to the deviant. Thus, the response to the deviant is influenced by two competing factors: lateral inhibition due to the standard and masker respectively attenuating and enhancing the response.

The results of Winkler et al. (1993) can be accounted for by the adaptation model: The amplitude of the N1 elicited by the standard grows steadily as ITI is decreased. In contrast, the response to the deviant remains stable and is enhanced for the shortest ITI, indicating the presence of lateral inhibitory influences. Subtracting the response to the standard from the response to the deviant yields an MMN response that is increasingly "masked" as the ITI is reduced. Rather than refuting the adaptation model, this finding provides the grounds for claiming that the effect of backward masking on MMN is due to lateral inhibition between populations of sharply tuned cells in auditory cortex.

6.12. MMN Is Elicited by a Decrement in Stimulus Duration and ISI

The adaptation model has been challenged by Näätänen and colleagues (Näätänen, 1990, 1992; Näätänen & Alho, 1995; Näätänen et al., 2007) on the basis that MMN is elicited by changes in purely temporal, nonspectral aspects of stimulation such as decrements in stimulus duration (Kaukoranta, Sams, Hari, Hämäläinen, & Näätänen, 1989; Näätänen, Paavilainen, & Reinikainen, 1989; Paavilainen et al., 1991) and ISI (Ford & Hillyard, 1981; Hari, Joutsiniemi, Hämäläinen, & Vilkman, 1989; Näätänen, Jiang, Lavikainen, Reinikainen, & Paavilainen, 1993; Nordby, Roth, & Pfefferbaum, 1988). Therefore, although MMN to tone frequency changes might well be accounted for by the adaptation model, MMN to temporal changes must, according to the memory interpretation, reflect a process that relies on some mechanisms other than standard-induced suppression on a neural map.

The above argument obviously rests on the notion that temporal stimulus structure cannot be spatially mapped by cortex. This notion is inconsistent with current knowledge about auditory processing, a central principle of which seems to be the transformation of sound spectra and auditory peripheral activity into spatial patterns of activation in cortex (as detailed in Section 5.2). Auditory cells exhibit a wide range of STRFs (e.g., Klein et al., 2000), and many of them are selective to spectro-

temporally complex stimulation (e.g., Rauschecker, 1997, 1998). It is hardly surprising, then, that such simple temporal features as stimulus duration and ISI are also accorded spatial representations: auditory cells *are* tuned to stimulus duration (He et al., 1997) and rate (Bieser & Muller-Preuss, 1996; Schreiner & Urbas, 1986, 1988). Neural mechanisms for how this mapping occurs have been suggested by May and Tiitinen (2001, 2004a), and an example of an adaptation model capable of accounting for MMN to decrements in ISI and duration is shown in Figure 3.

6.13. The Frequency Specificity of N1p Cannot Account for Behavioral Sensitivity to Attention Switches

Näätänen et al. (2005) pointed out that the relatively wide receptive fields of the cells generating the "N1p," as indicated by the results of Jääskeläinen et al. (2004), are unable to account for automatic attention switches to minute frequency changes (in the order of 1%; Berti, Roeber, & Schröger, 2004). This argument would seem to be designed to counter the notion put forward by Jääskeläinen et al. (2004) that posterior auditory cortex generating the N1p specifically filters superfluous sounds from entering awareness.

However, one might note that the credibility of the adaptation model does not depend on how the novelty information generated by the adaptation and lateral inhibition mechanisms is used by attention switching or "gating" mechanisms. According to the model, deviant or novel sounds are differentiated from a repetitive environment at different resolutions by cells with different tuning widths (see Sections 6.2 and 6.3). Therefore, to add to the speculation, the auditory cortex can be seen to provide a whole range of novelty signals, at different resolutions, appropriate for different conditions. If the primary task of the subject involves close attentional engagement to a particular sound source (such as in laboratory conditions), the novelty signals generated by sharply tuned cells (i.e., those underlying the "N1a") could obviously be envisioned to become available for attentional mechanisms, and thus even minute changes are reflected in behavioral responses (such as in Berti et al., 2004). However, if the primary task involves some sound source other than the repetitive one, information from other modalities, or even ignoring all sensory information, performing this primary task would be made impossible if any slight change in the environment would automatically initiate an attention switch. In these conditions, it is appropriate that only sufficiently novel sounds are "gated to consciousness," in which case broadly tuned cells (underlying the "N1p") would become useful. It remains an open and interesting question, albeit beyond the scope of the current review, how the width of this "gate" is modulated by attention and task.

6.14. The Case for the Memory-Based MMN: Where Is the Evidence?

Much research on MMN seems to have focused on gaining results that would refute the adaptation model, ostensibly because these kinds of results have been taken as ipso facto evidence *for* the memory-based model. This stance was explicated by, for example, Näätänen and Winkler (1999), who explained that the memory-based model must hold "because an account of the MMN in terms of new afferent elements activated by the deviant stimulus has been definitely ruled out" (p. 835). Unfortunately, in the process, the question of finding direct evidence for the memory-based model in the form of falsifiable predictions seems

to have been overlooked. It took almost 20 years of MMN research before Schröger and Wolff (1996) suggested an experimental condition through which the contribution of fresh-afferent activity to the MMN can be controlled for, and several studies have used this condition to show that a "genuine" memory-based MMN can be elicited (Campbell et al., 2007; Horváth et al., 2008; Jacobsen, Horenkamp, et al., 2003; Jacobsen & Schröger, 2001, 2003; Jacobsen, Schröger, & Alter, 2004; Jacobsen, Schröger, & Sussman, 2004; Jacobsen, Schröger, et al., 2003; Maess et al., 2007). However, as demonstrated in Section 6.6, these results are perfectly consistent with the adaptation model, and therefore they do not provide evidence for the memory-based interpretation on the one hand and reason for discarding the adaptation model on the other.

May et al. (1999) suggested that the oddball condition employed together with the deviants-alone condition could provide positive evidence for an MMN generator, assuming that only suppressive modulation mechanisms (i.e., adaptation and lateral inhibition) affect the cortical areas producing the N1: If the response to a stimulus presented as a deviant among standards is larger than that to the same stimulus presented without the intervening standards, the enhancement must be due to activity originating from some other areas than those producing the N1. However, experiments that have used this setup (Elangovan et al., 2005; Jääskeläinen et al., 2004; Korzyukov et al., 1999; May et al., 1999; Umbricht et al., 2005) have been unable to yield positive proof for the memory-based model of MMN. Further, results concerning the plasticity of cortical cells cast doubt on whether even the deviants-alone setup suggested by May et al. (1999) can offer a reliable test for the presence of a memory-based MMN. As described in Section 6.6, receptive fields in auditory cortex can be expanded by auditory stimulation (Calford, 2002; Calford et al., 1993). In particular, when oddball stimulation is applied for several minutes to networks of cortical cells, these start to exhibit amplified responses to the deviant stimulation (Eytan et al., 2003). It is therefore feasible, even in the framework of the adaptation model, that a deviant stimulus elicits an equally large or even larger response in the oddball condition than in the deviants-alone one (or the control condition proposed by Schröger & Wolff, 1996). This, obviously, should go some way to allay the concerns Näätänen et al. (2005) had on the fresh-afferent origin of the responses in Experiment 2 of Jääskeläinen et al. (2004).

In sum, it would seem that the memory-based model of MMN lacks positive evidence. What, then, would constitute positive proof of an MMN generator that operates according to the memory-based interpretation of MMN, that is, a population of cells responding *exclusively* to change in a *non-silent* environment? A convincing case for a "genuine" MMN generator should probably rely on "local," intracortical and/or electrophysiological in vivo evidence. This would require, first, the identification of cells that respond to an auditory stimulus when that stimulus is presented as the deviant in an oddball setting and remain inactive when that stimulus is presented as a standard or a rare stimulus alone (which is contradicted by the results of Kropotov et al., 2000). Second, the activity of these cells should be linked to the noninvasively measured MMN, that is, single-unit activity should be temporally aligned with MMN and be of sufficient quantity to "compete" with fresh-afferent activation in forming the response to the deviant. Unfortunately, none of the studies dealing with intracortical measurements of MMN have been able to satisfy these conditions.

6.15. Summary

Over the years, no positive evidence *for* the memory-based interpretation of MMN generation has been introduced. Instead, the arguments brought against the adaptation model have increased in number and become more complex. Taken as a whole, the case against the adaptation model might seem convincing already because of the sheer number of points of argument it contains. However, contrasting previous attempts (Näätänen, 1990, 1992; Näätänen & Alho, 1995; Näätänen & Winkler, 1999; Näätänen et al., 2005, 2007), the current review contains, to our knowledge, the first critical examination of the arguments against the adaptation model.

As shown above, none of the arguments against the adaptation model withstand critical examination. Further, despite their number, the reasons why they fail boil down to just a few: The case against the adaptation model is based, first, on the questionable assumption that the N1 is produced by generators that are fixed in terms of latency of activation (Sections 6.1, 6.6, and 6.10), spatial distribution (Sections 6.2 and 6.3), and morphology of the ERP/ERF (Section 6.9). Second, the case rests on a view on the dynamics and feature selectivity of cells in auditory cortex (Sections 6.1, 6.4–6.8, 6.11–6.12) that appears to stem from a time when afferent activation in cortex was conceived in terms of simple tonotopic maps capable of representing only the frequency content of sound, and that, too, in a highly linear fashion (i.e., without lateral inhibition, plasticity, and temporal dynamics).

Third, the rejection of the adaptation model is based on circular argumentation in specific cases (Sections 6.1 and 6.7) and also in a wider and more fundamental sense: Namely, the separation of the MMN from the ERP/ERF, and therefore all MMN research, is founded on the axiomatic assumption that the N1 is elicited in an invariant manner by both the standard and the deviant and can therefore be subtracted from the MMN-containing deviant response. Thus, when the MMN is found to differ from the standard-elicited N1 in terms of latency, morphology, spatial distribution of measurement, and sensitivity to experimental manipulation (Sections 6.1–6.12), the MMN, according to the memory-based interpretion, cannot be a morphed N1—because the N1 is elicited in an invariant manner. However, this premise/conclusion on the separability of the N1 and MMN should be rejected because (a) no evidence for the fixed N1 has been presented and (b) the case for the N1 to be generated by fundamentally dynamic generators is strong. Indeed, even a memory-based interpretation of experimental results indicates that the N1 shows such large variability during oddball stimulation that *any* observable MMN is *always* contaminated by the N1 (Horváth et al., 2008). Thereby, because no evidence for the separability of the N1 and MMN exists, there remains no reason to abandon the adaptation model. A dichotomist, at this point, might get carried away and claim that the memory-based model must fail because an account of the MMN in terms of new afferent elements activated by the deviant stimulus has been definitely ruled in.

With less haste, and without ruling out the possibility that a third possible explanation might eventually arise, it would seem that many of the experimental findings on which the arguments against the adaptation model are based can be seen as evidence *for* this model and, when considered in this new context, may actually point to new ways in which MEG and EEG measurements might be used to probe auditory information processing. Having lightened the payload, we return to the adaptation model proper and consider its implications for understanding auditory processing and auditory cognition in general.

7. The Value of MMN in Light of the Adaptation Model

MMN research during the past decades has been accompanied by an increasingly complex theoretical framework for explaining the MMN in terms of a memory-based process rather than an afferent one. Accordingly, the N1 and MMN are thought of as indices of two functionally distinct and separate processes, feature analysis and change detection, respectively. However, despite its established position, this framework has numerous theoretical and practical problems (as discussed in Section 3) that limit the use of MMN in basic and clinical research. Perhaps the most serious of these problems stems from the fact that, with the adaptation model having been discarded, no one has been able to suggest an acceptable physiologically grounded alternative: Despite a rich body of intracortical results on auditory function from animal models, we simply do not know (i.e., cannot agree on) how the MMN is generated. Other major problems include difficulties with associating MMN with a behaviorally relevant sensory memory system, the lack of direct evidence for a memory-based MMN, the problem of the "automaticity" and attention independence of the MMN, and the problem of "N1 contamination" of the MMN response to such a degree that the amplitude and latency of the assumed memory-based MMN cannot be determined with the methods used in MMN research. In this section, we examine how the adaptation model could solve these problems and provide for a stronger link between the MMN and physiological concepts on the one hand and psychological ones on the other.

7.1. The Adaptation Model: The First Physiologically Viable Explanation of MMN

The adaptation model we are proposing, in the footsteps of Butler (1968), provides the first viable explanation of MMN in physiological terms: *it* suggests that repetitive stimulation suppresses those cells optimally tuned to this stimulation, leaving other cells in a state where they are able to respond strongly. The MMN to an infrequent deviant stimulus results from the differential suppressive effects at the respective auditory field locations mapping the rare and repetitive stimulation. Thus, the MMN can be explained without recourse to hypothetical cells dedicated to change detection (as well as computation, amplification, transient detection, feature detection, extrapolation, and sensory memory) whose existence remains unconfirmed, but, rather, through the experimentally found properties of cells in auditory cortex. This explanation blurs the distinction between N1 and MMN by suggesting that MMN to a sound presented as a deviant is due to the activity of cells that, under conditions where the sound is presented as a standard, produce the N1. Not only does this model agree with electrophysiological and intracortical findings, but it also accounts for the numerous noninvasive results that have previously been taken as evidence for the memory-based explanation (see Section 6).

The immediate benefit from the adaptation model is that it suggests answers to basic, previously unanswered questions concerning the cognitive interpretation of MMN, namely, what, in neurophysiological terms, is the memory trace underlying MMN generation, how does the comparison process producing MMN work, what is the functional and spatial relationship between the trace and comparison process, and, indeed, how is the MMN

generated from the interaction between the two? To reiterate, the *memory trace* is the time-evolving poststimulus suppression distributed spatially across auditory cortical areas; the *comparison process* emerges out of auditory cells having unique STRFs, that is, they are differentially selected to spectral content within variable-length time windows *and* to the temporal order in which this content is presented. For example, in the elementary case of frequency MMN, the comparison process is the tonotopic mapping itself. Thus, the memory trace is a physiologically inherent part of the comparison process, modulating it directly, and this intertwined nature of the two underlies the generation of the MMN. As a beneficial byproduct, this description of the memory trace and comparison process also makes redundant the problematic dichotomy between physiological and cognitive explanations at the heart of the prevailing theory of MMN (Näätänen, 1990, 1992).

However, the adaptation model should not be considered complete in any sense. The modeling work carried out by May and colleagues (May, 1999; May & Tiitinen, 2001, 2004b; May et al., 1999) and the simulations in the present review are limited in describing the dynamics of, at the most, four cortical areas. They are not intended as full descriptions of auditory cortex in all its complexity, but, rather, serve to demonstrate the principle that the N1 and MMN can be generated in the framework of the adaptation model without recourse to a black box of complex exogenous and endogenous processing. Thus, these models should be seen as a potential starting point for elaborated descriptions of neural dynamics in realistic simulation environments, allowing much more fine-grained modeling of cellular dynamics, neuropharmacological effects, synaptic plasticity, and MEG/EEG generation. Importantly, although neurophysiological evidence points to spatial mapping being the general principle whereby sound structure is represented in the brain (e.g., Shamma, 2001; see Section 5), what is currently not known is how these spatial mappings are achieved through the neural interactions of auditory cortex. Thus, future work will undoubtedly include more sophisticated descriptions of the architecture of auditory cortex (see Section 6.1), whose functional interconnectivity has recently been probed with intracortical measurements in humans (Gourévitch et al., 2008; Guéguin et al., 2007). Recent work using dynamic causal modeling (DCM; Friston, Harrison, & Penny, 2003) suggests that the MMN can be accounted for by adaptation (i.e., intrinsic or within-source changes) in auditory cortex (Kiebel, Garrido, & Friston, 2007) and by modifications of bottom-up and top-down connections between cortical areas (Garrido, Kilner, Kiebel, & Friston, 2007; Garrido, Kilner, Kiebel, Stephan, & Friston, 2007) in a way that is consistent with the predictive coding model of Friston (2005). As this approach does not yet describe why certain populations become adapted by the standard and others not, it may be beneficial to combine these efforts with the currently advocated physiologically plausible ("mechanistic") information processing models of how sound features are actually represented in auditory cortex.

7.2. MMN as an Index of Mapping Strategies of Auditory Cortex
As the evidence seems so far to point to the possibility that *any* kind of audible change in a repetitive auditory environment is able to elicit an MMN (for a review, see Picton et al., 2000), spatial mapping may be a general principle by which the auditory cortex represents sounds. That is, if any two auditory events sound different, they are necessarily mapped to different sets of cells. Thus, the adaptation model of MMN suggests that human auditory cortex, apart from containing tonotopically (Howard

et al., 1996; Lauter, Herscovitch, Formby, & Raichle, 1985; Pantev et al., 1988; Romani, Williamson, & Kaufman, 1982) and amplitopically (Pantev et al., 1989) organized fields, also contains cells that are tuned to ISI, stimulus duration, spatial location of sound origin, tone step direction, and the spectrotemporal structure of complex stimuli such as speech sounds.

In this context, oddball measurements interpreted through the adaptation model might offer a way to establish how different auditory areas are specialized in processing various aspects of sound information: When the standards are presented at fast ISIs, the enhanced response to the deviant originates primarily in areas that exhibit tuning to the parameter of deviance, and, therefore, reconstructing the intracerebral sources to deviant responses might be useful in revealing regional specializations. In particular, cells that exhibit low selectivity between the standard and the deviant stimulus will produce an amplitude enhancement of the response to the deviant that is of a lower magnitude than that produced by cells with high selectivity. Therefore, identifying the areas producing the largest differences between the standard and deviant responses (i.e., the lowest adaptation effect on the response to the deviant) will disclose where in the brain the stimulus feature in question receives specialized processing. In these efforts, one could also employ more efficient, N1-based stimulation paradigms designed to tease out stimulus selectivity through the use of sequences of alternating stimuli (see Butler, 1972). Indeed, this approach was recently demonstrated by Ahveninen et al. (2006), who found evidence for separate processing streams for identity and location information.

Zatorre, Belin, and Penhune (2002), reviewing hemodynamic and patient studies, suggested that the left auditory cortex has better temporal resolution than the right auditory cortex, which, in turn, has a superior spectral resolution. The adaptation model may give new, MEG-based ways to investigate this issue through the adaptation of the N1. For example, intracortical measurements in humans point to the left hemisphere having a superior ability to distinguish between sounds, both speech and nonspeech, with a fast temporal structure (Liégeois-Chauvel, de Graaf, Laguitton, & Chauvel, 1999). This specialization could be investigated with MEG: A prediction of the adaptation model is that when oddball stimulation utilizes standards and deviants defined by brief temporal differences (e.g., in terms of voice onset times of syllables as in Liégeois-Chauvel et al., 1999), the result is a stronger adaptation of the response to the deviant in the right hemisphere, in the case of both speech and nonspeech sounds. Further, as the adaptation model provides an explanation of the MMN in terms of stimulus selectivity and adaptation (rather than a description in terms of a memory trace and a comparison process), it could offer a rephrasing of MMN results on language laterality (reviewed in Näätänen et al., 2007) into terms closer to those used by the wider neuroscientific community. For example, in view of the left-hemispheric predominance of MMN to vowel identity changes (Näätänen et al., 1997) and N1 measurements using natural vowel sounds (Mäkelä, Alku, & Tiitinen, 2003), the prediction provided by the adaptation model for hemodynamic and intracortical measurements is that the left hemisphere is more sensitive than the right not only to the temporal but also to the spectral content of speech sounds.

7.3. MMN as a Tool for Studying Receptive Field Plasticity and Perceptual Learning
N1 and MMN results indicate that auditory cortex forms acoustic representations with a lifetime of seconds (Böttcher-Gandor &

Ullsperger, 1992; Lu et al., 1992b; Mäntysalo & Näätänen, 1987). These can be contrasted with memory representations lasting for hours to weeks and associated with perceptual learning. Such long-term representations can be observed as modifications of receptive fields in auditory cortex of animal models and have been studied with single- and multi-unit measurements since the 1980s (for reviews, see Weinberger, 1993, 2004). In the auditory cortex, classical and instrumental conditioning with tones—the original methods for studying perceptual learning—leads to increased responses to the frequency of the conditioned stimulus (CS) and to decreases in responses to other frequencies so that the best frequencies of individual neurons shift toward the frequency of the CS. This kind of receptive field (RF) plasticity can be observed both when the CS is the only auditory stimulus used in the training (Bakin & Weinberger, 1990; Diamond & Weinberger, 1986, 1989) and when the animal learns to discriminate between the CS and a tone of a different frequency (Bakin, South, & Weinberger, 1996; Edeline & Weinberger, 1993). Using a variation of the oddball paradigm, Blake et al. (2002) presented owl monkeys with two to six "standard" tones of one frequency followed by target (or deviant) tones of a higher frequency. After instrumental conditioning, the animals learned to respond to the presentation of the target, and this behavioral learning was associated with increased responses to the target frequency and to decreased responses to the standard and to other nontarget stimuli. Further, RF plasticity is not restricted to frequency representations in auditory cortex. Plasticity of the representation of temporal features was demonstrated by Bao, Chang, Woods, and Merzenich (2004), who trained rats to respond to noise pulses presented at a fast rate. After training, neurons in A1 exhibited greater responses to high-rate auditory stimuli. Plasticity related to perceptual learning can also be observed as modifications of topographic maps in auditory cortex. Using the oddball stimulation paradigm, Recanzone, Schreiner, and Merzenich (1993) trained adult owl monkeys to discriminate small differences in the frequency of standard and target tones. The authors found that the improvement in behavioral performance correlated with an increase of the cortical area in A1 representing the behaviorally relevant frequencies. More recently, Polley et al. (2006) trained rats to attend to either frequency or intensity within an identical set of tone stimuli. They found that, in both the primary and secondary auditory areas, the animals exhibited enlarged topographic representations of the target feature, that is, expansions of the representation of either the target frequency or intensity on the tonotopic and amplitopic map, respectively, depending on the learning task. Again, the degree of topographic map plasticity within the task-relevant stimulus dimension was correlated with how well the animal had learned the task.

Taken together, the above results show the following: First, the auditory cortex is shaped by auditory input during learning tasks in a task-specific way. Second, this shaping is directly reflected in changes in behaviorally measurable perceptual acuity, and, therefore, there is a demonstrable link between plasticity of auditory cortex and perceptual learning. Third, in the specific framework of oddball stimulation, perceptual learning leads to a higher ability to discriminate the deviant from the standard; this improvement is correlated with individual neurons increasing and decreasing their response to the deviant and standard, respectively, as well as with an increase in the number of neurons responding to the deviant.

In the framework of the adaptation model, these observations have straightforward implications for amplitude modifications of the MMN. Namely, if the cells generating the N1 exhibit similar learning-related plasticity as found in animal models, perceptual learning should lead to increased N1 responses to the deviant coupled with unvarying (or even decreased) responses to the standard, the end result being an enhanced MMN response. This increase should correlate with perceptual acuity, that is, behavioral improvements in detecting the deviant. Interestingly, several MMN studies looking at the link between perceptual learning and the MMN have found exactly this pattern of results consistent with the adaptation model. When subjects learn to perform a discrimination task involving temporal sound patterns (Atienza et al., 2002; Gottselig, Brandeis, Hofer-Tinguely, Borbely, & Achermann, 2004; Näätänen, Schröger, et al., 1993; Tervaniemi, Rytkönen, Schröger, Ilmoniemi, & Näätänen, 2001), speech sounds (Kraus et al., 1995; Menning, Imaizumi, Zwitserlood, & Pantev, 2002; Tremblay, Kraus, Carrell, & McGee, 1997; Tremblay, Kraus, & McGee, 1998) or pure tones (Menning, Roberts, & Pantev, 2000), the magnitude of the MMN, measured before and after training, correlates with performance in the behavioral task. In the studies where the responses to the standard and deviant are shown (i.e., in all except Menning et al., 2000), the increased MMN seems clearly to be the result of an enhanced response to the deviant, the amplitude of the response to the standard remaining stable (although there occasionally appear changes in the response to the standard also; Kraus et al., 1995). In their interpretation of this change in the MMN amplitude, Näätänen et al. (2001) emphasized the emergence and gradual improvement of the neural representation of the standard pattern so that slight changes could then be detected against it. However, in the context of the adaptation model and the results from animal models reviewed above, the increase in the MMN amplitude occurring as a result of learning could be explained through the cortical representations of the deviant changing as a result of recruitment on cortical maps. That is, there is an increase in the number of neurons responding to the deviant, and this results in stronger noninvasive responses.

Importantly, the framework of the adaptation model offers a considerable simplification for studying these effects. Any changes responsible for an enlarged response to the target stimulus when used as a deviant in the oddball paradigm should also be visible when the target is presented repetitively in the testing phase. Therefore, in order to observe the enhanced cortical representations of the target stimulus, one can avoid the time-consuming oddball paradigm (where the target occurs infrequently) and use the simple "N1 paradigm" instead (where the target is the only stimulus). The benefits of this (as evidenced by the multitude of N1 studies of, for example, our own research on the processing of speech and the spatial quality of sound; see Section 3) would be a reduction in measurement time by an order of magnitude and/or an increase in the quality of the data through raising the number of responses to be averaged. Indeed, this approach would mirror the induction/expression and learning/performance dissociation utilized in animal neurophysiology (e.g., Diamond & Weinberger, 1989) and is validated by the results of Tremblay, Kraus, McGee, Ponton, and Otis (2001) as well as Tremblay and Kraus (2002). Dispensing with MMN measurements, these authors found that, when subjects learned to discriminate between consonant–vowel syllables, the N1-P2 response complex more than doubled in amplitude for the speech sounds. Similarly, the N1 has been found to reflect perceptual learning in discrimination tasks involving tones (Cansino & Williamson, 1997) and vowels (Reinke, He, Wang, & Alain, 2003).

Finally, one may note that the logic for using N1 measurements for studying perceptual learning could be extended to examining cortical organization resulting from long-term environmental exposure (e.g., Pantev et al., 1998).

7.4. Oddball Responses with No "N1 Contamination"

A practical problem in experimental research has been to avoid the fresh-afferent "N1 contamination" of the MMN, generally assumed to occur for large deviances when nonadapted ("non-refractory") neurons are activated (e.g., Näätänen, 1992). Indeed, it is sometimes acknowledged that the response to the deviant might inevitably include fresh-afferent contamination, and much effort has been expended in showing that, buried in the response to the deviant, a "genuine" memory-based MMN really exists (Campbell et al., 2007; Jacobsen, Horenkamp, et al., 2003; Jacobsen & Schröger, 2001, 2003; Jacobsen, Schröger, & Alter, 2004; Jacobsen, Schröger, & Sussman, 2004; Jacobsen, Schröger, et al., 2003; Maess et al., 2007; Näätänen & Winkler, 1999; Schröger & Wolff, 1996). However, no method has been introduced conclusively to tease out the genuine memory-based MMN from N1 contamination, the conventional subtraction curve being an overestimation of the MMN and the difference between the oddball response and the response in the control condition introduced by Schröger and Wolff (1996) providing an underestimation. The results of Horváth et al. (2008) are especially troublesome for MMN research, because they show that already at the minutest deviations at which a reliable MMN is elicited, the MMN is N1-contaminated. Thus, the unfortunate consequence of N1 contamination is that, not only is it impossible to identify the supposedly genuine MMN for its peak amplitude and latency, but even establishing its presence requires lengthy control measurements, which should be carried out every time MMN is measured—something which is seldom done.

Luckily, the adaptation model obviates all these problems: If there is no afferent N1 separate from a genuine MMN response, there is no N1 contamination to worry about. This implies that research efforts could straightforwardly concentrate on the "genuine" responses elicited by the standard and deviant, perhaps disentangling the contributions from different cortical areas through methods suitable for identifying the spatially distributed nature of cortical activity. These methods include multiple source analysis (Auranen et al., 2007; Inui et al., 2006; Jun et al., 2005), estimation of distributed sources (Lin, Belliveau, Dale, & Hämäläinen, 2006; Uutela, Hämäläinen, & Somersalo, 1999), and combined fMRI and MEG measurements (Liu, Belliveau, & Dale, 1998; Liu, Dale, & Belliveau, 2002; Jääskeläinen et al., 2004). In these efforts, the subtraction curve might continue to be useful in the sense that it indicates that auditory cortex is able to differentiate between the standard and the deviant. However, its interpretation in physiological terms is far from straightforward. At the very least, the currently available evidence does not support the existence of dedicated "MMN generators" postulated by the memory-based model. Also, although the subtraction method is useful for identifying cognitive functions of brain areas in hemodynamic measurements, especially when carefully applied with factorial analysis (Friston et al., 1996), the issue becomes more complicated in the case of MEG and EEG because of the temporal resolution of these methods. This is, essentially, because the contributions of amplitude and latency modulations are confounded in the difference curve and can only be uncovered by focusing on the genuine responses elicited by the standard and deviant stimulus. For example, a subtraction curve obtained for a particular cortical area and comprising a negative phase followed by a positive one, or vice versa, can arise out of morphological modulations (i.e., amplitude increases and decreases) of the response produced by that area. However, the very same difference curve could also be due to response with a fixed amplitude and morphology shifted purely in latency. To study what the actual modulations and the concomitant interactions between various cortical areas are, one needs to examine the actual brain responses rather than their differences.

7.5. MMN, Automaticity, and the Effect of Attention

The automaticity and preattentiveness of the MMN has been one of the central issues concerning the way the MMN should be interpreted and has been the cause of much debate over the years. The adaptation model may provide a new angle to the ongoing discussion and offer a way to resolve this issue.

The model of basic sensory analysis proposed by Näätänen (1990, 1992) assumes that the MMN is strongly automatic, that is, independent of attention. This position was originally based on the observations that during dichotic stimulation the MMN is not affected by whether the stimuli are presented in the attended or unattended channel (Alho, Sams, Paavilainen, Reinikainen, & Näätänen, 1989; Näätänen, Gaillard, & Mäntysalo, 1980; Näätänen et al., 1978, see also Alho, Woods, & Algazi, 1994; Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993). However, Woldorff, Hackley, and Hillyard (1991) found that, when the attention of the subject is focused on a difficult task in the attended channel, the MMN elicited by slight intensity changes in the unattended channel is almost eliminated. In response, Näätänen (1991) pointed out that this attentional modulation of the MMN could have been due to an attention-related N2b component overlapping with the MMN in the "attend" condition and that the attentional modulation of the MMN may be specific to intensity MMN only. Näätänen (1991) postulated further that attention only affects "amplificatory" neurons contributing to the MMN and that the comparison process is really based on fully automatic "computational" neurons. No evidence for the existence of amplificatory and computational neurons has been provided, however.

Subsequent evidence indicates that the modulation of the MMN by the direction of attention cannot be accounted for by the N2b (Alain & Woods, 1997; Muller-Gass, Stelmack, & Campbell, 2006; Näätänen, Paavilainen, et al., 1993; Szymanski, Yund, & Woods, 1999; Trejo, Ryan-Jones, & Kramer, 1995; Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998) and that attention affects MMN to frequency changes (Muller-Gass et al., 2006; Trejo et al., 1995) as well as to changes in intensity (Muller-Gass et al., 2006; Näätänen, Paavilainen, et al., 1993; Szymanski et al., 1999; Woldorff et al., 1998), duration (Dittmann-Balcar, Thienel, & Schall, 1999; Muller, Achenbach, Oades, Bender, & Schall, 2002), spatial location (Arnott & Alain, 2002), tone patterns (Alain & Woods, 1997), and speech sounds (Szymanski et al., 1999). Further doubt about the automaticity of the MMN is, obviously, cast by results showing top-down effects on the MMN. Namely, the subject's prior knowledge of stimulus structure affects the amplitude of the MMN (Sussman, Winkler, Huotilainen, Ritter, & Näätänen, 2002). The MMN amplitude also depends on the subject's task during the measurement both when the MMN is measured for unattended stimuli (Alain & Izenberg, 2003) *and* when it is measured in the passive "read" condition (Muller-Gass, Stelmack, & Campbell, 2005; Sabri, Liebenthal, Waldron, Medler, & Binder, 2006). Further, it is

doubtful whether automaticity holds even in a proposed diluted form, whereby the MMN is attention-independent only in the sense that it is elicited even when the subject is not attending to the deviant stimulus (e.g., Näätänen & Alho, 1995). Arnott and Alain (2002) demonstrated that the MMN can be completely abolished for tones presented at one spatial location when attention is directed to another location. Näätänen et al. (2007) defended the automaticity of the MMN even in this case by stating that "a small MMN residual may nevertheless have remained" (p. 11). This argument, however, is rather odd: If any slight activity in the absence of directed attention can be called automatic, it becomes doubtful whether any nonautomatic, "attentive" processing occurs in the brain at all.

Recently, Näätänen et al. (2007) stated that the automaticity of MMN is strongly supported by results showing that MMN can be measured in comatose patients (e.g., Kane, Curry, Butler, & Cummins, 1993), anesthesia (e.g., Yppärilä, Karhu, Westerén-Punnonen, Musialowicz, & Partanen, 2002), certain sleep stages (e.g., Atienza & Cantero, 2001), and in newborns (e.g., Ceponiené et al., 2002; see Section 6.9). Although these results demonstrate that MMN can be elicited—and, therefore, in the currently proposed framework, adaptation modulates auditory cortex—in various stages of consciousness and development, the experimental fact remains that MMN is modulated by attention. Thus, the problem of fitting the square peg of an automatic, attention-independent generator into the round hole of an attention-modulated process remains. It is hardly resolved by the unverified suggestions that the deviance detection system really *is* automatic, but that either its input (Ritter, Sussman, Deacon, Cowan, & Vaughan, 1999) or "amplified" output (Näätänen, 1991) is modulated by attention. Also, the insistence on the automaticity of the MMN has unforeseen theoretical complications. Namely, as the studies demonstrating MMN in sleep and newborns include results showing a lack of the N1 response (e.g., Alho et al., 1990; Atienza & Cantero, 2001; Ruusuvirta et al., 2003; Winkler et al., 2003), it follows from the reasoning employed by Näätänen et al. (2007) that the N1 must therefore be nonautomatic. This leads to very strange consequences for the model of central auditory processing proposed by Näätänen (1990, 1992): As the N1 response (exogenous yet apparently nonautomatic) and the MMN (endogenous but automatic) reflect detection of stimulus onsets and stimulus changes, respectively, onset detection would seem to require a certain level of consciousness and development whereas change detection does not. Unfortunately, the model does not explain how the central auditory system is able to detect stimulus change in a state where it is unable to detect the transition from silence to sound.

The adaptation model contributes to this debate by redefining it. All the above cited studies focused on the subtraction curve between the responses to the standard and deviant. However, in view of the adaptation model, as the MMN does not represent genuine brain activity (i.e., it is not a real "component" of the ERP and ERF but, rather, an end result of the off-line subtraction procedure), the question of its automaticity becomes irrelevant. Put simply, it does not matter whether or not the MMN can be modulated by attention, because any empirical investigation on the effect of attention on auditory processing should concern itself with the genuine responses to the standards and deviants. The question then becomes: How does attention and task affect the respective N1 responses to the standard and the deviant? In many of the above cited studies where the ERPs and ERFs to the standard and deviant have been shown or analyzed, these responses are enhanced by the subject paying attention to the stimuli (Alain & Woods, 1997; Alho et al., 1989; Arnott & Alain, 2002; Muller-Gass et al., 2006; Näätänen, Paavilainen, et al., 1993; Trejo et al., 1995; Woldorff et al., 1991, 1998; see also Szymanski et al., 1999).

The observation of attention-related modulation of the genuine, directly recorded responses obtained in the oddball paradigm may offer a way to connect MMN research to other neuroscientific investigations showing that attention directly modifies the functioning of auditory cortex. Already middle-latency evoked responses exhibit attention dependence (Woldorff & Hillyard, 1991; Woldorff et al., 1993), and source modeling results (Fujiwara, Nagamine, Imai, Tanaka, & Shibasaki, 1998; Okamoto, Stracke, Wolters, Schmael, & Pantev, 2007) as well as subdural recordings in humans (Neelon, Williams, & Garell, 2006a, 2006b) suggest that attention enhances the N1. These findings are consistent with hemodynamic studies showing that attention enhances the activity of auditory cortex (Alho et al., 1999; Jäncke, Mirzazade, & Shah, 1999; O'Leary et al., 1997; Petkov et al., 2004; Shomstein & Yantis, 2004; Zatorre, Mondor, & Evans, 1999). Intracranial recordings in humans further show that selective attention modulates activity both in primary auditory cortex and in secondary areas (Bidet-Caulet et al., 2007). Interestingly, recent single-cell recordings show that during active listening tasks, when animals attend to specific target stimuli, STRFs of cells in primary auditory cortex can be modulated within seconds of the beginning of the task (Fritz, Elhilali, David, & Shamma, 2007; Fritz, Elhilali, & Shamma, 2005a, 2005b, 2007; Fritz, Shamma, Elhilali, & Klein, 2003). This modulation depends directly on the frequency of the target stimulus the animal is engaged in detecting. For example, in a two-tone frequency discrimination task, responses are enhanced for the rarely occurring target stimulus and can be suppressed for the frequently occurring reference stimulus (Fritz, Elhilali, & Shamma, 2005b). This pattern of "fresh-afferent" activity could obviously contribute to an attentional enhancement of the MMN. Similar results have recently been obtained in humans: Kauramäki, Jääskeläinen, and Sams (2007) and Okamoto, Stracke, et al. (2007) demonstrated an attention-related sharpening of the frequency tuning of the cell populations generating the N1. In the framework of the adaptation model, this alteration of the tuning of the cells generating the N1 would explain the attention dependence of the MMN. That is, the broader tuning associated with unattended sounds leads to an increased standard-induced adaptation of the cells tuned to the deviant, and thus the MMN is diminished, especially at small separations between the standard and the deviant. Given the above converging evidence that attention modulates the functioning of the auditory cortex, the adaptation model can be used to formulate specific hypotheses about the mechanisms underlying these modulations. For example, as the responses obtained in the oddball paradigm reflect lateral effects on tonotopic maps, it may be possible to use these responses to probe whether attentional focus has a dynamic width that depends on task difficulty.

In a wider perspective, the notion that auditory processing can be automatic or preattentive needs to be reevaluated. The idea that some part of auditory cortex is hardwired, operating in a bottom-up manner independently of attentional and task effects, is already undermined by the results discussed above. Complementing these results, the response properties of primary auditory cortex are modulated by behavioral task (Durif, Jouffrais, & Rouiller, 2003; Scheich, Brechmann, Brosch, Bud-

inger, & Ohl, 2007), and, for example, the activation of auditory cortex as indexed by the N1 is dependent on the visual memory task the subject is engaged in (Dyson, Alain, & He, 2005; Valtonen, May, Mäkinen, & Tiitinen, 2003). Also, multimodal integration occurs already in the core and belt areas of auditory cortex (Fu et al., 2003; Kayser, Petkov, Augath, & Logothetis, 2007; Kayser, Petkov, & Logothetis, 2008). Taken together, the evidence clearly points to auditory cortex being affected, already at the core level, by "higher" cognitive processing. Thus, when one also regards the abundance of top-down projections found in the auditory pathway at all levels (Kaas & Hackett, 2000; Pandya, 1995; Scheich et al., 2007; Winer & Lee, 2007), the automaticity proposal becomes somewhat improbable. In truth, if attentional engagement is able to modulate activity even in the human cochlea as measured through otoacoustic emissions (Ferber-Viart, Duclaux, Collet, & Guyonnard, 1995; Froehlich, Collet, Chanal, & Morgon, 1990; Froehlich, Collet, & Morgon, 1993; Giard, Collet, Bouchet, & Pernier, 1994; Maison, Micheyl, & Collet, 2001; Meric & Collet, 1992; Meric, Micheyl, & Collet, 1996; Puel, Bonfils, & Pujol, 1988; for a review, see Giard, Fort, Mouchetant-Rostaing, & Pernier, 2000), it is difficult to conceive how *any* automatic and preattentive processing could take place in the auditory system at all.[4]

The automaticity of MMN was a central issue in the development of the model of attention in central auditory processing, as it appeared to provide the first objective, physiological measure of the extent to which stimuli are processed independently of attention (Näätänen, 1990, 1992). The concept of automaticity originates from the earliest theories of selective attention. Broadbent's (1958) landmark model of the human information processing system, deduced from results indicating that at any time the brain processes and stores a great deal more information than it holds in the focus of attention, proposed three stages of memory processes. All stimuli are initially processed and briefly held in an unlimited-capacity sensory memory buffer (referred to as echoic memory in the auditory modality; Neisser, 1967). Attention then filters out most of this information and only a subset is allowed into short-term memory (STM) and further processing, including semantic analysis and consolidation into long-term memory. This so called early-selection model was later modified with emphasis on the location of the fixed attentional filter in the assumed pipeline-like process. Results indicating that semantic information (e.g., one's own name) in an unattended channel can lead to attention being automatically switched to this channel led to the development of so called late-selection theories (Deutsch & Deutsch, 1963). According to these, all stimuli are fully processed both for their physical features and semantic content, and attention merely chooses which fully processed items are allowed into STM and conscious awareness. The search for the location of the attentional filter produced the much-used concept of the automatic process, that is, processing of stimuli carried out before the attentional filter and therefore without intention, awareness, or capacity limitations (Posner & Snyder, 1975). Current thinking has abandoned the dichotomy between early and late selection as well as the pipeline leading from one subdivision of

memory to the next; it is now agreed that attention affects the processing of physical cues (contrary to the late-selection model) and that (contrary to the early-selection model) unattended stimuli are not merely held in a sensory buffer but are processed to some degree, at least for their physical properties (e.g., Cowan, 1995). The proposed automaticity of the MMN allowed the conclusion that sensory information is fully processed before it reaches the focus of attention.

Indeed, the results showing that the N1 and MMN responses are generated even when the subject is not paying attention to the stimuli indicate that auditory cortex is activated by sounds outside the attentional focus. However, in view of the above cited studies, it is misleading to refer to the processing associated with N1 and MMN as automatic, because attention clearly affects all stages of auditory sensory processing. There seems to be no specific location in the auditory pathway that forms the borderline between automatic and nonautomatic processing, and so the effect of attention is not a division of the pipeline of auditory processing into pre- and postattentive sections. Instead, attention could be seen as a modulation occurring *along* the entire length of the pipeline and realized through the combination of forward and backward projections. Also, the strength of this modulation seems to depend on the difficulty of the task so that the more demanding the task, the stronger the effect is peripherally (Giard et al., 2000). Thus, attention modulates the activity of auditory cells responding to a specific set of sounds, and this subset of cells keeps changing as a function of the attentional focus and task difficulty. In this framework, where sensory processing is continuously being adjusted by the focus of attention, the concept of automatic, attention-independent processing loses its meaning.

In sum, experimental evidence shows that the MMN can be modulated and even abolished by attention. Further, the notion that the MMN represents automatic, preattentive cortical processing can be rejected for two reasons. First, according to the adaptation model, the MMN as a subtraction curve does not represent the activity of a separate generator, and, therefore, by extension, its dependence on controlled experimental variables, such as attentional focus, cannot be used as an indicator of how any particular cortical area is sensitive to these variables. Second, the notion of automatic processing lacks evidence and is highly unlikely, given our current understanding of how auditory cortex is modulated by attention and task.

7.6. Implications for Understanding the Interplay of Memory and Attention

Cowan (1984, 1988, 1995) has extensively studied the links between memory and attention and combined two research traditions in psychology: the research on selective attention (e.g., Broadbent 1958; Deutsch & Deutsch, 1963; Treisman, 1964a, 1964b) and the research on the orienting of attention (Sokolov, 1960). In view of the MMN having been linked to the orienting process and memory, a reevaluation of this response in terms of the currently proposed framework may suggest novel insights into the operation of memory and attention.

Cowan (1984) reviewed the experimental evidence pertaining to sensory memory and concluded that there are two types of sensory store both in the auditory and visual modalities. The shorter one lasts up to 300 ms and is experienced as sensation whereas the longer one lasts up to 20 s, is experienced as memory, and, according to Cowan (1988), may, in fact, coincide with the STM system. Cowan and associates further concluded that the MMN might be a manifestation of sensory memory that repre-

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[4]The results reviewed here, obviously, make questionable the usefulness of the endogenous/exogenous division of ERP/ERF components (Donchin, Ritter, & McCallum, 1978). By the same token, there seem to be no cells in auditory cortex (e.g., those generating the N1) that can be labeled as "afferent"; the labels "afferent" and "efferent" are sensible only when applied to individual pathways, that is, to the direction of impulses traveling along any particular bundle of axons.

sents the status of a tone as a repetitive event (Cowan, 1995; Cowan et al., 1993; Winkler & Cowan, 2005). In the current adaptation-based context, sensory memory and STM are physiologically realized through the mechanisms of poststimulus suppression. Importantly, the adaptation model, while being consistent with the link between sensory memory and N1 found by Lu et al. (1992a), solves the problems of linking MMN to sensory memory (discussed by Ritter, Deacon, Gomes, Javitt, & Vaughan, 1995). The primary problem is that, even though sensory memory results from just a single presentation of a stimulus, the trace inferred from MMN data using the memory-based framework requires several presentations of the repetitive signal before a deviant elicits the MMN (Cowan et al., 1993; Horváth et al., 2001; Näätänen, 1992; Sussman et al., 2003; Winkler et al., 2001). However, in the context of the adaptation model, the multitude of results showing that the N1 attenuates with stimulus repetition and that the largest decrease generally occurs between the first and the second stimulus (e.g., Bourbon, Will, Gary, & Papanicolau, 1987; Budd et al., 1998; Frühstorfer, 1971; Frühstorfer et al., 1970; May & Tiitinen, 2004a; Ritter, Vaughan, & Costa, 1968; Rosburg, 2004; Rosburg et al., 2004, 2006; Roth & Kopell, 1969; Woods & Elmasian, 1986) allows one to conclude that a sensory memory trace (in the form of poststimulus suppression) is left already by the first stimulus. An easily obtainable measure of the relative strength of this trace is the ratio by which the N1 diminishes between the first and the second stimulus. Importantly, this conclusion on the presence of a memory trace after the first stimulus can also be drawn from the data of Cowan et al. (1993), even though these authors were unable to measure an MMN response to the second stimulus. Thus, the adaptation model offers a straightforward bridge between the concept of sensory memory and its physiological realization.

According to the habituation theory proposed by Cowan (1995), the overall distribution of attention is determined by voluntary attentive processing and orienting. All incoming stimulation makes contact with and activates features of long-term memory (LTM), the activated parts of which make up the contents of STM. A subset of the latter constitutes the focus of attention, which is presumably attracted by newly activated features, thereby causing orienting. Habituation of the orienting response due to stimulus repetition leads to attention no longer being involuntarily recruited to the stimulus. Voluntary attentional processes are then able to choose freely among activated LTM elements without strong competition from external distractors. Habituation therefore leads to apparent filtering of most sensory information in an unchanging environment, and dishabituation leads to the recruitment of attention to sudden physical changes regardless of which channel they occur in.

How the neural model and comparison mechanism underlying the orienting response (OR) manifest themselves physiologically has remained an open question, as emphasized by Cowan (1995). Possible physiological counterparts suggested by Näätänen (1990, 1992) are the N1 and MMN. However, the link between the MMN and OR is rather weak, as MMN is neither sufficient nor necessary for the elicitation of the OR. On the one hand, MMN does not always lead to an OR (Lyytinen, Blomberg, & Näätänen, 1992). On the other hand, given a series of identical stimuli with long ISIs, no MMN is elicited (Böttcher-Gandor & Ullsperger, 1992; Mäntysalo & Näätänen, 1987), though both N1 (Böttcher-Gandor & Ullsperger, 1992; Mänty-

salo & Näätänen, 1987) and the OR (Sokolov, 1960) are. With a conceptual marriage between N1 and MMN offered by the adaptation model, the problem is transformed into finding the correlational link between the amplitude of the genuine auditory response and the elicitation of the OR. Specifically, one might hypothesize a threshold level for the N1 amplitude above which an OR is always elicited, though, again, this threshold would probably depend on the current allocation of attention.

Further, the adaptation model could be seen to contribute to the theory of attention by offering a physiological explanation to both the nature of the memory trace and comparison process underlying habituation and dishabituation. It suggests that, the memory trace is a suppression of activity on the spatial map on which the stimulus is represented, the comparison process is this mapping itself. In terms of Cowan (1988), stimuli making contact with LTM can be seen as stimulus-selective cells being activated in various maps in the cortical sensory areas (as well as in areas performing more elaborate, e.g., semantic, processing). Therefore, the comparison process can be seen as being an integral part of LTM, and the contents of STM are equivalent to activation of the cells responding selectively to the stimulus. At the same time, the attentional focus, a subset of STM representations, is partly determined by the suppressive memory trace, which determines the strength of activations of sensory features in LTM. Repetitive stimuli are mapped onto suppressed parts of the relevant cortical maps, leading to attenuated, that is, habituated activations. The larger the change represented by a novel stimulus, the less it coincides with the suppressive memory trace on the map, and therefore the larger the dishabituation.

7.7. The Promise of Clinical Applications

MMN has been advocated as a tool for evaluating abnormal brain function in a large number of clinical conditions (Näätänen & Escera, 2000; see Section 1): "It can be registered in the absence of attention and with no task requirements, which makes it particularly suitable for studying different clinical populations" (Näätänen, 2003, p. 179). However, the usefulness of the MMN as a tool is restricted by issues of reliability and validity.

In the clinical context, the MMN has problems in terms of *specificity* (the probability that the measure gives normal readings for patients and control subjects not suffering from the clinical condition being tested for), *sensitivity* (the probability that the measure gives abnormal reading for patients), and *reliability* (the within-subject consistency of the measure across time). The general pattern, on the group level, seems to be that, when abnormalities in the MMN can be associated with a clinical condition, this abnormality is a diminished amplitude of the MMN, at which point speculation typically commences on whether the memory trace or comparison process has been affected. This is the case in conditions such as dyslexia and specific language impairment (for a review, see Bishop, 2007), schizophrenia (for reviews, see Javitt, 2000; Umbricht & Krljes, 2005), as well as degeneration due to aging and Alzheimer's disease (for a review, see Pekkonen, 2000), to name but a few (see Näätänen & Escera, 2000). An interpretation of these attenuations based on the memory-based approach, whereby only the subtraction curve is of interest, has difficulties differentiating between clinical conditions. An exception would seem to be provided by the study of Umbricht et al. (2003), who observed that the MMN attenuation can be used to distinguish schizophrenics from sufferers of bipolar disorder and depression. However, as

pointed out by the authors, this differentiation works only on the group level; at the level of the individual subject, the MMN offers a poor indicator of schizophrenia both in terms of specificity and sensitivity (i.e., many nonschizophrenics exhibit MMN attenuation, and many schizophrenic patients have robust MMN responses). The specificity of MMN is further undermined by the findings that, in healthy subjects, it is often difficult to identify the MMN (Dalebout & Fox, 2000, 2001; Joutsiniemi et al., 1998; Kurtzberg, Vaughan, Kreuzer, & Fliegler, 1995; Lang et al., 1995; McGee, Kraus, & Nicol, 1997; Ponton, Don, Eggermont, & Kwong, 1997; Sharma et al., 2006; see also Picton et al., 2000); for example, the identification rate for MMN to easily discriminable speech sounds can be as low as 29% (Dalebout & Fox, 2001) or even 25% (Wunderlich & Cone-Wesson, 2001), and as many as a third of healthy subjects fail to exhibit an MMN response to clearly discriminable frequency deviants (1000 vs. 1100 Hz; Lang et al., 1995). Clearly, as low and indistinguishable amplitudes occur commonly not only in clinical groups but in healthy subjects also, the MMN is a very unspecific measure of abnormal auditory processing.

The sensitivity of MMN as a clinical measure is difficult to evaluate because the vast majority of clinical studies have addressed alterations of the MMN on the group level only. Although attenuation of the MMN related to schizophrenia is a robust feature on the group level (for a review, see Umbricht & Krljes, 2005), and in some cases there is little amplitude overlap between schizophrenics and control subjects (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002), its sensitivity is weakened by results showing that many schizophrenics have MMN amplitudes of the same magnitude as nonschizophrenics (Bramon et al., 2004; Umbricht et al., 2003). Also, in one of the few studies to report on the MMN responses of individual subjects, Shafer, Morr, Datta, Kurtzberg, and Schwartz (2005) found cases where sufferers of specific language impairment had robust MMN responses but poor ability to discriminate speech sounds.

The intersession, trial–retrial reliability of MMN has been addressed in many studies with variable results (Chertoff, Goldstein, & Mease, 1988; Deouell & Bentin, 1998; Escera & Grau, 1996; Escera, Yago, Polo, & Grau, 2000; Frodl-Bauch, Kathmann, Möller, & Hegerl, 1997; Kathmann, Frodl-Bauch, & Heger, 1999; Lang et al., 1995; Pekkonen, Rinne, & Näätänen, 1995; Tervaniemi et al., 1999). Dalebout and Fox (2001) criticized these studies for not employing signal detection techniques to objectively validate the presence of the MMN (i.e., to avoid false positive identifications; see Dalebout & Fox, 2000; McGee et al., 1997; similar criticism can also be directed at the studies of Kujala, Kallio, Tervaniemi, & Näätänen, 2001, and Hall et al., 2006). Also, in the cases where MMN appeared to be reliable with only specific stimulus and recording parameters (Deouell & Bentin, 1998; Escera & Grau, 1996; Pekkonen et al., 1995), the trial–retrial correlations may have been spurious due to the large number of statistical tests performed. Indeed, Dalebout and Fox (2001), using objective signal detection techniques, found that the reliability of MMN could not even be addressed due to the very low MMN identification rate. In the specific case of language disorders, the MMN would seem to be an unreliable measure even on the group level. In her recent meta-analysis, Bishop (2007) found that the results linking MMN to dyslexia and specific language disorder are highly inconsistent in terms of effect size, statistical significance (i.e., many studies show non-significant effects), and even effect direction (i.e., in most studies dys-

lexia attenuates the MMN, but in some it is amplified). Also, there is little evidence linking effect size with disorder type or MMN attenuation with poor speech discrimination. Further, as pointed out by Bishop (2007), the MMN is unreliable as a clinical measure of sound discrimination in the sense that many patients who exhibit no MMN can, nevertheless, reliably discriminate the deviants from the standards (Shafer et al., 2005; Sharma et al., 2006). Similarly, in healthy subjects, it can be difficult to detect MMN even for easily discriminable sound contrasts (e.g., Dalebout & Fox, 2001; Lang et al., 1995; Wunderlich & Cone-Wesson, 2001). It seems, then, that the reliability of MMN can be questioned on multiple grounds. As Sharma et al. (2006) succinctly stated: "Despite MMN's great theoretical appeal as an objective measure of auditory discrimination, the poor reliability of MMN across individual subjects is problematic if MMN is to be used as a clinical tool for diagnosis of APD [auditory processing disorder]" (p. 1140).

In summary, the MMN is largely unspecific, insensitive, and unreliable with respect to the clinical conditions that have received attention as potential beneficiaries of MMN measurements. This means that the MMN has limited usefulness as a clinical tool, contrary to the claims to the contrary (Näätänen, 1995, 2000, 2003; Näätänen & Alho, 1995; Näätänen & Escera, 2000). These problems are likely to stem from the low signal-to-noise ratio brought about by the very definition of MMN as the subtraction between the averaged responses elicited by rare sounds on the one hand and frequent sounds on the other. The rareness of the deviant means that the number of presentations is necessarily limited, and thus the response to the deviant is inherently noisy. Also, as pointed out by Picton et al. (2000), the noise in the response to the standard is added to the noise in the deviant response in the subtraction procedure, and thus the MMN is noisier than the genuine, already noisy response to the deviant. Clearly, the adaptation model offers amelioration by suggesting that one should avoid using the subtraction curve altogether and concentrate investigative efforts on the genuine N1 responses, which, compared to the MMN, have superior trial–retrial reliability (Dalebout & Fox, 2001; Lew, Gray, & Poole, 2007) and signal-to-noise ratios (Martin & Boothroyd, 1999; see also Picton et al., 2000).

As demonstrated in Figure 11A,B, performing the MMN subtraction may lose much valuable information on the way clinical conditions modify brain function. Importantly, these modifications can occur for the response to the standard and/or the deviant. Thus, focusing only on the subtraction curve fails to reveal, for example, whether an abnormal MMN is due to alterations in the response to the standard or the deviant in terms of latency, amplitude, or both. Conversely, severe abnormalities of the ERP may, potentially, yield an MMN that appears to be normal. This may partly explain the low specificity and sensitivity of the MMN. In contrast, the study of the N1 to repetitive stimuli could offer a more fine-grained view into abnormal auditory processing. Namely, attenuations of the MMN can be traced down to at least four factors that can be observed in N1 measurements already: First, an abnormal slowing down of adaptation decay (i.e., an increase in memory span) would, in effect, lower the steepness of the ISI-amplitude curve of the N1 response (Figure 11C). This would result in a decrease of the MMN amplitude, especially when the interdeviant interval is short and intermediate (i.e., close to the exponential time constant of the ISI-amplitude curve; Figure 11D). Second, adaptation decay time might be diminished (i.e., memory span is
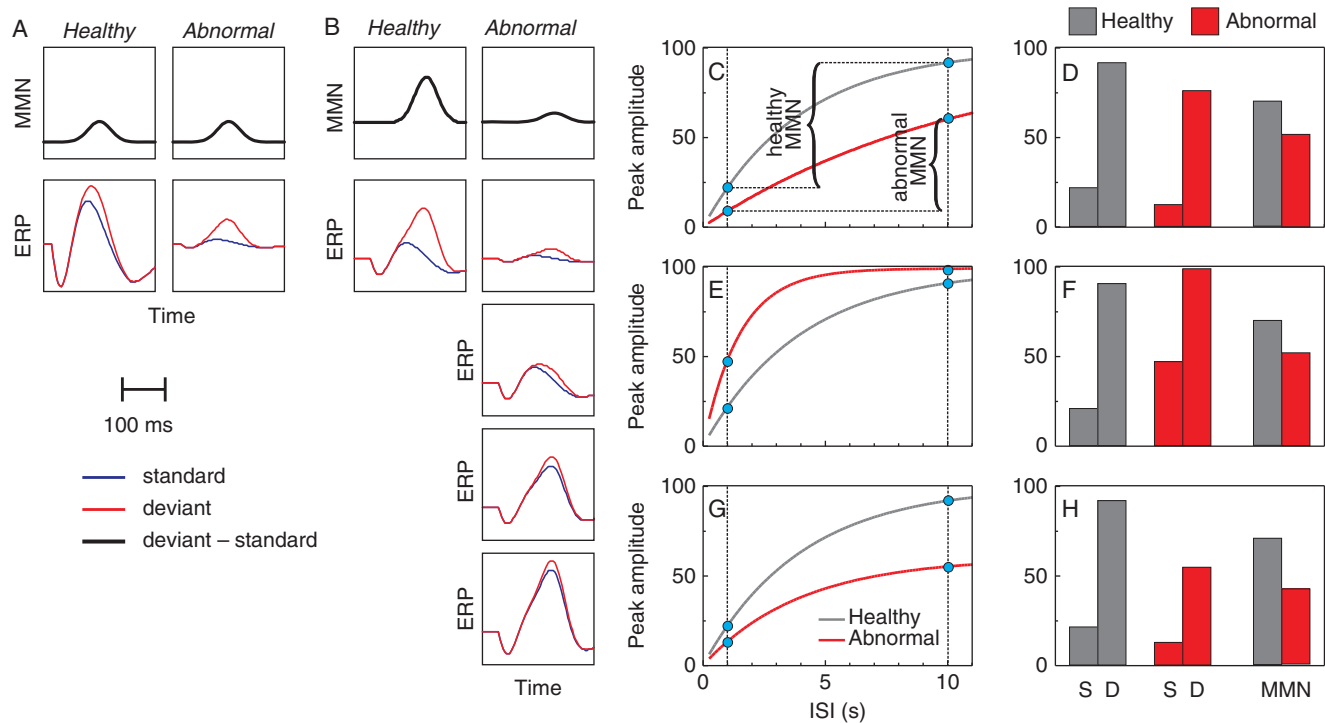
Figure 11. Hypothetical ERP measurements demonstrating how information about brain function is lost when focusing on the MMN only. A: The MMN may appear normal although the ERP is severely affected by the clinical condition. Thus, the sensitivity of MMN can be compromised. B: An abnormally weak MMN may result from any number of changes (both increases and decreases) in the latency and amplitude in the response to the standard, the deviant, or both. The MMN in itself does not reveal which changes have occurred. Thus, the specificity of the MMN is compromised in relation to that of the genuine ERPs. C: Possible causes of the diminished MMN are demonstrated in terms of abnormalities in the adaptation of the N1. The dependence of the amplitude of the N1 in normal subjects is described by an exponentially saturating function (black curve; N1[ISI] = A[1exp(ISI/τ)], 4-s time constant τ, asymptote $A = 100$). When adaptation decay is abnormally slow (red curve; $\tau = 11$ s), the N1 amplitude is diminished compared to the healthy N1. The amplitude of the response to the standard is estimated as the N1 elicited at the relatively short ISI of 1 s (left dotted line). The amplitude of the response to the deviant is estimated by the N1 presented at an ISI matching the average interdeviant interval (10 s). D: The peak amplitudes of the responses to the standard (S) and deviant (D) estimated from the N1[ISI] function are shown for the healthy (gray) and abnormal (red) case. The MMN responses, calculated as the D-S difference, are diminished in the abnormal case. E: When the N1 has an abnormally fast decay of adaptation ($\tau = 1.5$ s), the peak amplitude becomes enhanced. This effect is larger at short ISIs (i.e., at interstandard intervals) than long ISIs (i.e., interdeviant intervals). F: The result of the abnormality in the N1[ISI] function is, again, a diminished MMN response. G: Compared to the healthy N1, the strength of the response is diminished ($A = 60$) in the abnormal case. H: The result is, yet again, a diminished MMN in the abnormal case. Thus, the MMN is blind to a large variety of abnormalities that can readily be observed in the ERP/ERF. On this basis, the N1 and the genuine ERP/ERF may offer more powerful indices of abnormal brain function than the MMN.

shortened), in which case the ISI-amplitude curve is lifted, especially at short ISIs at which the standards are presented (Figure 11E). The resulting increased response to the standard would then diminish the MMN (Figure 11F). Third, although adaptation decay may remain unaffected, the N1 response strength may be proportionally lowered at all ISIs (Figure 11G). In terms of the ISI-amplitude curve, the upper bound of the curve is decreased, but the time constant is left untouched. This would decrease the MMN, especially at long interdeviant intervals (Figure 11H). Fourth, adaptation and response strength may remain intact, but the effect of the standard stimulus on the populations responding to the deviant may change. This could be brought about through modifications in the cortical projective fields and/or in the strength of lateral inhibition. For example, an increased overlap of the respective neural populations activated by the standard and deviant stimuli would diminish the MMN and, possibly, the behaviorally measured sound discrimination ability of the subject or patient. Changes in MMN may be due to any one of the above factors or a combination of them, but just looking at the difference curve, regrettably, leaves one blinded

and provides no information on how the ERPs/ERFs are affected by the clinical condition.

For example, both aging (Pekkonen, Jousmäki, Partanen, & Karhu, 1993; Pekkonen et al., 1996) and Alzheimer's disease (Pekkonen, Jousmäki, Könönen, Reinikainen, & Partanen, 1994) diminish the MMN to frequency changes when long ISIs of several seconds are used, but not when stimuli are presented at faster rates of 1/s. In view of the adaptation-based explanations discussed above, this could be a result of a lowering of N1 response strength at long ISIs. In accord with this, Papanicolaou, Loring, and Eisenberg (1984) varied the ISI in the 650–4650-ms range and found that aging dramatically decreases the N1 and P2 amplitudes at the slowest presentation rate only. Also, the results of Fabiani, Low, Wee, Sable, and Gratton (2006) suggest that at fast ISIs (400 ms), the N1 attenuates to a lesser degree in aged subjects than in young controls. A similar age-related enhancement of the N1 at short ISIs, although unanalyzed, seems to be evident in the results of Horváth, Czigler, Winkler, and Teder-Sälejärvi (2007). Taken together, these results suggest that aging may change adaptation and response strengths, in effect skewing

the amplitude-ISI function so that, at short ISIs, the N1s of aged subjects are more prominent than those of young subjects, but at long ISIs, the reverse is observed: Young subjects exhibit N1s of a larger amplitude than aged subjects. These changes then carry over to MMN measurements, diminishing the difference wave, especially at long ISIs. In addition, it is possible that a stronger cortical activation by the standard measured in the aged leads to enhanced lateral suppression, further diminishing the response to the deviant.

Although the link between MMN reduction and language disorders is unclear, there is a tendency to measure significant dyslexia-related attenuations of the frequency MMN when short ISIs are used (Bishop, 2007). In the context of the adaptation model, this could be due to a slowing down of adaptation decay. This abnormal extension of sensory memory may affect the processing of temporal information as suggested by the rapid temporal processing theory of language and literacy impairments (Tallal & Piercy, 1973a, 1973b). Also, an effect of weakened adaptation is evident in the case of dyslexic adults: In the study by Baldeweg, Richardson, Watkins, Foale, and Gruzelier (1999), one of the few studies to analyze (or even show) the responses to the standard, the attenuation of the MMN is accompanied by an increase in the amplitude of the N1 to the standard. Although this effect was found to be statistically nonsignificant, it does pose the question of what the contribution of an increased N1 to the MMN attenuation was in the other studies linking adult dyslexia with MMN but analyzing the difference wave only (e.g., Kujala, Lovio, Lepistö, Laasonen, & Näätänen, 2006; Kujala et al., 2000; Schulte-Körne, Deimel, Bartling, & Remschmidt, 2001).

The adaptation model provides for a possible explanation of the link between schizophrenia and a diminished MMN. This link has been intensively studied and appears to be a robust phenomenon (for reviews, see Javitt, 2000; Umbricht & Krljes, 2005), with MMN reductions increasing as the probability of the deviant is lowered (Javitt, Grochowski, Shelley, & Ritter, 1998; Shelley, Silipo, & Javitt, 1999). However, schizophrenia consistently diminishes the N1 also (Boutros et al., 1997; Clementz & Blumenfeld, 2001; Clunas & Ward, 2005; Ford, Mathalon, Kalba, Marsh, & Pfefferbaum, 2001; Gilmore, Clementz, & Buckley, 2004; Kayser et al., 2001). In studies where the ISI is varied, schizophrenics and healthy control subjects start diverging with respect to the N1 amplitude at ISIs beyond approximately 1 s, and the N1 reductions become increasingly large as ISI is increased (Roth, Goodale, & Pfefferbaum, 1991; Roth, Horvath, Pfefferbaum, & Kopell, 1980; Shelley et al., 1999). Clearly, in the framework of the adaptation model, the MMN is attenuated in schizophrenics because the N1 to the deviant is more reduced than the N1 to the standard. Also, as the probability of the deviant is lowered, the interdeviant interval is increased, leading to further reductions in the N1 to the deviant and, thus, to the MMN (although the difference curve may still have a weak dependence on the interdeviant interval; Javitt et al., 1998). It remains an interesting question what the actual effect of schizophrenia is: Is the adaptation time constant of the N1 increased or is the upper bound of response strength (i.e., of the ISI-amplitude curve) decreased? Interestingly, a further factor influencing the frequency MMN can be identified in organizational changes found in the auditory cortex of schizophrenics. Rojas et al. (2002), using magnetic N1 measurements, found that schizophrenia fundamentally alters the spatial representation of frequency in auditory cortex and suggested that this is expressed as less specific frequency tuning. In the framework of the adap-

tation model, this greater overlap between adjacent frequency representations would translate directly into diminished MMNs found in schizophrenics.

In sum, the adaptation model, by shifting the focus of investigation not only to the N1 elicited by the standard but also to that elicited by the deviant, may offer a palliative to the problems of reliability, sensitivity, and specificity afflicting MMN as a clinical tool. In all cases where the MMN is attenuated due to some clinical condition, the memory-based interpretation wipes out the information in the changes in the responses to the standard and deviant and leads to the unspecific conclusion that automatic change detection has somehow been compromised. In contrast, the adaptation model suggests that abnormal MMN can be explained as resulting from abnormalities in at least three separable factors: (1) adaptation decay time, (2) cortical response strength, and (3) the ability of cortex to discriminate differences between sounds.

Notably, the above effects can be measured directly, without using the oddball paradigm, with its inherent data quality limitations and long recording times. Changes in adaptation are best judged by using the N1 paradigm (i.e., repeating stimuli) and varying the ISI, thereby arriving at the ISI-amplitude curve. Further, it might be possible to measure the ability to discriminate two sounds by using an N1 paradigm where the response to a repetitive stimulus is compared to the response elicited by alternating stimuli (see Butler, 1972). The use of N1 measurements in clinical settings, as delineated here, would benefit from the superior reliability of the N1 response and could avoid confounding the effects of adaptation with discrimination ability. The N1 may also offer a clinical tool for studying aspects of cortical organization related to plasticity and learning (e.g., Tremblay & Kraus, 2002; Tremblay et al., 2001; see Section 7.3). Thus, the adaptation model may further widen the existing avenues of the clinical usefulness of the N1 as an objective measure of hearing thresholds and functional hearing loss (Hyde, 1997; Lightfoot & Kennedy, 2006). These attempts may also benefit from new ways to elicit transient, N1-like brain activity that predicts behavioral signal detection with high accuracy (Mäkinen, May, & Tiitinen, 2004; Matilainen et al., 2007; Talvitie et al., 2007; Tiitinen, Mäkinen, Kicic, & May, 2005; Tiitinen et al., 2007).

7.8. Modifications to the Theory of Auditory Processing
The memory-based model of MMN is at the center of the theory of central auditory processing proposed by Näätänen (1990, 1992). This theory stems from the tradition of information processing models popular in the 1960s and 1970s that described human cognition in terms of interconnected processing modules (e.g., Atkinson & Shiffrin, 1968; Broadbent, 1958; Waugh & Norman, 1965) or sequential processing stages (e.g., Sternberg, 1969, 1975). Similarly to these approaches, it renders auditory cortex as a flowchart of specialized channels and modules, each with a clear-cut function, and proposes that auditory analysis can be divided into *task-related* and *task-unrelated* varieties. The task-unrelated analysis is carried out by the *transient-detector* system generating the N1 and a parallel *permanent feature-detector* system providing information for sensory memory and the comparison process generating the MMN. In addition, the task-related analysis is carried out by a specialized system producing an attentional trace for use in selective attention tasks and generating the processing negativity (PN). Thus, the division corresponds with the interpretation of ERP results so that each

system produces its own, dedicated component of the event-related response. In this scheme, information flows mostly in a feedforward direction, targeting higher "executive" processes. Also, there is a clear division between attention-dependent processing producing the endogenous PN component and automatic, attention-independent processing occurring in the systems generating the exogenous N1 response and the endogenous MMN response.

By far the least complicated and most uninteresting response in this framework is the N1, generated by a system that detects the occurrence of transient events (i.e., changes in energy due to stimulus onsets and offsets). Admittedly, the status of the N1 has been upgraded since the early 1990s, and it is currently thought to index the "prerepresentational" activation of afferent neurons analyzing physical features of present sensory input (Näätänen & Winkler, 1999), thereby, presumably, causing fresh-afferent contamination to the MMN subtraction curve (see Section 7.4). In contrast, the MMN generator is thought to form predictions of sensory events through extrapolatory neurons (Näätänen, 1992) and stimulus representations through higher order, cognitive processes (Näätänen & Winkler, 1999), including sensory memory encoding, change detection, auditory stream formation and segregation, sound-object formation, preattentive sound anticipation, processing of abstract sound patterns, sound categorization based on relations between sound attributes, recognition and discrimination of familiar sounds, and permanent categorical sound perception, to name but a few (Näätänen et al., 2001, 2007). This imbalance in the sets of functional significances attached to the N1 and MMN is perplexing given that the responses are generated so close to each other in time and cortical location.

The theory of central auditory processing (Näätänen, 1990, 1992; Näätänen & Winkler, 1999) can be criticized and modified in light of the adaptation model and current neurophysiological evidence from auditory cortex. First, the adaptation model eliminates the many difficulties entailed by the theoretical position that the N1 and MMN *must* be generated by separate transient-detector and feature-detector systems. To begin, there is no need to expound the existence of afferent and extrapolatory neurons. In collapsing these two categories into one, the adaptation model abolishes the need to explain how extrapolatory neurons might operate and why they would *not* detect such a blatant change in the environment as a sound breaking a long silence. In this vein, there is no need to assume that two different systems perform detection of stimulus events that have the same behavioral and informational value: sudden changes in the environment manifesting themselves either as sound following silence or sudden change in a nonsilent environment. Instead, one might suggest that involuntary attentional shifting mechanisms (Cowan, 1995; Sokolov, 1960) are able to base their decision whether to act or not on information indicating how rare the stimulus is provided by just one system: the set of cell populations constituting auditory cortex, exhibiting various STRFs, and becoming adapted with repeated stimulation. Further, one can do away with the need to assume that one sensory area comprises two modular systems, a prerepresentational and a representational, cognitive one, operating according to different principles and with completely different functions. Also, as the theory of central auditory processing (Näätänen, 1990, 1992; Näätänen & Winkler, 1999) apparently requires two separate feature detector systems, one for the N1 generator and another one feeding the MMN generator, the adaptation model avoids the problem of explaining

why and how two sets of parallel feature processing systems have evolved and, importantly, where the independent physiological evidence for this duplication can be found (e.g., a suggestion in terms of the multiple tonotopically organized core areas would be a welcomed specific hypothesis that could actually be tested).

Second, the existence of the modular systems proposed in the theory by Näätänen (1990, 1992) is problematic from the point of view of the neuroanatomy and -physiology of the auditory cortex: In such a strongly recurrent system, with multiple feedforward, lateral, and feedback connections, it is difficult to see how any one, prerepresentational part could operate in functional and physiological isolation from other, more cognitive processes. Further, the suggestion that auditory cortex contains an automatic processing channel unaffected by task and attention is contradicted by the findings in animal models that the response properties of cells already in primary auditory cortex are modulated by top-down factors such as attention, expectation, and task (Durif et al., 2003; Fritz, Elhilali, David, et al., 2007; Fritz, Elhilali, & Shamma, 2005a, 2005b, 2007; Fritz et al., 2003; Ohl & Scheich, 2005; Polley et al., 2006; Selezneva, Scheich, & Brosch, 2006; for a review, see Jääskeläinen, Ahveninen, Belliveau, Raij, & Sams, 2007). In addition, fMRI measurements have revealed that memory and categorization tasks affect the activation of human auditory cortex (Brechmann & Scheich, 2005; Brechmann et al., 2007; Scheich et al., 2007). Indeed, with the N1 being associated with activation outside the core areas, namely, in the belt and parabelt areas of PT and STG (Inui et al. 2006; Jääskeläinen et al., 2004; Liégeois-Chauvel et al., 1994; Lütkenhöner & Steinsträter, 1998; Yvert et al., 2005), requiring previous core area activity (Kaas & Hackett, 2000), and with primary auditory cortex being "positioned at a confluence of bottom-up dedicated sensory inputs and top-down inputs related to higher-order sensory features, attentional state, and behavioral reinforcement" (Polley et al., 2006, p. 4970), it is hard to find any correspondence between the basic tenets of the MMN-based theory of auditory processing and current empirical and theoretical understanding of the physiology of auditory cortex.

A modified theory of auditory processing based on the current understanding of the auditory system should probably take into account that the auditory cortex is characterized by parallel and serial processing, where each area is influenced both by bottom-up sensory input and top-down input depending on the global state of the brain mediating task and attention effects. However, before this mainly physiological knowledge can be consolidated into an information processing theory, one should probably start by querying what the auditory system fundamentally does (i.e., by first formulating a "computational theory" in terms of Marr, 1984). As described by Bregman's (1990) theory of auditory scene analysis, the auditory system faces the twofold challenge of segregating multiple concurrent sound streams from each other and temporally integrating the information related to each stream into an auditory object. These phenomena have been approached in MMN studies (e.g., Sussman, 2005; Sussman, Ritter, & Vaughan, 1999; Winkler et al., 2003) but, as Snyder, Alain, and Picton (2006) put it, "although the MMN indicates that stream segregation has occurred, it reveals little about the neural mechanisms underlying streaming because it does not track ongoing processing of tone patterns" (p. 3). We tentatively hypothesize that stream integration could be indexed by sustained activity elicited by sound streams and that stream segregation is expressed by auditory cortex supporting separate,

spatially constrained "bubbles" of sustained activity. Preliminary support for this comes from the study of May and Tiitinen (2004a), who found that tones presented rapidly—that is, as a single stream—elicit a sustained response (see Section 6.4).

In their review, Fay and Popper (2000) pointed out that, because stream segregation is evident in vertebrates, including mammals, birds, and fish (for a demonstration of this phenomenon in insects, see Schul & Sheridan, 2006), it is probably the most basic task carried out by all auditory systems. Stream segregation might, therefore, not require the phylogenetically late arrival of the auditory cortex but, instead, might be carried out already by subcortical structures. As these structures also appear to analyze the spectral features of auditory input, this would leave auditory cortex the task of binding information over time, that is, integrating sound streams into auditory objects (for reviews, see Nelken, 2004; Nelken, Fishbach, Las, Ulanovsky, & Farkas, 2003). This task of auditory object formation is probably expressed in the cells in auditory cortex being sensitive to the spectral structure of sound *and* to its temporal context. It seems that the sound environment, including its temporal dimension, is represented at each moment by a set of variables evolving on multiple time scales: the spatial distribution of activity evolving on the near instantaneous, millisecond time scale and the synaptic efficacies changing on several time scales from tens of milliseconds to hours. Similarly, sound representation in auditory cortex is affected by top-down influences mediated on fast time scales (e.g., showing up as attentional enhancement and task dependence of activations and fast-acting modifications of receptive fields) and slower time scales (evident as perceptual learning). Attention may be seen as a global property of the entire auditory system, where the attentional focus expresses itself as a temporary enhancement of stimulus selectivity (i.e., the ability to carry out more fine-grained analysis) for a subset of cells responding to the stimulus being attended to, and where this enhancement, in terms of Cowan (1995), may be an expression of short-term memory. Thus, the system is inherently modifiable, lacking modules with fixed input–output transformations, but instead representing sounds spatially in a way that depends on context, task, and attention.

In this scheme, it would seem to be difficult to approach the functioning of auditory cortex through parceling the auditory ERP/ERF into "components," each with its own "generator" process. The component obviously loses its explanatory power both when it is defined at a coarse resolution encompassing all auditory areas and at a fine resolution capturing the specific pattern of activity within and across auditory areas (even assuming that this could be done). Specifying components on an intermediate level, in terms of the activation of the different areas of auditory cortex (once the areas of human auditory cortex have been fully charted), may also turn out to be unsatisfactory. Current evidence suggests that the snapshot of activations taken at the peak of an ERP/ERF deflection is part of a continuum of a continuously changing distribution of activity (e.g., Inui et al., 2006; Lütkenhöner & Steinsträter, 1998; Yvert et al., 2005) that would make the component structure also a continuously changing entity. Further, to characterize such dynamic behavior, the component approach may be inappropriate because of its inherent focus on localizing *activations*. Rather than occurring in isolation, activations are the result of regionally specific *interactions*, the description of which may be the key to a more complete understanding of auditory processing (Friston et al., 1996). Beyond this, one might envisage research trying to uncover how the

actual representations of sound are transformed in these interactions. Thus, although the peaks and troughs of the ERP/ERF continue to be useful landmarks for brain research, the concept of the "component" might be reaching the end of its usefulness. Rather than to postulate potentially fictional discontinuities in brain function, it may be more useful to try to untangle the time–space map of the evolution of cortical activity and the underlying connectivity supporting this evolution.

8. Adaptation and Information Processing in Auditory Cortex: A Synthesis

Despite the wealth of results pertaining to auditory cortex, the way the auditory system analyzes and represents natural, continually changing auditory environments is far from clear. The auditory system lacks the neat, organizational structure found in the visual cortex for representing scenes through overlapping feature maps (e.g., Swindale, 2000; Swindale, Shoham, Grinvald, Bonhoeffer, Hübener, 2000). As pointed out by Shamma (2001), this processing principle does not provide a straight analogy for the auditory system, which primarily binds stimulus entities across time rather than space: It is unclear what the auditory equivalent of the visual field could be. In this sense, the binding problem is especially hard to understand in the case of the auditory system because it is unclear what, in terms of neural representations, is to be bound. Therefore, stimulus selectivity in auditory cortex has an unclear computational purpose, and we still have a fragmentary picture of how the structure of the auditory environment relates to responses of individual cells or populations, what the functional purpose of attentional and other top-down modulations of activity is, and how stimulus-specific adaptation contributes to all of this.

The adaptation model explains the emergence of the MMN in terms of adaptation, but it leaves open one important question: In analyzing sound, what does auditory cortex really do with adaptation, the decline of neural responsiveness with repeated stimulation? In the context of MMN research, one could obviously argue that adaptation underlies auditory sensory memory. That is, although the presence of a stimulus is coded as activation of cells tuned to that stimulus, the memory for the stimulus—or, more properly, the statistical structure of past stimulation—is encoded as long-term suppression of activity for these cells. As discussed above, this coding scheme would agree with behavioral observations whereby a single presentation of a stimulus is sufficient for a sensory memory trace to be formed (see Section 7.6). However, it begs the question of how the information residing in this memory trace becomes accessible to other cortical processes, for example, those allowing human subjects to make appropriate judgments in psychophysical experiments (reviewed in Cowan, 1984). It is possible that adaptation forms sensory memory traces that are quiescent in the sense that their presence can only be detected by using probe stimuli (e.g., deviants in the oddball paradigm), and, in this context, the main role of adaptation and sensory memory might be to contribute to the change detection ability of the organism.

However, this linking of adaptation to sensory memory and change detection may be missing something important. Namely, understanding the computational solutions of sensory systems requires an understanding of their purpose in an evolutionary perspective (e.g., Churchland, Ramachandran, & Sejnowski, 1995). Although change detection may be of importance for

survival, is it really the primary function of auditory cortex (e.g., might this purpose be better served by the nonclassical auditory pathway leading to the limbic system)? Similarly, one could question whether sensory memory is the all-important end-all ability of auditory cortex (for a discussion on the validity of the concept of sensory memory, see Cowan, 1995). If the auditory cortex has other functions, how does adaptation contribute to these—could the purpose of adaptation be something more fundamental, with the sensory memory and change detection phenomena being merely by-products of this process?

The purpose of auditory cortex may become clearer by considering that natural environments hardly ever contain simplified, repetitive sounds utilized in laboratory conditions generally and in the oddball paradigm in particular. Instead, spectrally and temporally complex sounds abound (e.g., Nelken, Rotman, & Bar Yosef, 1999), and humans, among other organisms, are well adapted to perceiving their auditory environments as spectrally and temporally structured. Thus, one could propose that the auditory pathway is optimized for extracting this structural information. Nelken (2004) and Nelken et al. (2003) suggested that, as all auditory feature (spectral) information seems to be available already subcortically, in the inferior colliculus, it would make feature analysis a redundant task for auditory cortex. Rather, the purpose of auditory cortex would be to integrate the information provided by subcortical structures across time and thereby to form auditory objects. One could take the argument of Nelken and colleagues further by noting that biological cognitive systems as evolutionary products represent optimal solutions for information processing in species-specific contexts. Therefore, it is possible that to understand human audition one should start from the notion that human auditory cortex is specialized in forming auditory objects typical to human environments, such as those arising out of speech. On this basis, it becomes risky to use results based on the occurrence of rarely occurring "odd" stimuli within a stream of simplified, repetitive stimulation to construct general theories of auditory analysis.

Assuming, then, that the auditory cortex is geared toward extracting and recognizing structure in complex natural stimuli, the role of adaptation in the service of the auditory system becomes an intriguing question. The extraction of structure is reflected in a variety of cells, ranging from those exhibiting sensitivity to sequences of tones (Brosch & Scheich, 2008; Brosch & Schreiner, 1997, 2000; Brosch, Schulz, & Scheich, 1999; McKenna et al., 1989), tones and noise (Kilgard & Merzenich, 2002), and temporally modulated sounds (Bartlett & Wang, 2005) to those tuned to spectrotemporally complex stimuli. For example, in the lateral belt area of the maqacue monkey, cells exhibit selectivity to species-specific vocalizations (Rauschecker et al., 1995) and to the temporal order in which complex sounds are combined (Rauschecker, 1997). Whereas selectivity to a complex stimulus is expressed as increased firing of cells, stimulus-specific adaptation leads to decreased neural responses (Ulanovsky et al., 2003). Therefore, as the two apparently have opposite effects, it is not immediately clear how adaptation could contribute to selectivity to complex stimuli.

The relationship between adaptation and stimulus selectivity might be revealed by considering what the effect of adaptation is in a neural network when the afferent stimulation is "natural," that is, when it is in continuous flux and rarely becomes repetitive. One can approach this problem by forgetting, for the moment, the complexities of real biological networks of the brain and by considering classical artificial neural networks. So-called feedforward networks comprise a layer of input neurons that are connected to a layer of output neurons (either directly or via one or more layers of "hidden" neurons). The pattern of activity in the input layer (i.e., the stimulus) leads to a particular activation pattern in the output layer. Which input–output transformation is realized depends on the structure of the network, that is, the set of synaptic weights by which the neurons are connected to each other. Adaptation in this context can be described as the modification of each weight depending "locally" on the activation values of the cells connected by the weight. Thus, in the case of each output cell, the input changes not only the activation value of the cell but also the synaptic weights by which subsequent input is delivered. Consequently, the structure of the network changes after each stimulus in a stimulus-specific manner. Importantly, the input–output transformation now becomes dependent on the history of previous stimulation, that is, the set of past activity patterns *and* their temporal order.

In more formal terms, a simple network consisting of one input and one output layer of linear neurons connected to each other by the set of weights denoted by the matrix $\mathbf{W}$ effects the transformation $\mathbf{u} \rightarrow \mathbf{v} = \mathbf{W} \cdot \mathbf{u}$, where $\mathbf{u}$ and $\mathbf{v}$ are vectors describing the activity values of the input and output layer, respectively. (Here, for simplicity, the neurons display instantaneous dynamics, that is, they settle "immediately" into their input and output patterns.) Adaptation, having a much slower decay times constant (seconds) than the membrane time constant of neurons (tens of milliseconds), can in this simplified scheme be approximated by a set of quasistatic values $\mathbf{a}$ (0%–100%) by which the activity of the input neurons are multiplied: $\mathbf{u} \rightarrow \mathbf{v} = \mathbf{W} \cdot \mathbf{A} \cdot \mathbf{u}$ where $\mathbf{A}$ is a diagonal matrix with elements $\mathbf{a}$. The stimulus specificity and slow decay of adaptation can be incorporated by requiring that, at the presentation of a stimulus pattern $\mathbf{s}_i$, the adaptation vector $\mathbf{a} = \mathbf{a}_i$ depends on all the previous patterns $\mathbf{s}_{i1}$, $\mathbf{s}_{i2}$ .... Further, the contribution of each pattern to adaptation decreases with the number of intervening ones: $\mathbf{a}_i = a_i (s_{i-1}, s_{i-2} \ldots) = f(s_{i-1}, i-1) + f(s_{i-2}, i-2) + \ldots$, where $f(x, y)$ is a monotonically increasing function of y. Importantly, the output of this neural network now becomes dependent not only on the input and the weight matrix, but also on the previous input patterns *and* their temporal order: $\mathbf{u} \rightarrow \mathbf{v}$ ($\mathbf{u}$; $\mathbf{s}_{i-1}$, $\mathbf{s}_{i-2}$) = $\mathbf{W} \cdot \mathbf{A}_i$ ($\mathbf{s}_{i-1}$, $\mathbf{s}_{i-2} \ldots$) $\cdot \mathbf{u}$.

Already this extremely simplified example demonstrates that adaptation can, in principle, be used for more exciting things than to encode stimulus statistics and to detect oddballs. Namely, stimulus-specific adaptation, by bestowing *memory* to the network, gives it the characteristic of sequence sensitivity and thereby the ability to differentiate in its output temporally structured information. Further, if the input layer is equated with the tonotopic map, adaptation makes it possible for the neural network to process spectrotemporally complex auditory information, that is, potentially to discern and categorize ecologically valid signals such as speech (for a similar mechanism in terms of slowly decaying inhibitory postsynaptic potentials, see Buonomano & Merzenich, 1995).

Figure 12 demonstrates a biologically "enhanced" example of the above principle (May & Tiitinen, 2007): 500 cortical columns with dynamics similar to the ones used in the previous simulations, including adaptation with a 5-s decay time constant, were recurrently connected to each other, and the resulting network was presented with spectrotemporally structured stimulation, that is, two-tone stimuli with an SOA in the order of seconds as well as sequences of spectrally complex stimuli lasting several
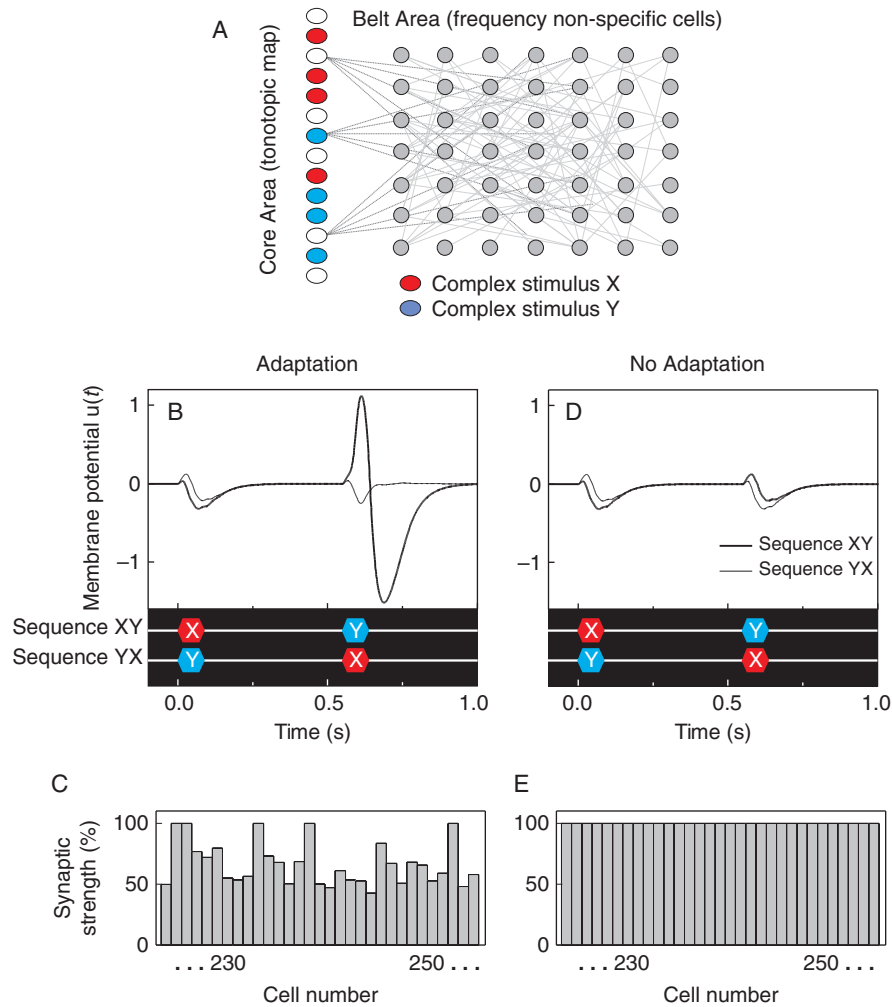
Figure 12. A: Schematic diagram of the model of temporal binding through adaptation. Spectrally complex stimuli activate specific (e.g., red or blue), tonotopically organized "core" area sites. This leads to activation of the nontonotopic columns of the "belt" area via random weights. In simulations, two types of complex tones (X and Y) were used, each activating a separate set of five core sites. B: In simulations where adaptation with a decay constant of 5 s was used, the belt area included units that responded only when the spectrally complex stimuli were presented in a specific order. In this example, the sequence XY elicits a prominent response, whereas when YX is presented, the unit responds only weakly. C: An example of how adaptation affects the synaptic weights is shown. Stimulus Y is about to commence, and stimulus X has resulted in a unique and complex configuration of synaptic weights. D: Adaptation has been removed from the network by decreasing the adaptation decay constant to 30 ms. As a result the selectivity to pairs of complex stimuli is removed. In this example, weak responses are elicited by both XY and YX sequences. E: The synaptic weights at the onset of Y following X form a uniform set. These simulations demonstrate that stimulus-specific adaptation provides a memory mechanism for the neural network, thus endowing its units with sequence sensitivity. Adapted from May and Tiitinen (2007).

seconds. Interestingly, the network contained cells that responded selectively to this stimulation, that is, they exhibited largest responses only at the end of each sequence (and attenuated responses to the spectral composition of the sequence end when presented in isolation). To show the contribution of adaptation to this selectivity, the adaptation decay constant was dropped to 30 ms. As expected, the resulting network, deprived of its memory, contained no sequence-sensitive neurons.

These simulation results demonstrate that adaptation could be what makes the auditory cortex tick. In fact, we propose that, although adaptation makes possible change detection and the generation of the MMN, its real purpose is to contribute to the main task of auditory cortex: to integrate information over time and to form representations of auditory objects. This hypothesis could be tested by expanding on the link found by Lu et al. (1992a) between behavioral measurements of sensory memory decay and N1 adaptation. For example, the simulation results of Figure 13 suggest that the time it takes the N1 to recover to its maximum strength could *directly* correlate with the maximum length of a repeated stimulus sequence at which the subject recognizes that stimulation is periodic. Also, one could suggest that adaptation, in fact, underlies the potential effectiveness of MMN as a clinical tool. That is, the myriad of clinical conditions that affect the MMN (see Näätänen & Escera, 2000) do so in virtue of an effect on adaptation in auditory cortex. As discussed in Section 7, this hypothesis could be verified by complementing clinical-MMN experiments by merely measuring the time constant of the recovery of the N1 (and perhaps combining these measurements, when appropriate, with behavioral testing of the patient's ability to integrate auditory information over time). If the N1 recovery time correlates with the severity of the clinical condition and behavioral measurements, one would, in the N1, have
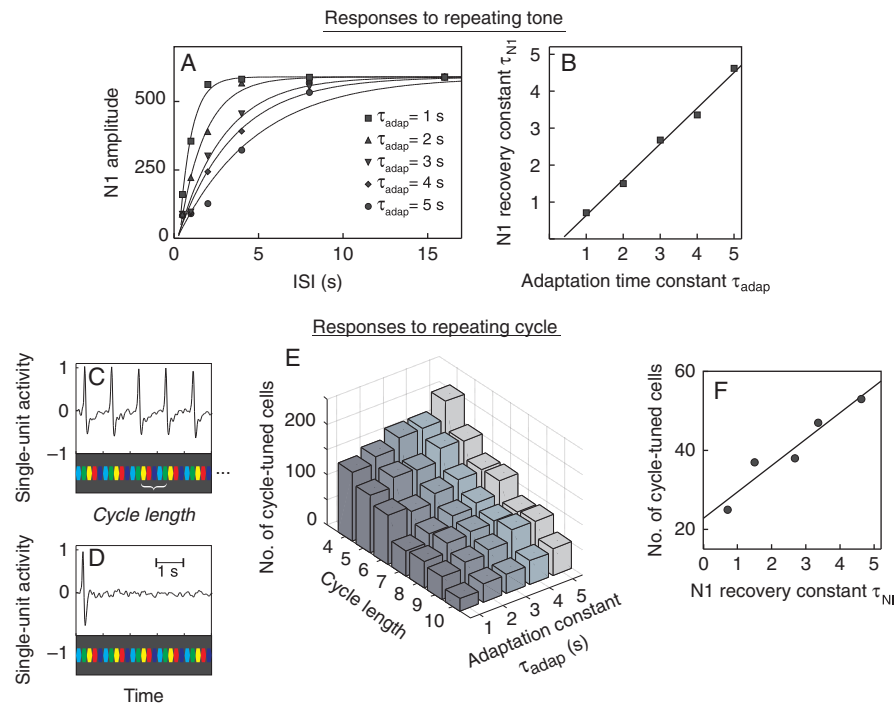
Figure 13. A demonstration of how N1 measurements may be used to predict the ability of auditory cortex to integrate complex information over time. A: The network shown in Figure 12 was presented with repetitive transient stimuli at different ISIs and using different adaptation decay constants. This resulted in a transient "N1" response whose amplitude increase as a function of ISI could be described by the exponential recovery function used in Figure 11 and by Lu et al. (1992b). As the adaptation time constant α_{adap} was increased, the recovery of the N1 peak amplitude became slower. B: The recovery time of the N1 was encapsulated by the time constant τ_{N1}. This had a linear dependence on the adaptation time constant. C: The network was presented with a "frozen" sequence of five different stimuli (i.e., repeated over and over). This example shows a unit that responded selectively to the repeating pattern, that is, a prominent response was elicited at each stimulus cycle. D: As an example of a unit that was not tuned to the repeating stimulus sequence, the figure shows the activity of a unit that responded only at the start of the stimulation but failed to react when the stimulus sequence was repeated. E: The number of units tuned to repeating cycles increased as cycle length was shortened. Importantly, it increased also as a function of the adaptation decay constant (which determines the N1 recovery as shown above). F: As a result, the number of cycle-tuned cells depends linearly on the N1 recovery time constant. Thus, in this model, the N1-ISI function can be used to predict the ability of the network to integrate complex information over time.

a more efficient clinical tool than the MMN. Finally, given that primary areas of human auditory cortex may have shorter adaptation time constants than secondary areas (Lu et al., 1992b), which is consistent with secondary areas having a lower temporal resolution (Giraud et al., 2000; Gourévitch et al., 2008), we can already begin to formulate the next step in the investigation: How are the variable adaptation time constants combined with the serial structure of the auditory cortex to subserve the formation of auditory objects?

9. Summary

Since its discovery by Butler in 1968, early descriptions in the 1970s (Snyder & Hillyard, 1976; Squires et al., 1975), and memory-based interpretation in 1978 by Näätänen and colleagues, the differential response to the deviant in the oddball paradigm—the MMN—has become an important phenomenon in cognitive neuroscience. This is evidenced by the array of cognitive and sensory processes it is claimed to reflect, the number of articles written about it, and the network of laboratories worldwide that use it. The MMN has even gained a dedicated scientific conference of its own.

However, the currently prevailing memory-based view of the MMN seems to have major problems that have been previously overlooked (see Section 3). For example, the rationale for extracting the MMN through subtraction is unfounded; there is no conclusive way to separate the MMN from the "exogenous" N1 component; there is no convincing neurophysiological evidence for MMN generation according to the memory-based interpretation; the memory-based interpretation has been constructed as a negation to the adaptation model (i.e., because the latter, apparently, *cannot* hold, the former *has to be* true). The memory-based interpretation, therefore, rules out an explanation of the MMN based on the known properties of auditory cortex, namely, adaptation and spatial representation of sound structure. Importantly, the rejection of the adaptation model and the validity of the memory-based model are based on circular argumentation (see Section 6.15).

On a brighter note, because none of the arguments against explaining MMN in terms of adaptation are watertight, there seems to be room to reconsider the merits of the adaptation model (Section 7): (a) An explanation of MMN in terms of adaptation would be aligned with the current view on the functioning of auditory cortex and offer ways of more tightly linking noninvasive measurements with physiological findings on sound representation, plasticity, perceptual learning, and

top-down influences on auditory processing. One may hope that this will result in MMN being nudged toward the limelight of mainstream physiological auditory research, thereby offering new ways of linking psychological concepts with descriptions of their neural underpinnings. (b) Although the adaptation model has here been offered as an alternative to the memory-based model, it, in fact, provides a bridge between the two levels of explanation represented by these models. In so doing, it also suggests new ways to explore the connections between noninvasively measured brain responses and behaviorally measured cognitive phenomena such as memory, sound perception, discrimination, attention, and learning. (c) The adaptation model is good news in terms of data quality and response reliability. Because the response to the deviant is an enhanced N1 response, there is no N1 contamination to worry about. Thus, one can avoid time-consuming control measurements for fresh-afferent activity. Crucially, in the context of the adaptation model, one can approach the response to the deviant, uncorrupted by noise introduced by the subtraction procedure, as a legitimate object of investigation. (d) In the framework of the adaptation model presented here, the MMN (that is, the deviance-enhanced N1) could be reevaluated as being a useful tool for cognitive neuroscience in virtue of its reflecting key features of auditory

processing in cortex, primarily adaptation and the spatial representation of sound. As such, past MMN results could be of value in the construction of physiologically viable models of auditory information processing. However, the oddball paradigm may not always be needed for studying the above features of auditory cortex. Instead, it may be possible to probe these through using conventional, high-quality N1 measurements. This might be beneficial, especially for developing the clinical applicability of noninvasively measured brain responses.

Finally, despite the effort and joy that has gone into critically reviewing and reinterpreting the deviance-elicited auditory deflection, the MMN, we feel we ought to temper our excitement. Namely, approaching auditory processing through MMN measurements may be missing something important: Although adaptation probably underlies MMN and change detection, it may have a more fundamental role in allowing auditory cortex to integrate sound information over time (see Section 8). Importantly, the strategies the auditory system uses to cope with natural sound environments can hardly be described in terms of change detection. That is, the ability to react to rare, mismatching events embedded in repetitive ones may just be a by-product of the main task of the auditory system: the segregation, or matching, of the soundscape into meaningful streams of sound.

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APPENDIX: NEURAL MODELING METHODS

Overview

We simulated tonotopically organized core, belt, and parabelt areas of auditory cortex. We also included populations of broadly tuned cells driven by afferent input from the thalamus. Each area comprised a set of interconnected columns, the dynamics of which were described through a model capturing recurrent excitation as well as the inhibitory effects due to adaptation, intracolumn synaptic inhibition, and, in the core area, lateral inhibition. These simulations were not intended to be a literal description of auditory cortex and, thus, should not be mistaken for proof of how the MMN is generated. Instead, they demonstrate that the framework of the adaptation model is compatible with the results of previous MMN research. Further, these demonstrations are offered as potentially helpful hypotheses for future research.

Column Model

The microcolumn is considered to be the basic anatomical and functional building block of cortex, and it shows stereotypy across cortical areas (for reviews, see Buxhoeveden & Casanova, 2002; Silberberg, Gupta, & Markram, 2002). It is characterized by feedback inhibition and strong recurrent excitation that amplifies the afferent input arriving from the thalamus (Douglas & Martin, 1990, 1991). In the present simulations, we used a simplified description of the column by pooling the excitatory and inhibitory cells into respective populations. Thus, each column i contained a pool of excitatory (pyramidal) cells with an average membrane potential u_i that was transformed into the average firing rate through a sigmoidal function g:

$$u_i(t) \rightarrow g(u) = \begin{cases} 0, & u \leq \theta \\ \tanh[\frac{2}{3}(u - \theta)], & u > \theta \end{cases}, \quad (1)$$

where $\theta = 0.1$ is the threshold for firing. The population average of the membrane potential of the pyramidal cells evolved according to the dynamic equation

$$\tau_m \dot{u}_i(t) = -u_i(t) + I_{rec}(t) + I_{inh}(t) + I_{lat}(t) + I_{aff}(t) + I_{ctx}(t), \quad (2)$$

where $\tau_m = 50$ ms is the membrane time constant (see Koch, Rapp, Segev, 1996), I_{rec} is the recurrent excitation due to local interactions (from the local and nearby columns), I_{inh} and I_{lat} represent synaptic inhibition due to local and lateral interactions, respectively, I_{aff} is the afferent thalamic input, and I_{ctx} is corticocortical input from other auditory areas.

For tonotopically organized columns with sharp tuning, the recurrent excitation is given by

$$I_{rec}(t) = \sum_j w_{ee}(i,j)k_j g[u_j(t)], \quad (3)$$

where $w_{ee}(i,j) = A_{rec} \exp[(ij)^2/0.5]$ is the strength of the excitatory connection between column i and column j. With the maximum strength of the afferent input being 1.0, we set the strength of the recurrent excitation to be an order of magnitude larger, $A_{rec} = 10$, so that the result is an effective amplification of the feedforward input to the column (Douglas et al., 1995).

The term for local synaptic inhibition was given by

$$I_{inh}(t) = w_{ei1}g[v_j], \quad (4)$$

where $w_{ei1} = 5$ is the synaptic weight between the pyramidal cell population and the inhibitory interneurons of the column. The dynamic variable v conveys the synaptic input from the interneurons and evolved according to

$$\tau_{inh}\dot{v}(t) = -v(t) + w_{ie1}g[u_t(t)], \quad (5)$$

where $w_{ie1} = 5$ is the weight of the synaptic connections mediating the driving input from the pyramidal cell population. The weights for local inhibition were chosen to satisfy the requirement that inhibition balances recurrent excitation so that the firing rate of the pyramidal cells is not driven into the saturation range. The time constant $\tau_{inh} = 50$ ms results in inhibitory input to the pyramidal cells with a time course corresponding to that of the fast inhibitory postsynaptic potentials (IPSPs) associated with GABA$_A$ synapses. These IPSPs peak at approximately 50 ms and last for 200–300 ms (for a review, see Nicoll, Malenka, & Kauer, 1990).

In accordance with results from the auditory cortex of monkey (Shamma & Symmes, 1985), lateral inhibition was restricted to the core area. In each column i of the core area, the term for lateral inhibition was given by

$$I_{lat}(t) = w_{ei2}g[y_t(t)], \quad (6)$$

where $w_{ei2} = 1$ is the synaptic weight between the pyramidal cell population and the interneurons mediating lateral inhibition. Lateral inhibition was driven by the activity of the pyramidal cells of the neighboring columns and evolved according to

$$\tau_{lat}\dot{y}_i(t) = -y_i(t) + \sum_j w_{ie2}(i,j)g[u_i(t)], \quad (7)$$

where $\tau_{lat} = 10$ ms is the onset time constant (when the right-hand side [r.h.s.] of Equation 7 is positive) and $\tau_{lat} = 1.5$ s is the decay time constant (r.h.s. < 0). The decay time constant was chosen on the basis of results showing that the lateral inhibition affecting N1 generation has a lifetime of seconds (Okamoto et al., 2004). Although the mechanisms of lateral inhibition in cortex are currently unknown, the slow IPSPs due to GABA$_B$ action have the required lifetime in the order of 1 s (for a review, see Nicoll et al., 1990) and could therefore be a contributing factor. Lateral inhibition originating from each column was symmetrically distributed in sidebands on either side of the column defined through the connection weights w_{ie2}, which had an intracolumn value of 2, a maximum of 6 at one column distance, and decreased linearly to 0 by distance 30.

In vivo results indicate that forward masking of cortical cells is due to synaptic depression rather than to IPSPs (Wehr & Zador, 2005). Accordingly, adaptation was assumed to affect the excitatory synapses of the model so that the effective synaptic weights become products of the constant weight terms $w_{ee}(i,j)$, w_{ie1}, $w_{ie2}(i,j)$ in column i and a time-evolving adaptation term $a_i(t)$, which depends on presynaptic activity originating from column j:

$$\tau_{adap}\dot{a}_i(t) = -a_i(t) - g[u_j(t)] + 1, \quad (8)$$

where $\tau_{adap} = 10$ ms is the onset time constant (r.h.s < 0), $\tau_{adap} = 5$ s is the recovery time constant (r.h.s. > 0). Although this is, of course, a minimalist description, lacking the multiple time scales of adaptation found in auditory cortex, it does, however, capture the essential combination of rapid onset of adaptation and slow recovery found by Ulanovsky et al. (2003, 2004).

The broadly tuned populations of each area were approximated as receiving the same feedforward input and being identically connected with other broadly tuned columns of the area. This allowed us to speed up computation time by describing the broadly tuned populations as a single lumped column per area. In this approximation, Equation 3 was transformed into $I_{rec} = A_{rec}ag[u(t)]$.

In the primary auditory cortex of cat, masking tuning curves (MTCs) can be narrower, equally wide, or wider than frequency tuning curves (Brosch & Schreiner, 1997; Calford & Semple, 1995). In the above model, forward masking displays two of these types: Due to the combination of adaptation and lateral inhibition, the MTC is broader than the frequency tuning curve for sharply tuned columns; for broadly tuned columns, the situation is equivalent with the MTC coinciding with the tuning curve.

Afferent and Inter-Area Connectivity

A total of four auditory areas were simulated in the Matlab environment. These corresponded to serially connected core, belt, and parabelt areas (Eggermont & Ponton, 2002; Kaas & Hackett, 2000; Pandya, 1995) and an area contributing to the P2 response. Each area comprised tonotopically organized columns with sharp tuning as well as columns exhibiting broad tuning. The presence of both types of cells in core and belt areas is supported by single and multi-unit measurements (Irvine & Huebner, 1979; Kajikawa et al., 2005; Merzenich & Brugge, 1973). Top-down connections were omitted in the current simulations, thus speeding up computation time by an order of magnitude. This omission can be partly excused by the results of Garrido, Kilner, Kiebel, & Friston (2007), who found that top-down connections affect primarily the shaping of neural responses at latencies greater than 200 ms, that is, beyond the range that is currently under investigation. It should also be noted that properly modeling the generation of the P2 should include the contribution of top-down activity.

The afferent input to each column of the core area was modulated between 0 and 1. Tonal stimulation targeting frequency-tuned column i resulted in nearby columns j also receiving input according to $I_{aff}(j,i) = \exp[(-i-j)^2/4]$. The frequency-location mapping was adopted from the Auditory Image Model (AIM; Patterson, Allerhand, & Giguère, 1995), with 420 columns corresponding to the hearing range of the AIM. Adaptation in precortical processing was ignored due to its relatively short decay time of milliseconds (e.g., Brosch & Schreiner, 1997). This is also consistent with the finding that auditory thalamic cells are insensitive to the probability of a stimulus in the oddball paradigm and that stimulus-specific adaptation underlying MMN is cortical in origin (e.g., Ulanovsky et al., 2003; see Section 5.1).

The connections between the core, belt, and parabelt areas were topographic. However, the projective fields from the core to the belt and the belt to the parabelt were more spread than those targeting the core. This was implemented in order to include the feature of the belt and parabelt areas whereby their cells exhibit tonotopic organization but respond more vigorously to narrow bands of noise than to tones (Kosaki, Hashikawa, He, & Jones, 1997; Rauschecker & Tian, 2004; Rauschecker et al., 1995). Thus, the feedforward excitation to column i of the belt area arriving from column j of the core area was $I_{ctx}(i,t) = w_{ff}(i,j)g[u_j(t)]$, where u_j signifies core activity and $w_{ff}(i,j) = A_{ff}\exp[(ij)^2/b_{ff}]$ is the

synaptic weight between the core and belt areas ($A_{ff} = 1$, $b_{ff} = 1$). A similar setup was assumed for feedforward activity from the belt to the parabelt area ($A_{ff} = 3.5$, $b_{ff} = 2$) and from the parabelt to the P2 area ($A_{ff} = 2$, $b_{ff} = 1$). For the broadly tuned cells, $I_{ctx}(i,t)$ was determined by setting $w_{ff} = 3$ for the core–belt and belt–parabelt inputs, and $w_{ff} = 1.5$ for parabelt–P2 input. The total number of simulated columns per area depended on the simulated experiment and comprised those activated by the stimulation. For example, in Figure 9, a total of 120 frequency-tuned columns were included in the simulations (= 1,920 variables in total).

Event-Related Responses

It is generally assumed that the MEG and EEG reflect the dendritic activity of pyramidal cells due to the parallel alignment of their apical dendrites (e.g., Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). The MEG/EEG response of the model was assumed to be directly proportional to the magnitude of the spatially summed excitatory input to the pyramidal cells. This approximation is justified by theoretical considerations (May, 1999) and simulation results (May, 2002) using realistic neuron models in the NEURON simulation environment (Hines & Carnevale, 2002). Also, intracortically obtained quantitative estimates and current-source density studies show that ERPs are generated by excitatory synaptic mass activities, with inhibitory inputs and neurons having only very minor contributions (for reviews, see Mitzdorf, 1985, 1994). Dendritic trees of inhibitory neurons are generally nonaligned, causing a closed field invisible to field potential and magnetic field measurements. Furthermore, although inhibition is an essential functional feature of cortical neural networks, inhibitory currents are far weaker than excitatory currents because the reversal potentials of inhibitory channels are much closer to the resting potential than are excitatory reversal potentials. For simplicity, as the electrically and magnetically measured N1 responses resemble each other quite closely (e.g., Huotilainen et al., 1998; Virtanen, Ahveninen, Ilmoniemi, Näätänen, & Pekkonen, 1998), we modeled the spatial gradient of the MEG only. To this end, the contribution of the activity of each area to the spatial gradient of the magnetic field was weighted by the cubed inverse distance of the area to the assumed sensor location. This is straightforward to derive from the magnetic field's diminishing according to the inverse squared distance between the source and the sensor (Hämäläinen et al., 1993). With these considerations, the MEG signal is given by

$$\text{MEG}(t) = \sum_k \frac{\alpha_k}{(d_k)^3} \sum_{i,k} (I_{rec}(i,t) + I_{aff}(i,t) + I_{ctx}(i,t)), \quad (9)$$

where k indicates area and column type (sharply vs. broadly tuned), d_k are the distances between sensor and source area, and α_k are weightings encapsulating the parameters of polarity, number of tonotopic maps and cells in each area, and the orientations of the cells depending on the curvature of auditory cortex. The distances for the different areas were: $d_{core} = 87$ mm, $d_{belt} = 78$ mm, $d_{parabelt} = 79$ mm, and $d_{P2} = 84$ mm. These estimates were derived from the study of Inui et al. (2006), showing source locations for activations in HG (core area) and PT (parabelt area). The 9-mm lateral shift in activity is also in line with intracortically obtained estimates of auditory cortex activation (Yvert et al., 2005). The distance for the P2 area was based on the

finding that the source of the P2 is 5 mm more medial than that of the N1 (Lütkenhöner & Steinsträter, 1998). The weightings for the tonotopic areas were: $\alpha_{core} = 1$, $\alpha_{belt} = 1$, $\alpha_{parabelt} = 3$, and $\alpha_{P2} = 2$. The corresponding weightings for the broadly tuned cells were multiplied by 10 to reflect the assumed larger number of columns responding to the stimuli. The polarities were chosen to match the results of Inui et al. The magnitudes were chosen so that the simulations in Figure 5 replicated the "double-peak" measurements where the N1 is followed by an MMN wave of comparable magnitude (e.g., Sams, Paavilainen, et al., 1985).