Mismatch Negativity and Stimulus-Specific Adaptation in Animal Models

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Abstract. Animal models of MMN may serve both to further our understanding of neural processing beyond pure sensory coding and for unraveling the neural and pharmacological processes involved in the generation of MMN. We start this review by discussing the methodological issues that are especially important when pursuing a single-neuron correlate of MMN. Correlates of MMN have been studied in mice, rats, cats, and primates. Whereas essentially all of these studies demonstrated the presence of stimulus-specific adaptation, in the sense that responses to deviant tones are larger than the responses to standard tones, the presence of real MMN has been established only in a few. We argue for the use of more and better controls in order to clarify the situation. Finally, we discuss in detail the relationships between stimulus-specific adaptation of single-neuron responses, as established in the cat auditory cortex, and MMN. We argue that this is currently the only fully established correlate of true change detection, and hypothesize that it precedes and probably induces the neural activity that is eventually measured as MMN.

Keywords: change detection, novelty detection, sensory memory, habituation, auditory cortex, electrophysiology

Introduction

Mismatch negativity (MMN) is a component of auditory evoked potentials in humans. It is measured using an *oddball design*: A sound sequence, in which rare sounds (*deviants*) are intermixed with a common sound (*standard*). Under these conditions, the deviant often evokes a stronger neural response, expressed as a more negative potential, than the standard (Näätänen, 1992). The MMN is usually defined operationally as the difference between the average evoked potential to the deviant and to the standard, and is interpreted as reflecting a process of change detection, whereby incoming stimuli are compared to a *sensory memory trace* of the standard stimulus, and an enhanced response is elicited when the sensory input differs from this memory trace.

The MMN has a number of features that makes it attractive for neuroscientists. On the one hand, it mirrors electrical activity that is related to higher organizational aspects of the sensory stream and, therefore, might provide information about higher order processing in the auditory system – providing an important link between the short term, single-sound research that is characteristic of current auditory electrophysiological research and the cognitive aspects of sound perception. On the other hand, it is preattentive and, therefore, can be studied in nonbehaving animals. Furthermore, it is reasonably easy to evoke and has been at least partially localized to auditory cortex, making it experimentally accessible.

Beyond its appeal for basic understanding of brain function, animal research allows the use of a perturbative, pharmacological approach to the study of MMN. MMN has been shown to be decrease under several pharmacological manipulations, and it would be helpful to study the effects of the same pharmacological agents at the single-unit, or even intracellular level, as this could shed light on the cellular and synaptic mechanisms that may be shared by the single-neuron responses and MMN. In the longer run, such research could provide therapeutic targets at the cellular level for treating various mental and neurological disorders that have been shown to be accompanied by a reduced MMN in human patients (Umbricht & Krljes, 2005).

A number of studies in animals have confirmed the presence of evoked potential components and local field potentials that are similar to MMN. A single-neuron correlate, however, remains elusive. We have recently described a single-neuron change response in cat auditory cortex, which shares many properties with MMN (Ulanovsky, Las, & Nelken, 2003).

We will begin this review by considering some methodological issues facing the study of the correlates of MMN in intracortical activity. We will then briefly review animal studies of MMN, and finally discuss our single-neuron results and their relationships with MMN.

Table 1. Summary of recording techniques used to study MMN correlates. The "spatial scale" represents the approximate radius of the brain-volume from which neural signals are integrated.

Technique	Spatial scale	Electric signals	Species	Parameter of deviance
Scalp-recorded potentials	30 mm (Freeman et al., 2003)	Synaptic potentials	Mouse (Umbricht et al., 2005)	Frequency, duration
			Human (reviewed in Näätänen, 1992)	Multiple parameters
Epidural potentials	3 mm (Freeman et al., 2003)	Synaptic potentials	Cat (Csépe et al., 1987; Csépe, 1995; Pincze et al., 2001, 2002)	Frequency
			Rat (Ruusuvirta et al., 1998; Lazar and Metherate, 2003; Eriksson and Villa, 2005; Astikainen et al., 2006)	Frequency, frequency × amplitude
Local field potentials	1 mm (Destexhe et al., 1999)	Synaptic potentials	Cat (Csépe, 1995)	Frequency
			Macaque (Javitt et al., 1992; Javitt et al., 1994; Javitt et al., 1996)	Frequency, amplitude
Multiunit activity (MUA)	0.1 mm (Abeles, 1982)	Spikes	Macaque (Javitt et al., 1992; Javitt et al., 1994; Javitt et al., 1996)	Frequency, amplitude
Single-neuron responses	0.01 mm	Spikes	Cat (Ulanovsky et al., 2003; Ulanovsky et al., 2004)	Frequency, amplitude

Methodological Considerations

Terminology

MMN is a scalp-evoked potential, and as such it could sum activity across many cortical areas. Single-neuron response components are, therefore, not MMN, even if they share many properties with the MMN.

Between the scalp-recorded potentials (which may reflect a mixture of a large number of sources) on one hand, and the single-neuron responses on the other hand, there exist other measurable neural signals that represent intermediate spatial scales (Table 1).

Epidural potentials, recorded with an electrode on the dura, are somewhat more spatially-confined than scalp-recorded potentials (Freeman, Holmes, Burke, & Vanhatalo, 2003). Local field potentials (LFPs), the slow potentials recorded from an electrode inside brain tissue, represent even more spatially-confined sources (Destexhe, Contreras, & Steriade, 1999). While an MMN-like effect in epidural potentials may still be a *bona fide* MMN, LFPs are too local to be called MMN – a correlate at the LFP level may, at best, represent a small portion of the currents that produce MMN at the scalp. Thus, the neural correlates at the LFP level – or smaller spatial scales, down to the single neuron level – require a different name in order to clearly distinguish between them from the "global" MMN signal, which reflects global activity across multiple auditory cortex fields.

The closest known single-neuron phenomenon to MMN is stimulus-specific adaptation (SSA). SSA is a decrease in the response to a repeated stimulus, which does not generalize to other stimuli. The use of the term "adaptation" here is somewhat unfortunate. According to Dudai (2002, p. 112), adaptation is "Use-dependent response decrement that occur because of sensory and peripheral processes." Stimulus-specific adaptation is not use-dependent (see below), and therefore is not adaptation in this sense. The right term for SSA is probably "habituation," defined as "The gradual diminution of the response to a stimulus following the repeated presentation of the same, or a similar, stimulus" (Dudai, 2002, p. 112). Among the hallmarks of habituation, according to Dudai (2002), are stimulus specificity; rate sensitivity; and dishabituation, a recovery following the presentation of another stimulus – all of which have also been observed in SSA (Ulanovsky et al., 2003; Ulanovsky, Las, Farkas, & Nelken, 2004). Thus, SSA should be properly called *single-neuron habituation*, but the term SSA has been used so often that it doesn't seem profitable to change it. It should be kept in mind that SSA, or single-neuron habituation, is a nontrivial effect – it cannot be accounted for by a modulation of the integration mechanisms of a neuron, since such changes would reduce all responses independently of the stimulus. Thus, use dependence or "fatigue" (e.g., changes in ion concentrations that reduce excitability, or increase in potassium currents in the soma, Sanchez-Vives, Nowak, & McCormick, 2000a,b) – all of which have been suggested as mechanisms of adaptation in the cortex – *cannot* account for SSA.

Properly speaking, the operational definition of MMN as the difference between the potentials evoked by standards and by deviants only shows the habituation aspect of MMN (presumably related to the formation of the memory trace, Näätänen & Winkler, 1999), and is not sufficient to demonstrate that it is sensitive to change *per se* (Jacobsen & Schröger, 2001). For that purpose, a number of additional controls are required, and these have been convincingly performed in human studies over the years. However, correlates of MMN in other neural signals reflect only part of the neural signals that give rise to MMN and, therefore, have to be retested with similar controls. Since we will argue that LFP correlates of MMN have not been controlled

tightly enough, we will use the term SSA when discussing both LFP and single-neuron responses; the term MMN will be reserved to scalp-recorded and epidural potentials.

Relationships Between MMN and Single Neuron Responses

It is commonly accepted that evoked potentials are caused by currents in the apical dendrites of pyramidal neurons of the cortex. When these currents are synchronous they produce an electric field that can be measured on the brain surface (Burkard, Don, & Eggermont, 2006). The currents that produce the evoked potentials probably represent mostly synaptic activity rather than spiking output (Burkard et al., 2006). Furthermore, a single neuron makes a tiny contribution to the surface potential, which is the result of the average activity of large neuronal populations.

As a result, there may be complex relationships between the single-neuron spiking activity, which is the usual variable measured when studying single neurons with a microelectrode, and the scalp-recorded evoked potential, which is the variable of interest when studying the MMN. In the simplest case, some spikes, forming a response component of a specific class of neurons in cortex, may have exactly the same properties as MMN. At the other extreme, it may be that there are no "MMN neurons" – rather, the input currents to many neurons have a small component that is MMN-like, and this component weakly modifies the responses of all neurons. If, however, this component is synchronous and occurs in a large enough neuronal population, it will sum up to a measurable evoked potential component on the surface. The reality may be anywhere between these two extremes.

Whereas most electrophysiological studies in animals use extracellular recordings, which report only spike timing of single neurons, it is possible (with additional effort) to record intracellularly from a neuron, getting the integrated membrane potential that drives the spikes of that neuron, which is a variable that reflects more closely the synaptic input than do the spikes themselves. Finally, new imaging techniques make it possible to record simultaneously from tens of single neurons, making it possible to study the correlations between them and, therefore, the presence of common, but weak, driving components of the kinds discussed above. All of these techniques may be necessary in order to fully identify the correlates of MMN in single-neuron responses.

In order to find the neural correlates of MMN, it is necessary to find the neurons that produce the currents that compose the MMN. Using the evoked potentials that are measured on the brain surface in order to derive the generator currents inside the brain is an ill-posed problem, having numerous, almost equally good, solutions (Lopes da Silva, Wieringa, & Peters, 1991). While it is mostly accepted that at least some of the generators of MMN lie in auditory cortex (Näätänen, 1992; Tiitinen, May, Reinikainen, & Näätänen, 1994; Picton, Alain, Otten, Ritter, & Achim, 2000), this still leaves a large territory to explore – auditory cortex of mammals has multiple fields (mouse: Stiebler, Neulist, Fichtel, & Ehret, 1997; rat: Doron, Ledoux, & Semple, 2002; cat: Nelken et al., 2004), some or all of which may be involved in generating MMN. Furthermore, MMN may be produced by activity outside auditory cortex (Deouell, 2007).Thus, the MMN recorded by a single electrode on the scalp may reflect a mixture of different response types from the different cortical fields, such as A1 (primary auditory cortex), A2, and AAF. This is particularly true for the smaller species (Table 1), in which an electrode may pick up signals from very large portions of the brain, or even the entire brain, as is probably the case in a tiny animal such as the mouse (Umbricht, Vyssotki, Latanov, Nitsch, & Lipp, 2005).

Properties of Auditory Neurons

Auditory neurons tend to have properties that complicate the interpretation of the results of many MMN paradigms. Consider a typical MMN study, in which the standard is a 1000 Hz tone and the deviant is a 1230 Hz tone. There is an implicit assumption in the subtraction of the evoked potentials produced by the standard and the deviant – the assumption is that the potentials produced by the two tones are equivalent, and that the only difference between them is caused by the manipulation of their probability within the sequence. This assumption is mostly valid when recording integrated responses such as scalp-evoked potentials (although there may be a general imbalance in the number of auditory-cortex neurons representing different frequencies). On the other hand, this assumption does not hold when studying single neurons. Single neurons throughout the auditory pathways tend to respond to pure tones within a restricted frequency range, which may depend on the amplitude of the sound (Pickles, 1988). Thus, even at the very periphery of the auditory system – in the auditory nerve – recording the responses of a neuron with a "best frequency" of 1230 Hz will produce larger responses to the 1230-Hz deviant than to the 1000-Hz standard in this example. Therefore, the usual operational definition of MMN cannot be used in the study of single-neuron correlates of MMN.

The problems posed by single-neuron selectivity are even harder in auditory cortex, and when studying MMN to more complex features. Some neurons in auditory cortex have offset responses that are sensitive to tone duration (He, Hashikawa, Ojima, & Kinouchi, 1997). Such neurons may mimic MMN for duration simply because of their sensory selectivity. Similarly, a deviant /pa/ over a background of standard /ba/ may give rise to spurious results because the onset of voicing may be strongly represented in the cortical responses to the /pa/ sound (Eggermont, 1995).

Recent studies of MMN for complex features are aware of these issues, and tend to at least partially control for

them. For example, the two sounds may be used in two different blocks, where one sound is used as a standard in one block and as a deviant in the other block (e.g., Pulvermuller & Shtyrov, 2003; Shtyrov & Pullvermuller, 2007). This control may, however, be insufficient when using complex sounds, because the adaptation patterns to the two sounds may differ. For example, each sound may contain a frequency component not present in the other one, giving rise to a simple frequency MMN that may be mistaken for an MMN because of a complex feature change. When studying single neurons, such methodological difficulties must be treated even more carefully, with sufficient controls for the physical aspects of the standards and deviants to exclude the possibility that the differences in responses are the result of physical differences in the stimuli.

In addition to stimulus selectivity, neurons in auditory cortex have complex temporal dynamics that may interact with the typical stimulus-presentation rates used for MMN studies. Although MMN has been measured with interstimulus intervals of several seconds, most MMN studies use higher stimulation rates – sometimes as high as three stimuli/s (e.g., Deouell, Parnes, Pickard, & Knight, 2006). One purpose of using such rates may be to reduce the purely sensory responses to the sound sequence, caused by "refractoriness" (Näätänen & Winkler, 1999), thus increasing the relative size of the MMN in the recorded signals. However, LFP and single-neuron responses are also "refractory" in a partially homologous manner: They are reduced when the stimulation sequence is fast and strongly dependent on the presentation-rate of the stimuli (Creutzfeldt, Hellweg, & Schreiner, 1980; Schreiner & Urbas, 1988). Although cortical neurons may follow repetitive stimulation at 3 Hz rather easily, their responses are, nevertheless, already reduced at this rate relative to, e.g., a rate of 1 Hz, especially in nonprimary areas (Irvine & Huebner, 1979). Thus, MMN paradigms that differ in their interstimulus intervals may engage very different mechanisms at the single-neuron level.

Controls

The considerations above imply that selecting the right controls for single-neuron MMN studies are extremely important. Differences in the size of the responses to two stimuli can occur because of many reasons.

The most important issue in the study of neural correlates of MMN, of course, is to determine whether the difference between the response to a standard and the response to a deviant is really the result of the relative rarity of the deviant. Just comparing responses to standards and to deviants is not good enough, because a larger deviant response may be the result of stimulus-specific adaptation, the reduction of the response to the standard, rather than because of any specific response to the change inherent in the rare appearance of the deviant stimulus.

Because of the possible interaction with stimulation rate, it seems that the best control here is the "deviant within many standards" approach (Jacobsen & Schröger, 2001). For frequency deviants, the deviant in such a block should be presented over a background composed of tones with many different frequencies, which span a relatively narrow frequency-range within the sensitive band of the neuron under study. Such a design controls for refractoriness and stimulus selectivity. This is the main control used in Ulanovsky et al. (2003). Another benchmark control is the "deviant without standards" control (Lazar & Metherate, 2003; Umbricht et al., 2005), in which deviants are played by themselves at the same rate in which they would appear in the oddball sequence (which is a much slower rate than the overall stimulus-rate in the deviant-with-standard block). In our view, this control is too strict, because it mixes together the effect of the strong rate-dependence of neural responses with the possible effect of the rarity of the deviant. This issue was indeed recognized by the MMN community (Jacobsen & Schröger, 2001; Schröger, 2007).

Next, it is important to control for the stimulus selectivity of the neuron. The first cure here is to compare the responses to the same physical stimulus in different blocks: one block in which the stimulus is the standard and another block in which the same stimulus is the deviant (i.e., switch from a standard-deviant block to a deviant-standard block). However, other features of the physical sequence may interfere with the interpretation of the results. For example, using two phonemes that vary in the shape of their power spectrum may lead to spurious results because the frequency content in a band that is present in one of the stimuli and not in the other may evoke a sensory response, or even a true MMN. In this case, it is incorrect to interpret the results as an MMN because of the detection of a change in the phonetic representation.

Controlling for such factors may be very complicated and requires a case-by-case verification. However, since thus far only a handful of examples exist for single-neuron correlates of MMN, we would argue that at the moment it makes sense to limit experiments to simple parameters such as frequency, amplitude, and duration, for which appropriate controls are reasonably easy to devise.

MMN and Animal Research

We will briefly summarize MMN studies in animals. Because of the problems in interpreting MMN to complex sounds in terms of neuronal responses, we will concentrate on studies that used simple acoustic features. Thus, we exclude here the studies of Kraus and colleagues (e.g., Kraus, McGee, Littman, Nicol, & King, 1994; King, McGee, Rubel, Nicol, & Kraus, 1995) and a recent paper by Erikson and Villa (2005), both of which used speech sounds to study change detection in animals. While both studies are important, they are less relevant to the goal of this paper.

Table 1 summarizes the studies that we are aware of on

MMN and related responses in animal models. There is an interesting dichotomy between the studies in rodents, which are primarily negative, and studies in carnivores (cat) and primates (macaque), which have reported positive results.

Both Umbricht et al. (2005, awake mice) and Lazar and Metherate (2003, anesthetized rats) reported no MMN to frequency deviants. In both studies, responses to deviants in the deviants-with-standards condition were compared to the responses to deviants in the deviant-alone condition (i.e., deviants in one condition were compared to deviants in another condition). Consistent with these results, an earlier study in rats (Ruusuvirta, Penttonen, & Korhonen, 1998) reported the presence of weak MMN when comparing deviants to standards but not when comparing deviants to deviants-alone. Umbricht et al. (2005) reported a weak MMN to duration deviants in mice; to the best of our knowledge, duration deviants have not been tested in rats.

In contrast, MMN was reported in cats using epidural electrode arrays (Csépe, Karmos, & Molnar, 1987; Csépe, 1995; Pincze, Lakatos, Rajkai, Ulbert, & Karmos, 2001). These studies compared the responses to deviants with the responses to standards. In Csépe's work, for example, the standards were 4 kHz tones and the deviants 3 kHz tones, with a rather high presentation rate of 2–3 stimuli/s. Under these circumstances, MMN-like potentials were also recorded in the auditory thalamus and in the preceding auditory station, the inferior colliculus (IC).

MMN was also reported in primates (Javitt, Schroeder, Steinschneider, Arezzo, & Vaughan, 1992; Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo, 1994; Javitt, Steinschneider, Schroeder, & Arezzo, 1996, all reports are in *macaca fascicularis*). Javitt and colleagues studied frequency deviants and amplitude deviants (deviants were low-level clicks over a background of louder standard clicks), mostly recording local field potentials. They compared the responses to the deviants with the responses elicited by the same stimulus when it was standard. Deviants elicited additional activity in the supragranular layers of primary auditory cortex. In addition, infusion of NMDA antagonists abolished the additional activity associated with the deviants, suggesting that NMDA receptors are important for the generation of MMN (Javitt et al., 1996).

While the presence of extra activity to low-level clicks is a powerful finding, the control used (in which the deviant stimulus was presented at the same rate as the standard) is appropriate for deducing the presence of SSA, but is insufficient to conclude that a true MMN has been evoked. Therefore, we prefer to call these findings SSA.

The almost dichotomic difference between the oddball responses in cats and primates and the lack of oddball responses in rodents may well be a species difference. However, there is another difference between the two sets of studies: The nature of the control condition. Whereas both of the rodent studies used as a control the responses to deviants played at a low rate (comparable to the rate of the deviants in the presence of standards), the cat studies subtracted standard response from deviant response, and in the primate studies, a high-rate sequence of deviants was used as a control. Thus, in the rodent studies, the negative results could be related to the use of a substantially stricter control. As mentioned above, this control may be unnecessarily strict.

Novelty Responses in Single Units

Stimulus-specific adaptation at the single-neuron level in the mammalian auditory system has been studied in a number of different paradigms. Oddball sequences have been used to study single-unit responses in rats (Perez-Gonzalez, Malmierca, & Covey, 2005) and in cats (Ulanovsky et al., 2003; Ulanovsky et al., 2004), but other paradigms indicating the presence of SSA have been tested in the gerbil (e.g., Spitzer & Semple, 1993), cats (Zhang, Nakamoto, & Kitzes, 2005; Nakamoto, Zhang, & Kitzes, 2006), and primates (Malone, Scott, & Semple, 2002).

Any review of short-term changes in neuronal responses must start by mentioning the studies of Weinberger and his colleagues, who were the first to realize the importance of short-term plasticity for auditory processing, and who mapped to a large extent the whole range of phenomena that are studied today. Specifically, Condon and Weinberger (1991) showed the presence of stimulus-specific adaptation in the auditory cortex of anesthetized cats. They alternated between stimulus-blocks in which they measured the frequency selectivity of neuronal clusters (using a series of tones with different frequencies), and stimulus-blocks that consisted of a single pure tone "standard." They demonstrated a small but highly specific reduction in the responses to the standard, occurring within minutes of the presentation of a standard-block and lasting for an hour or more. The importance of this paper was in demonstrating highly specific changes in what was considered as a major "invariant" of neuronal responses, the tuning curve. However, the time scale of this effect was far too slow to account for the fast buildup and breakdown of the trace that is manifested in MMN.

Fast stimulus-specific adaptation has been reported in the inferior colliculus and in the auditory cortex by a number of authors. Semple and coworkers (Spitzer & Semple, 1993; Sanes, Malone, & Semple, 1998; Spitzer & Semple, 1998; Malone & Semple, 2001; Malone et al., 2002) studied dynamical interaural cues (either phase or level) and demonstrated that the responses of neurons to the final interaural value depend on the history of stimulation. These effects were already strong in the IC, and became even stronger in auditory cortex (Malone et al., 2002). The interpretation of SSA in inferior colliculus was, however, challenged by McAlpine, Jiang, Shackleton, & Palmer (2000), who showed that the responses to the dynamic stimuli could also be accounted for by the history of the *response* rather than the history of the *stimulus*, suggesting simple adaptation mechanisms rather than stimulus-specif-

ic adaptation (i.e., they argued for *refractoriness* rather than single-neuron habituation as defined above). Nevertheless, the cortical effects are extremely strong and may well be shown to be stimulus-specific.

Of particular importance here are studies of responses to tone pairs, which go under the general name of "forward masking" in the single-neuron auditory literature. A number of such studies have been conducted in auditory cortex (Calford & Semple, 1995; Brosch & Schreiner, 1997; Wehr & Zador, 2005; Zhang et al., 2005; Nakamoto et al., 2006). Generally, a stimulus can affect responses to subsequent stimuli for hundreds of milliseconds after its offset, with recovery on the order of 1 s. While this finding may be a correlate of the refractoriness in the evoked potentials, there are strong indications that this refractoriness is, in fact, stimulus-specific. The stimulus-specificity issue was explicitly addressed by Zhang et al. (2005), who showed that the effectiveness of a stimulus in inhibiting later responses depended on how close it was to the best stimulus of the neuron, rather than on whether it was effective in eliciting a response. Thus, the forward masking was not the result of sensory adaptation, since even a stimulus that elicited a weak response, but was close to the best stimulus of the neuron, resulted in a subsequent suppression of the response to a best stimulus, while a stronger response to a stimulus farther away from the best stimulus could result in less suppression. Finally, at least some of these effects are cortical, as demonstrated by comparing thalamic and cortical suppression by Wehr and Zador (2005).

We hypothesize that the suppression found in these forward masking experiments, specifically its stimulus-specific aspects and cortex-specific, long time course, serve as a building block for creating the memory trace that is probed by oddball sequences in MMN experiments. However, many of the properties of this forward masking are incompatible with MMN, showing that, by itself, it is insufficient to account for MMN (Zhang et al., 2005; Nakamoto et al., 2006). For example, the suppression caused by a best-frequency tone is stronger on tones with frequencies away from the best frequency than on subsequent best-frequency tones. This is the reverse of the expected behavior of a "memory trace," which should presumably result in greater suppression of the same stimulus than of different stimuli.

In order to study MMN proper, it is necessary to use stimulus sequences in which a "trace" is generated, requiring multiple repetitions of the standard before a deviant occurs. Perez-Gonzalez et al. (2005) used such sequences in the rat IC. In this study, a certain stimulus parameter was kept constant for a number of stimuli (10–25), and then switched to a different value in an increasing (or more rarely, decreasing) order. The parameters were frequency, amplitude (at best frequency), duration, and modulation parameters. A small subset of neurons (25/409 cells, 6%) showed stimulus-specific adaptation, in the sense that their response decreased while the parameter value was constant but recovered once the parameter was changed. Of these, 22 neurons could be localized histologically and all of them were located outside the central nucleus of the IC. The authors conclude that novelty detection occurs in IC and presumably propagates to cortex. As a control, the authors used a randomized stimulus sequence, approximating the deviant-within-many-standards configuration. Unfortunately, the paper does not present an explicit comparison of the specific responses at the "novel" trials with the responses to the same stimuli at the randomized stimulus sequence (unlike Ulanovsky et al. 2003, where such a comparison was explicitly done). Thus, it is unclear whether the recovery of the response in this small subsample of neurons had a true component of change detection, or was solely a recovery of an adapted sensory response. Furthermore, stimulation rate had to be rather high (typically 4 stimuli/s, with only a few cases tested at 2.5 stimuli/s), and the acoustical differences between stimuli were rather large (i.e., large differences in frequency between standards and deviants, and similarly large distances for the other acoustical parameters tested).

Ulanovsky et al. (2003, 2004) tested neurons in primary auditory cortex and auditory thalamus of the cat with oddball sequences. In A1, they demonstrated strong and highly sensitive SSA for frequency deviants and a significant SSA for level deviants as well. SSA was widespread even at extreme stimulus parameters (frequency ratios of 10%) and was significant (although small) even for frequency ratios of 4%. These frequency ratios are substantially smaller than the width of frequency tuning curves of auditory cortex neurons (Ulanovsky et al., 2004; Moshitch, Las, Ulanovsky, Bar-Yosef, & Nelken, 2006), and also smaller than the width of peripheral tuning curves in the cat (Liberman, 1978). The effects were strong at a stimulation rate of 1.36 stimuli/s, and were significant even at a stimulation rate of 0.5 stimuli/s (although they disappeared at a rate of 0.25 stimuli/s). Two controls were used in this study: First, the probabilities of the two stimuli were switched, so they were presented both in a standard-deviant block and in a deviant-standard block (as well as in a 50–50% block). Second, the main control was to use the same tone as a deviant within many standards: Significantly higher responses to deviants over a background of a single standard were measured at frequency ratios of 10% and 37%, compared to the many-standards condition. At the same slow rates and small parameter differences, a restricted sample of thalamic neurons (from all subdivisions of the thalamus) did not show significant effects, either individually or as a population. Ulanovsky et al. (2003) concluded that the effects they measured were mostly cortical in origin.

Perez-Gonzalez et al. (2005) concluded that novelty detection already occurs in IC. In support of their conclusions, other studies reported SSA in mammalian IC (but see the caveats above). On the other hand, Ulanovsky et al. (2003, 2004) concluded that SSA is cortical. Why are there differences between these studies? There may be a number of nonmutually exclusive explanations. (1) Differences in the stimulation sequences. The stimulation paradigm and anal-

ysis were different in the two studies. In particular, stimulation rate was substantially faster in the rat study, and the acoustical differences between the standard and the deviant were larger. It is conceivable that the cortical mechanisms become more important at more extreme parameter values – i.e., at slower repetition rates and smaller acoustical differences. As mentioned above, SSA has been reported in cat IC and MGB by a number of groups, but for more extreme parameter values (see discussion in Ulanovsky et al., 2003). (2) Differences in the controls. Perez-Gonzalez et al. clearly showed the presence of stimulus-specific adaptation, but did not show that their responses were the result of change detection. (3) Differences in species. It could be that in the cat, SSA is more cortical whereas in the rat it already occurs in the IC.

Independent of these possibilities, there are some striking differences between the results in IC and in A1. In cortex, a substantial fraction of all neurons showed SSA at extreme parameters (frequency ratios of 10% and rather slow repetition rate) – approximately 76% of the neurons recorded in A1 (81/107) – whereas in the rat IC only a small minority (less than 6%) showed such effects. Furthermore, A1 is considered as a core station of the auditory pathways, whereas the effects in IC were localized to belt areas (ICx), which are known to be under strong cortical control. Thus, we believe that currently the simplest account of the IC results is that they reflect the massive feedback from auditory cortex to the IC, rather than being created *de novo* in the IC and propagating to A1.

Table 2. Comparison of the properties of MMN, as summarized from the literature, with properties of SSA, as reported by Ulanovsky et al. (2003, 2004)

Properties of MMN	Properties of SSA
(MMN = deviant – standard)	(DS = deviant – standard)
MMN exists in anesthetized cats	DS exists in anesthetized cats
MMN localized to auditory cortex	DS exists in auditory cortex
MMN magnitude monotonically related to Δf	DS magnitude monotonically related to Δf
MMN magnitude inversely related to probability of deviant	DS magnitude inversely related to probability of deviant
MMN latency inversely proportional to Δf	DS latency inversely proportional to Δf
MMN latency longer than latency of responses to the standard	DS latency longer than latency of responses to the standard
MMN increases with trial no.	DS increases with trial no.
MMN decreases for long interstimulus intervals	DS decreases for long interstimulus intervals
MMN stronger in the presence of one standard than in the presence of many standards	DS stronger in the presence of a standard than in the presence of many standards
MMN shows 1-trial effect even in 50–50% blocks, i.e., a stronger response when the current stimulus is preceded by a different stimulus in the previous trial	DS shows 1-trial effect even in 50–50% blocks, i.e., a stronger response when the current stimulus is preceded by a different stimulus in the previous trial
MMN exists for amplitude deviants	DS exists for amplitude deviants

DS = deviant – standard, in single auditory-cortex neurons.

SSA and MMN: Similarities and Differences

The survey of animal literature presented above suggests that because of the controls used, all the LFP and single-neuron correlates of novelty detection available today should be considered as SSA. In fact, of all of the animal studies reviewed here, only Ulanovsky et al. (2003) showed explicitly the presence of change detection, because the appropriate controls have not been used in other studies or have been used and failed.

So, assuming that the cat results, which are the most extensive at the moment, are typical of the mammalian auditory cortex in general – can we say that the SSA found in auditory cortex is a correlate of MMN?

As argued in Ulanovsky et al. (2003), there are many close analogies between SSA and MMN, summarized in Table 2. First, the magnitudes of MMN and of the SSA are both positively correlated with the frequency-difference between the standard and deviant (Δf) but negatively correlated with the probability of the deviant. Second, both MMN and SSA exist when comparing the responses to a deviant tone in a block containing a single standard, with responses to the same tone in a block containing many equiprobable tones. These two properties establish SSA in cat auditory cortex as a true index of change detection. In addition, the temporal dynamics of MMN and SSA are also similar: The latency of both MMN and SSA decrease with increasing acoustical difference between standard and deviant (i.e., negative correlation with Δf); the latency of the deviant-standard difference is longer than the latency of the sensory response; the magnitude of MMN and SSA increases over the course of a few standard trials; and their magnitude decreases with increasing interstimulus intervals. In addition, SSA in single neurons is evoked even in 50–50% blocks – when there are no standards or deviants to speak of – if one compares the response to a tone that is preceded by a different sound with the response to the same tone preceded by an identical sound (Ulanovsky et al., 2004); this local-context effect, termed the "1-trial effect," was observed also in MMN from humans (Sams, Alho, & Näätänen, 1983, 1984; Jaaskelainen et al., 2004).

On the other hand, there are some clear differences between MMN and SSA, as described by Ulanovsky et al. (2003, 2004). The most important of these is the timing of the SSA responses. Although they are delayed relative to the onset of the sensory response, they are nevertheless earlier than expected, even relative to the epidural poten-

tials recorded in the cat (Pincze et al., 2001). The fact that SSA in primary auditory cortex is expressed earlier than it should be, if it is to account for the corresponding evoked potentials, would suggest that the additional activity measured as SSA in primary auditory cortex is not the activity that produces the currents that are eventually interpreted as MMN. Instead, the most parsimonious explanation of this apparent inconsistency would be that SSA in primary auditory cortex is "upstream" of MMN generation: In other words, primary auditory cortex detects the change that would evoke MMN, but the MMN itself reflects the responses not only of primary auditory cortex, but also of higher auditory-cortical fields, which may have longer response latencies and whose responses depend on the earlier activity in A1. This view is consistent with the results by Pincze et al. (2001), which showed that MMN in cats is larger above A2 than above A1. Thus, as mentioned above, it is necessary to record LFP and single-unit responses to oddball stimuli in multiple fields of the auditory cortex, including at least A1 and A2, in order to determine the temporal relations between SSA in A1 and MMN across the entire auditory cortex.

Additional arguments against a role for SSA in the generation of MMN have been summarized by Näätänen, Jacobsen, & Winkler (2005). Whereas most of these arguments use the highly detailed phenomenology of MMN in humans and cannot be easily transferred to the cat or to other mammals, there are two arguments that may be tested in animal studies. The first is the presence of MMN for omitted stimuli (Näätänen, 1992), and the second is the presence of MMN when the standard is not defined as a single physical stimulus but rather by a conjunction of properties, or by a continuous trend – i.e., MMN to abstract changes (e.g., Tervaniemi, Maury, & Näätänen, 1994). Since these paradigms have not been tested in animals, we do not know at present whether they evoke MMN or similar novelty potentials.

However, it is important to note that the adaptation that Näätänen et al. (2005) seem to consider is of the afferent refractoriness type, and certainly does not have the rather sophisticated habituation-like properties of the SSA as described above, particularly by Ulanovsky et al. (2003, 2004). Importantly, habituation is considered a type of learning (albeit possibly the simplest type of learning: Dudai, 2002). Because of its nontrivial properties, single-neuron habituation (i.e., SSA) should be considered as a correlate of a memory trace, rather than as a purely afferent process. Thus, the coexistence of afferent-like and memory-like properties in SSA of auditory-cortex neurons may reconcile, to some extent, the different views about the role of afferent vs. memory-based mechanisms in MMN (Näätänen et al., 2005). Our suggestion is that the electrical activity that gives rise to MMN is neither purely afferent nor purely memory-related, but is both of the above – giving rise to the rich, varied, and still somewhat mysterious neural mechanisms underlying MMN.

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