ERP Repetition Effects and Mismatch Negativity Generation

A Predictive Coding Perspective

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Abstract. Neuronal adaptation is a ubiquitous property of the cortex. This review presents evidence from MMN studies that show ERP components with similar adaptive properties. Specifically, I consider the empirical evidence from the perspective of a predictive coding model of perceptual learning and inference. Within this framework, ERP and neuronal repetition effects (repetition suppression) are seen as reductions in prediction error, a process that requires synaptic modifications. Repetition positivity is a human auditory ERP component, which shows similar properties to stimulus-specific adaptation of auditory cortex neurons; a candidate mechanism for auditory trace formation.

Keywords: mismatch negativity, auditory processing, adaptation, predictive coding, schizophrenia, repetition suppression

Background

Mismatch negativity is one of the most studied and best understood human ERP components (Näätänen, 1992). Our considerable knowledge of MMN has undoubtedly enriched understanding of sensory memory and promoted its application to the study of developmental and neuropsychiatric disorders. Nevertheless, there are still critical issues to be resolved if MMN research is to deepen our understanding of the biological mechanisms involved. This is particularly true for research into schizophrenia, a disorder that, so far, has escaped a thorough description of the underlying pathophysiology. MMN deficits in patients with schizophrenia have been replicated many times since the original observations by Shelley et al. (1991), making MMN a robust biological marker of this complex mental disorder (reviewed in Umbricht & Krljes, 2005).

In this brief review I argue that computational models of perceptual learning can provide a framework to refine neurophysiological investigations of MMN generation, to foster understanding of its pharmacological modulation, and ultimately to help identify cortical mechanisms at fault in schizophrenia and other disorders. Here, I will focus on ERP repetition effects to standard tones that precede the elicitation of mismatch potentials by deviants. Our motivation for studying such effects, using MMN, was to illuminate the process of stimulus encoding into sensory memory thought to be impaired in schizophrenia as evidenced by behavioral data (Strous, Cowan, Ritter, & Javitt, 1995). Interest in stimulus repetition effects has also arisen from the quest for neural correlates of priming (Henson, 2003; Grill-Spector, Henson, & Martin, 2005).

The brain is organized according to two main principles: Functional specialization and segregation on the one hand, and functional integration on the other (Friston 2002, 2003). While the former is increasingly well understood, thanks to anatomical and neuroimaging investigations, the mechanisms of functional integration remain a challenge for contemporary neuroscience, requiring methods with resolution in both time and space. Given the considerable architectural complexity of the human brain, such an endeavor appears to be possible only when informed by computational principles of neural mass action and functional interaction between multiple cortical sites.

Here I will review ERP evidence in the light of a theory of perceptual learning (inference) proposed by Friston (2003), which attempts to tackle the problem of functional integration from a computational perspective, while being constrained by realistic neuroanatomical principles (Felleman & Van Essen, 1991). The main attraction of this theory for the present review is that it makes specific predictions for the behavior of ERP components elicited in oddball tasks such as those commonly used to elicit MMN (Friston, 2005a).

A Model of Perceptual Learning and Predictions for MMN Generation

The reader is referred to Friston (2003, 2005a) for a comprehensive neurobiological and mathematical treatment of the model (see also Rao & Ballard, 1999). Here I review some of its basic tenets as they appear relevant to MMN.
Multiple MMN Generators

A central assumption of the model is that perceptual learning is implemented via changes in connection strength between hierarchical sensory processing stages. This implies that prediction error (i.e., mismatch) signals can be elicited at each stage. The evidence for multiple mismatch generators is so far based on (a) the topographical distribution of MMN components, (b) the dependence of MMN components on experimental factors, (c) recent neuroimaging data, and (d) invasive ERP recordings in human and animal studies (for further discussion see Deouell, this issue).

Näätänen and Michie (1979) were first to suggest that MMN is composed of two subcomponents: a sensory-specific component generated in auditory cortices and a separate frontal component. It has been noted that the frontal (scalp negative) and temporal (scalp positive) MMN components are differentially dependent on stimulus characteristics such as the side of the stimulated ear (Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991). These two components also show distinct developmental changes (Gomot, Giard, Roux, Barthélémy, & Bruneau, 2000) and are differentially affected in patients with schizophrenia, with predominant impairment of the frontal MMN, while the temporal component is largely intact (Sato et al., 2003; Todd, Michie, & Jublonsky, 2003; Baldeweg, Klugman, Gruzelier, & Hirsch, 2002, 2004). These two components can also be distinguished by current source density distribution (Giard, Perrin, Pernier, & Bouchet, 1990), peak latency (Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000), and in response to attentional competition (Shalgi & Deouell, 2007). The label of “frontal” MMN does not necessarily imply a frontal cortex origin; it merely refers to its scalp distribution, which could also arise from generators along the lateral (Scherg, Vajsar, & Picton, 1989) and rostral portions of the superior temporal gyrus (STG), areas which contain high-order auditory cortices (Kass & Hackett, 1998). Invasive MMN recordings also point to multiple generator sites, including auditory cortex, association cortex of the STG (Kropotov et al., 1995, Halgren et al., 1995; Rosburg et al., 2005), as well as lateral (Baudena, Halgren, Heit, & Clarke, 1995; Liassis, Towell, Alho, & Boyd, 2001) and medial frontal cortex (Rosburg et al., 2005). While the latter locations require confirmation, the existence of STG generator sites outside A1 appear to be a more robust finding across animal (Csepe, Karmos, & Molnar, 1987) and human studies. Converging evidence for multiple generators comes also from neuroimaging studies (e.g., Mueller, Jueptner, Jentzen, & Muller, 2002; Opitz, Rinne, Mecklinger, von Cramon, & Schroger, 2002; Doeller et al., 2003).

It is less certain, at present, if there are functional interactions between these multiple generators, and if so, what their nature is. Notwithstanding the possibility that they could be activated in parallel by common input, their functional characteristics, such as dependence on physical stimulus characteristics and time course (Näätänen, 1992), so far support the hypothesis that the frontal activity is initiated by auditory cortex change-detection mechanisms (Näätänen & Michie, 1979; Rinne et al., 2000). In contrast, it is claimed that this bottom-up attentional function is a proposal based on fMRI studies that the fronto-temporal network activated during frequency deviance detection is involved in top-down contrast enhancement (Opitz et al., 2002; Doeller et al., 2003). However, the best evidence for such top-down modulation of auditory change-detection comes from studies showing MMN attenuation in patients with lesions of the dorsolateral prefrontal cortex (Alho, 2002).
Dependence on the Probabilistic Structure of the Stimulus Sequence

The oddball paradigm used to elicit MMN is a convenient model of perceptual (i.e., stimulus-to-stimulus) learning, where temporal information (of past stimulus) is used as a contextual (top-down) cue that must be weighted against the sensory (bottom-up) inputs. The model, therefore, predicts that the probabilistic properties of the stimulus sequence (global probability of events, local sequence effects) are encoded in the form of prior probability estimates (priors). Indeed, the dependence of MMN on deviant probability is a well-established experimental fact (Näätänen, 1983; Sams, Jarvilehto, & Soininen, 1983; Sams, Alho, & Näätänen, 1983; Imada, Hari, Loveless, McEvoy, & Sams, 1993), independent of interdeviant interval effects (Javitt, 1993) where the frequency of the standard tones changed abruptly (Ulanovsky et al., 2003, 2004; Nelken & Ulanovsky, 2005). Instead (Ulanovsky et al., 2003, 2004; Nelken & Ulanovsky, 2005). This notion is compatible with the observation that MMN subcomponents are differently sensitive to deviant probability. It is mainly the frontal MMN component that is probability dependent while the temporal component is much less so or not at all (Sams et al., 1983; Sato et al., 2000; Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005).

Another view on the differential adaptivity of the frontal and temporal MMN components suggests the possibility that the frontal MMN generator encodes the probability structure of the stimulus environment (i.e., generates top-down predictions), while the temporal component represents an error signal generated in a lower sensory level (Baldeweg et al., 2004; Haenschel et al., 2005). Clearly more evidence is needed to determine functional roles for MMN components and such progress will depend on the ability to accurately separate and localize MMN subcomponents (Rinne et al., 2000; Sato et al., 2000; Shalgi & Knight, 1998).
its modulation by attention suggests that RP may have multiple generators outside A1 – in analogy to MMN – but these remain to be determined.

Furthermore, because we changed the number of standards before the deviant in each stimulus train (i.e., the first of the new frequency standards), the ensuing MMN showed the expected memory trace effect, i.e., the MMN difference wave increased with the number of preceding standards. However, this effect was entirely because of the increase in RP with repetition, while the deviant negativity did not change. Again there is agreement with neuronal responses in cat A1: Rapid and stimulus-specific adaptation occurred only to repeated standards, but not to deviants (Ulanovsky et al., 2003). This is entirely consistent with perceptual learning of the standard as the main explanation for differences between responses to the standard and oddball stimuli.

The P50 repetition effect also allowed us to examine the controversial issue of the contribution of new (fresh) afferent input to MMN at the level of primary auditory cortex (A1) (see Näätänen, Jacobsen, & Winkler, 2005 for further discussion). At issue is the question if MMN is a differential response in the auditory cortex between habituated (by repeated standards) and nonhabituated (responding to deviants) N1 neurons (adaptation hypothesis proposed by Jaaskeläinen et al., 2004) compared to the alternative notion of MMN being elicited by neurons coding a memory representation of the standard stimulus (Näätänen, 1992). We predicted that if new afferent input contributes to MMN in the P50 latency window, then a stimulus (i.e., deviance) effect should be visible irrespective of the number of repetitions (i.e., a difference in P50 between frequency deviant and standards). However, no such effect was found; for neither passive nor active task conditions. In contrast, the stimulus (deviance) effect in the P50 window was significantly dependent on the number of standard repetitions (Figure 1D): P50 to deviants was larger (more positive) after less or equal than 6 standards (i.e., showing a repetition effect) but smaller after 36 (i.e., showing a mismatch effect). This suggests that the early detection of a deviant stimulus in A1 depends on a comparison with a memory trace of the standard, rather than new afferent input to A1.

These data also imply that increasing trace strength (i.e., number of repetitions) leads to more rapid mismatch detection starting from around 30–50 ms onward, visible also in the shortening of the onset latency of mismatch difference waves (data not shown in Figure 1), an effect accelerated by overt attention to the sounds (Haenschel et al., 2005). This early latency effect is also visible in other roving standard studies (Baldeweg et al., 2004; Baldeweg, Wong, & Stephan, 2006) as well as during the early (perceptual learning) phase of constant-standard experiments (Baldeweg, Williams, & Gruzelier, 1999). This effect could be

![Figure 1](http://example.com/figure1.png)
caused by two separate processes: either an acceleration of neural computation in the same auditory area or the backpropagation of auditory memory traces from higher to lower sensory levels with increasing trace strength resulting in earlier mismatch detection at lower processing levels. Preliminary findings from a combined ERP/fMRI study are indeed supportive of the latter hypothesis (Blankenburg et al., in preparation).

It is important to stress that the reported repetition effects in human ERP have so far only been observed for tone frequency, while in vivo recordings in A1 also showed SSA to sound intensity (Ulanovsky et al., 2003) and interaural phase disparity (Malone, Scott, & Semple, 2002). Clearly, further human studies are needed to test if similar repetition effects can be observed to other stimulus features.

Another interesting question concerns the RP correlate of long-term auditory memory traces, which can be probed passively using MMN as demonstrated by Näätänen, Schroer, Karakas, Tervaniemi, and Paavilainen (1993). Indeed, preliminary evidence (Figure 2) suggests that more persistent traces result in larger RP and enhanced MMN with shorter onset latency. Such traces were elicited in an experiment where one frequency standard (800 Hz) was presented 14 times more often than any of the other tones amid a sequence of 12 roving frequencies. Because at least three other roving frequency trains intervened before a repetition of the 800 Hz tone, progressively more persistent traces of this sound must have survived over the duration of the intervening trains. Further study is needed to identify the RP correlates of very short-term adaptation (over seconds and without intervening stimuli) from those of more long-term trace formation (i.e., a preattentive form of familiarity, lasting over tens of seconds to minutes and across intervening items). Again, there are parallels with neuronal adaptation (SSA) effects in A1 lasting over multiple, nested time-scales of similar duration (Ulanovsky et al., 2004).

Figure 2. Standard ERP, repetition positivity (RP), and MMN to persistent memory traces of an 800 Hz standard tone compared to other roving frequency standards. Results of a pilot experiment (Baldeweg, unpublished observation) in 9 healthy volunteers (4 female; age range 24–35 years) using a roving standard protocol as in Baldeweg et al. (2004) using either \( n = 2, 6, \) or 18 standard repetitions in each stimulus train. The 800 Hz tone was presented 14 times more often than any of the other 12 roving frequencies (ranging from 750–1200 Hz) and a minimum of three other stimulus trains intervened before its repetition. (A) mean standard ERP to \( n = 6 \) and 18 repetitions; (B) mean RP obtained by subtracting standard ERP to 2 repetitions from those to 18 and 6, respectively (according to Figure 1). Note the enhanced RP to 800 Hz tone compared to other roving standards. (C) mean MMN difference waves to 50 ms duration deviants immediately following the last standard (combined after 6 and 18 repetitions, all 25 ms duration). Note that the MMN following 800 Hz standard is enhanced and shows shorter onset latency compared when following other roving standards.

Neuromodulatory Effects on RP and MMN Generation

The predictive coding model postulates that learning effects (suppression of prediction error) must involve modulatory backward connections between hierarchical sensory levels. This implicates NMDA-type glutamate receptor and Ach receptor-dependent plasticity. In contrast, the propaga-
tion of prediction error per se, via forward (bottom-up) connections is mediated mainly via fast AMPA-type glutamate receptor-dependent processes (see Friston, 2005a, for further details). In the model Ach acts via modulation of NMDA-type glutamate receptors (Gu, 2000; Stephan, Baldeweg, & Friston, 2006). We, therefore, predicted that neuromodulation using antagonists and agonists of the NMDA and Ach receptors would influence the RP, inasmuch as it reflects the process of repetition suppression (and learning), while the negativity in response to the deviants (i.e., prediction error and inference) should be much less affected by such drugs.

The findings of two separate placebo-controlled studies in healthy volunteers confirm this hypothesis. The first study tested the influence of acute nicotine administration on RP and MMN using the roving-standard experiment (Baldeweg et al., 2006). Twenty healthy adult volunteers were assigned randomly to receive either a nicotine gum or placebo after a baseline ERP recording. Nicotine administration augmented MMN amplitude in the treatment group compared to the baseline recording, while no MMN change was found in the placebo group. The drug effect was the result of a selective enhancement of the frontal RP while the negativity to deviants remained unaffected. Furthermore, under nicotine stimulation this repetition positivity showed a more marked increase with stimulus repetition compared to baseline and placebo.

A second study tested the effect of the anesthetic ketamine (i.v. infusion, placebo: saline) in 18 healthy volunteers in a double-blind, cross-over design on RP and MMN using the same stimulation protocol (Baldeweg, Moelle, Merle, & Born, in preparation). Ketamine, like phencyclidine, is a noncompetitive antagonist of the NMDA receptor, which opens in response to binding of the neurotransmitter glutamate. Again, drug effects were found exclusively in ERPs to standards: The RP was reduced in the time window of 50–200 ms (p < .001) while the deviant negativity was unaffected. In contrast to the nicotine study, the ketamine effect on RP was more pronounced after few repetitions (less or equal to 6) than after many (n = 36), suggesting that these two neuromodulators influence short-term auditory plasticity with somewhat different time scales.

Independent evidence for a NMDA receptor role in MMN generation comes from studies in monkeys (Javitt, Steinschneider, Schroeder, & Arezzo, 1996) and humans (Umbricht et al., 2000), however, no specific test of RP effects was possible in those studies (see also reviews by Kahkonen, 2006; Umbricht & Krljes, 2005; Leung, Croft, Baldeweg, & Nathan, 2007). We have argued elsewhere (Stephan et al., 2006) for the utility of MMN in investigating the neuromodulatory effects on synaptic plasticity during human perceptual learning.

In summary, the evidence for neuromodulatory effects on RP and MMN available so far suggest that RP is particularly sensitive to such effects, in agreement with the predictions outlined above. More direct tests of neuromodulatory effects on the cortico-cortical connectivity between different MMN generators are under way using the DCM method (Stephan et al., 2006, Garrido, Kilner, Kiebel, Stephan, & Friston, 2007).

Discussion

Many of the points raised and interim conclusions drawn in this review are still speculative. However, the prospect of advancing our knowledge about the principles of functional integration in hierarchical sensory systems using MMN will undoubtedly stimulate further research. For example, model generalization across other sensory modalities can be tested using MMN to visual and somatosensory stimuli. While the predictions made at the outset have been supported by available empirical evidence, further experimental tests are needed in both human and animal models of MMN. It is possible that the more conventional, purely feedforward models, based on Hubel- and Wiesel-type cell properties of increasing receptive field complexity (Koch & Poggio, 1999), can account for the observed MMN effects. For example, feedback connections may only serve to modulate response magnitude in lower sensory levels, i.e., mediating selective attention (Koch & Poggio, 1999; Felleman & Van Essen, 1991). However, specific proposals would need to be developed, which can be tested experimentally, as suggested here for MMN. Before concluding I will briefly review other relevant theoretical considerations regarding MMN generation and repetition suppression (RS).

Theoretical Models of MMN Generation and RS

The notion of predictive coding is conceptually similar to the model adjustment hypothesis proposed by Winkler, Karmos, and Näätänen (1996) and that of primitive sensory intelligence (Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001) where MMN reflects the deviation from a preattentive extrapolation of invariant trends in the sound stream and the corresponding adjustments to this model (see also Winkler, 2007). A critical difference, however, is that Friston (2003, 2005a) makes specific proposals of how such a predictive sensory system is implemented in the brain. There have been few attempts at modeling neural repetition effects using artificial neural systems (see Henson, 2003). Sohal & Hasselmo (2000) describe a realistic model of inferior temporal (IT) neurons that show short-term RS (recency effects over few seconds) as well as long lasting familiarity effects across intervening items. Here, recency effects are caused by (nonsynaptic) neuronal adaptation and familiarity effects by synaptic modifications in feedforward synapses and local recurrent connections, modulated by cholinergic input from the basal forebrain. A different theoretical account attributes a role for cholinergic systems
in balancing bottom-up sensory evidence and top-down priors by encoding their relative uncertainty (Friston, 2005b; Yu & Dayan, 2002; see Baldeweg et al., 2006 for further discussion regarding MMN).

More recently Grill-Spector et al. (2005) reviewed evidence for three qualitative neural models of RS in the visual system: fatigue, sharpening and facilitation. They point out that different RS models could operate at different time scales and brain systems, perhaps supported by a variety of neuronal mechanisms. Some implications for audition have been discussed in Baldeweg (2006) and further parallels to auditory repetition effects are the high stimulus specificity and rapid onset, the asymptotic increase of RS with number of stimulus repetitions, and the persistence of RS despite intervening items. In addition, repetition effects were also observed in stimulus-evoked and induced oscillatory EEG activity at gamma and beta frequencies (Haenschel, Baldeweg, Croft, Whittington, & Gruzelier, 2000), however the EEG and ERP (or local field potential) correlates of SSA remain to be established (Nelken & Ulanovsky, 2007). In addition, the P50 repetition effects of Haenschel et al. (2005) show some similarity to fMRI adaptation effects in vision (Box 1 in Grill-Spector et al., 2005). Hence, a combination of electromagnetic and hemodynamic imaging is most likely to show which auditory regions show RS and if, indeed, they show hierarchical relationships, as predicted from the predominant rostral-to-caudal direction of descending (feedback) connections in STG (Galaburda & Pandya, 1983; Felleman & Van Essen, 1991).

The hypothesis that neuronal adaptation might account for aspects of MMN generation was first suggested by Näätänen (1984) and later revised by May et al. (1999). Näätänen assumed that repetition of standards leads to frequency specific inhibition of the tonotopic representation of the standard and in parallel to release from inhibition of all other (nonadapted) frequency representations. This model assumed the existence of separate “memory” neurons with sufficiently sharp tuning to explain the frequency resolution of MMN.

May and colleagues explored a neural network model of tonotopically organized auditory cortex, which included two separate inhibitory components: (1) local inhibition via neuronal adaptation (nonsynaptic spike frequency adaptation) and (2) nonlocal (i.e., synaptic) inhibition mediated via lateral inhibition. Experimental evidence on MMN latency and amplitude differences to varying degrees of frequency separation between standard and deviant supported the model’s predictions that MMN generation is the result of a combination of both mechanisms. In contrast to Näätänen’s original model, May et al. suggest that MMN is generated by neural responses (N1) to the deviant in a delayed and attenuated form, proportional to the strength of lateral inhibition caused by the standard. As discussed above, direct evidence for neuronal adaptation underlying MMN generation is now available from single neuron studies in A1. Indeed, this important property of cortical neurons has long been suspected to be a dominant mechanism of cortical memory functions (Creutzfeld, 1977).

Specifically, Ulanovsky et al. (2003) discussed the existence of two separate forms of adaptation (SSA): a subcortical form with coarse stimulus specificity, requiring continuous stimulation or only short gaps, and cortical SSA, which develops rapidly, has a long onset latency, long memory (more than 1.7 s), and high stimulus specificity. They argue that MMN generation in A1 could be supported by the cortical form of SSA. SSA is also likely to exist in other auditory cortical fields, and could even be larger in A2 than in A1 (Pinezic, Lakatos, Rajkai, Ulbert, & Karmos, 2001). The study of functional interactions between generators of MMN and SSA in different cortical fields will be critically informative for theoretical models. The current model would predict that A2 exerts top-down influence on SSA in A1, in analogy to the corticofugal effects of A1 on neuronal activity in the auditory thalamus (Villa et al., 1991; Villa, Tetko, Dutoit, de Ribauipierre, & de Ribauipierre, 1999).

Furthermore, Ulanovsky et al. (2004) reviewed two classes of neuronal adaptation mechanisms: (1) activity-dependent mechanisms operating at the output of neurons and (2) stimulus-specific adaptation of neuronal inputs. Their findings argue against mechanism (1) and suggest that input mechanism such as synaptic depression and facilitation play a major role in SSA, mediated via intracortical processing rather than depression of afferent thalamocortical synapses. This conclusion is in agreement with the findings of neuromodulatory effects on RP reviewed here, if we assume that RP is indeed an ERP correlate of SSA.

Unravelling the network mechanism responsible for SSA, RP, and MMN are likely to be of considerable theoretical interest (see Grill-Spector et al., 2005) and clinical relevance. First, identification of the mechanisms mediating the cortical form of auditory SSA could lead to a reconciliation of the debate on the existence of separate MMN “memory” neurons (see also Näätänen et al., 2005). While the high frequency resolution of MMN could be acquired by neurons contributing to N1 generation through stimulus repetition, as shown for SSA in A1 neurons (Ulanovsky et al., 2003), the latter studies also concluded that SSA is an intracortical phenomenon mediated by specific synaptic mechanisms rather than neuronal fatigue. The predictive coding model would suggest that “memory” is a property of the (predominantly top-down) connections between higher and lower sensory levels.

Secondly, there is also a clinical perspective. MMN and RP are severely diminished in patients with schizophrenia and the degree of impairment in such basic auditory plasticity correlates with markers of disease severity, such as cognitive and functional impairment (Baldeweg et al., 2004; Light & Braff, 2005). Given the etiological heterogeneity of schizophrenia it would be advantageous to identify neurophysiological correlates of distinct cellular and molecular aberrations (Stephan et al., 2006). For example, there are two established neuropathological features of schizophrenia that have direct implications for MMN generation and predictive coding models: (1) the loss of dendritic spines in supragranular layer (II/III) pyramidal neurons (Garey et al., 1998; Glantz & Lewis, 2000) and (2) functional impairment of cortical inhibitory interneurons (Lewis, Hashimoto, & Volk, 2005). Mechanism (1) impacts directly on the intracortical generation of the deviant.
negativity (MMN) in supragranular layers of auditory cortex (Javitt et al., 1996) and, according to predictive coding models, serves as an error detector projecting forward to the next cortical level (Rao & Ballard, 1999; Friston, 2005a). Mechanism (2) might interfere (in combination with [1]) with the relaying of predictive information via top-down and lateral connections (David et al., 2005). It is conceivable that deficits in RP and deviant negativity generation in patients with schizophrenia can be partly dissociated depending on the predominant focus of cellular abnormalities. This could have implications for the design of targeted therapeutic interventions.

Summary

Here I reviewed empirical evidence on MMN generation from the perspective of a predictive coding model of perceptual learning (Friston, 2003) that attempts to shed light on general principles of cortical organization and functional integration. A number of specific hypotheses for MMN generation were confirmed: (1) There is evidence for multiple, hierarchically deployed MMN components; (2) MMN encodes the probabilistic structure of the sound environment; (3) there are distinct ERP repetition effects to standards – RP, a possible correlate of SSA of auditory cortex; and (4) neuromodulatory effects to NMDA receptor antagonism as well as to nicotine were restricted to the RP. This is in line with synaptic changes in modulatory backward connections that lead to an efficient suppression of prediction error (repetition suppression). A number of further hypotheses regarding the interaction of auditory cortical regions can be tested in suitable experimental models. Furthermore, how predictive codes guide auditory perception, as suggested recently for visual object recognition (Summerfield et al., 2006), is another interesting avenue for research.

Acknowledgment

I am grateful to Karl Friston and Klaas Enno Stephan for discussion and comments on this manuscript.

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Accepted for publication: July 16, 2007