The role of the human auditory middle latency response in auditory novelty detection

Heike Corinna Althen

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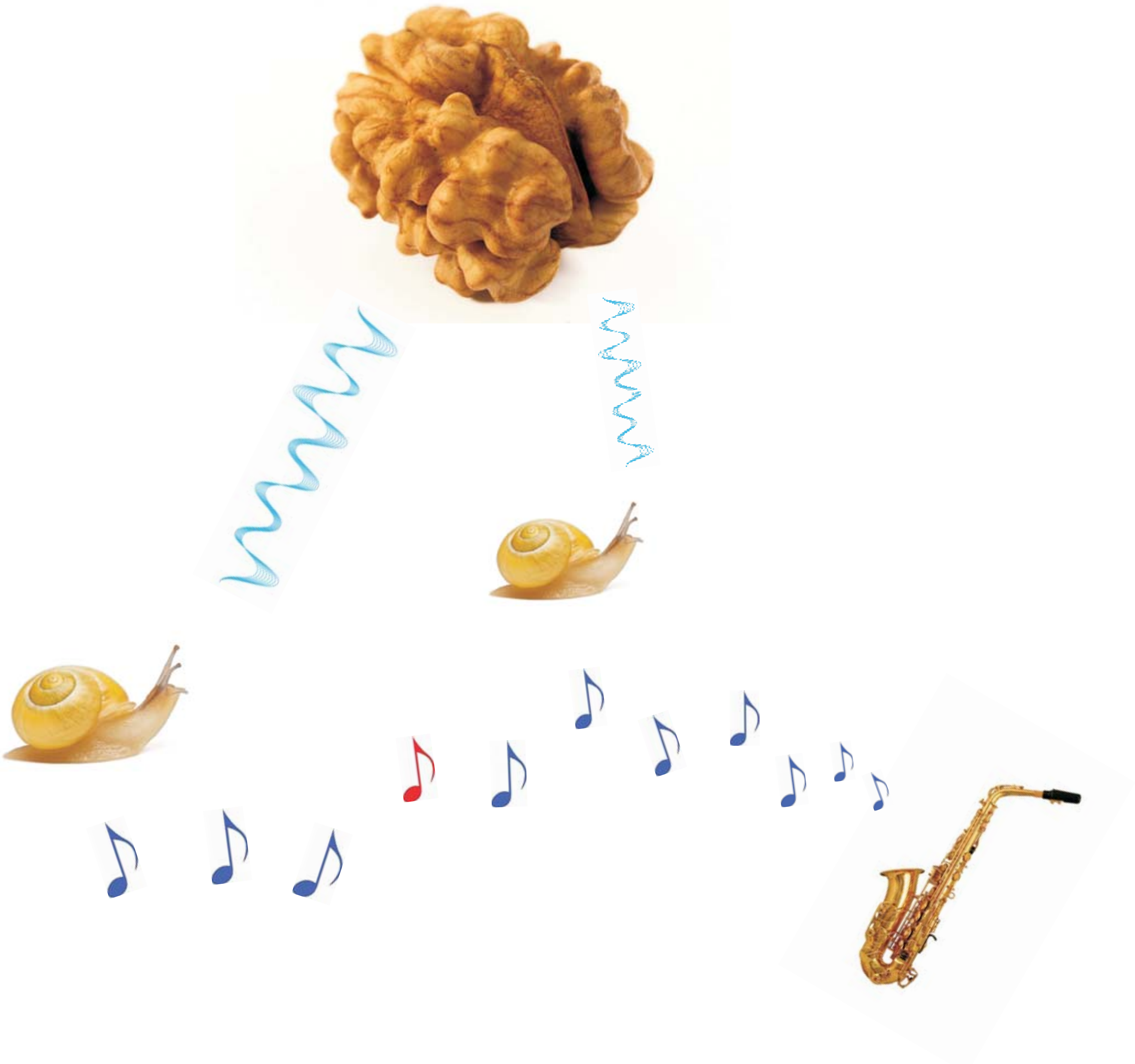
PhD thesis
Heike Althen



Departament de Psiquiatria i Psicobiologia Clínica

Facultat de Medicina

Universitat de Barcelona

The Role of the Human Auditory Middle Latency Response in Auditory Novelty Detection

Thesis submitted by

Heike Corinna Althen

To obtain the

Grau de Doctor per la Universitat de Barcelona

in accordance with the requirements for the

European PhD Diploma

Programa de Doctorat en Biomedicina

Supervised by

Dr. Carles Escera (University of Barcelona)

Barcelona, November 2013

Universitat de Barcelona

Cognitive Neuroscience Research Group

BrainLab

Acknowledgements

I want to thank Dr. Carles Escera for having given me the possibility to do my PhD thesis in his lab. Thank you, Carles, for supervising this thesis with so much dedication! And especially, for enabling me the assistance of plenty of congresses and workshops, what has been a unique professional and personal experience.

It was a wonderful time being a member of the brainlab and I will never forget the uncountable cava breaks, dinners, Feuerzangenbowle-evenings, crazy video shootings and the lab meeting in Cardona - good times with my colleagues! Thanks to all, who helped me to design, run, analyze and write up my experiments, especially Sabine. And to all who listened to my doubts and encouraged me to approach my work self-confidently - Mareike, Miriam, Sumie - just to mention a few of you. Besides, I would like to thank the Catalan government for funding this PhD thesis.

I also want to thank Dr. Minna Huotilainen and the Faculty of Psychology at University of Barcelona for having given me the possibility to spend three months in the Cognitive Brain Research Unit at University of Helsinki. Thanks to the lab engineers for their technical support and to all who integrated me by singing Finish songs in the lab choir, showing me Helsinki life-style, and much more - I had a great time!

Last but not least I want to thank my parents for their steady support throughout the years of my PhD studies!

This work has been carried out in the Cognitive Neuroscience Research Group (Centre of Excellence established by the Generalitat de Catalunya) at the Department of Psychiatry and Clinical Psychobiology, Faculty of Psychology, University of Barcelona, led by Dr. Carles Escera and partially in the Cognitive Brain Research Unit at the Institute of Behavioural Sciences, University of Helsinki under the supervision of Dr. Minna Huotilainen.

It was supported by a personal grant from the Catalan Government (FI-HA067910), the research programme Bilingüismo y Neurociencia Cognitiva (Percepción Auditiva y Atención) Programa Consolider-Ingenio 2010 (CDS2007-00012) of the Spanish Government, the ERANET-NEURON project PANS financed by the Spanish Government (EUI2009-04086) and a grant for a stay in an European Research Centre by the Faculty of Psychology, University of Barcelona.

CONTENTS

SUMMARY

One way of structuring the huge amount of sound input reaching the human ear, is extracting sound objects, which are formed by stimuli having a certain regularity in common. Such regularities are stored in sensory memory traces, what enables us to make predictions about forthcoming auditory events and to detect mismatching sounds in an automatic manner. Since mismatching stimuli are often of high importance, they are detected pre-attentively and can trigger an involuntary attention switch towards them. This is essential for an adequate reaction to meaningful auditory stimuli in everyday life and particularly in dangerous situations. The auditory-event related potential which reflects the process of detecting mismatching sounds is called mismatch negativity (MMN), usually peaks at 150 to 250 ms from stimulus onset and has bilateral sources in auditory and prefrontal cortex. MMN is elicited by deviants violating auditory regularities, like in a simple "oddball paradigm", which is composed of unchanging repetitive "standard" sounds and rare, randomly occurring, deviating sounds (so called deviants), as well as by violations of more complex auditory regularities. Recently, it was discovered that simple auditory deviations are reflected at earlier latencies than those of the MMN as indicated by deviance-related modulations of the human middle latency response (MLR) of the auditory evoked potential at 20 to 50 ms from stimulus onset. This was an important finding, as it indicates that the detection of deviant sounds is a faster and more basic property of the auditory system than originally thought.

The objective of this doctoral thesis was to examine the role of the MLR in the auditory novelty detection system. More concretely, and based on the hypothesis that the auditory novelty system works in a hierarchical manner, the aim was to study whether deviations of more complex regularities can be detected at the level of the MLR. To this end, the MLRs in response to deviant and standard stimuli violating and following auditory regularities with different degrees of difficulty were recorded. At the same time MMN was analyzed, in order to have a direct comparison of the MLR and the long-latency auditory evoked potentials (AEPs) to standards and deviants. The first study had the objective of testing whether intensity deviants of an oddball paradigm would evoke any modulations of the MLR. Lower intensity deviants elicited a slight negativity at the transition from the Na to the Pa wave, in comparison to the response elicited by physically identical standard stimuli. In addition, an MMN was elicited. The second study aimed at testing whether deviance from a hypercomplex invariance is encoded at the level of the MLR. The auditory sequence presented, was a feature-conjunction paradigm with two types of standard stimuli, each with a distinct combination of stimulus frequency and stimulus source location, and two types of deviant stimuli, each with the frequency of one standard stimulus, and the location of the other. In order to compare the results with MLRs elicited by stimuli of a simple auditory regularity, an additional simple oddball paradigm with frequency deviants was presented. In this paradigm, the Nb wave of the MLR was enhanced in response to frequency deviants compared to standard stimuli. However, comparison of the MLRs to deviants and standards of the feature-conjunction condition yielded no differences. An MMN was elicited in both paradigms. In the third study the application of the optimum-2 version of the multi-feature paradigm for MLR studies and the MLR in response to double deviants were probed. Frequency and intensity single deviants as well as frequency-intensity double deviants were presented in a multi-feature paradigm, where on average every fourth stimulus was a deviant. Furthermore, a short oddball paradigm with the same double deviants was presented. Double deviants of the multi-feature paradigm elicited a stronger enhancement of the MLR than the single deviants, and this amplification was additive. Comparison of the MMNs in response to double

deviants presented in the oddball and in the multi-feature paradigm revealed no differences in amplitude or latency.

We conclude that the early deviance detection at the level of the MLR occurs only for simple auditory regularities, as in the case of feature repetitions in the simple oddball paradigm, or in the multi-feature paradigm, where formation of the standard trace does not require extracting feature-combinations. Furthermore, the results of the present thesis suggest that deviations in frequency and intensity are processed independently from each other. Based on evidence from the present thesis and from other studies, we further conclude that the regularity encoding and deviance detection of stimuli presented in more complex auditory regularities than the simple oddball or the multi-feature paradigm require higher-order brain mechanisms than those reflected in the MLR. This goes in line with the hypothesis of a hierarchically organized auditory novelty system. Concerning the cellular mechanisms underlying auditory deviance detection, it has been proposed that stimulus-specific adaptation (SSA) to stimulus probabilities observed in animal auditory subcortical and cortical structures could be the single neuron correlate of the deviance-related activity in the human AEP due to its similar characteristics to MMN. Yet, MMN occurs somewhat too late to be considered a direct human scalp correlate of the release from SSA measured in single cells. The deviance-related modulations in the MLR have shorter latencies than MMN. Moreover, their brain sources are supposed to be spatially different and to be located upstream to those of MMN. Therefore, it is probable that the deviance-related modulations in the MLR represent a more direct correlate of the early cellular SSA, than MMN.

ABBREVIATIONS

ABR	auditory brainstem response
AC	auditory cortex
AEP	auditory evoked potential
EEG	electroencephalogram
FFR	frequency-following response
IC	inferior colliculus
MGB	medial geniculate body
MLR	middle latency response
MMN	mismatch negativity
SOA	stimulus onset asynchrony
SSA	stimulus-specific adaptation

INTRODUCTION

The acoustic environment is rich in sound stimuli, like voices, music or sounds of clinking glasses on a cocktail party, which have different sources, frequencies, intensities and other varying acoustic features. As hearing is an undirected sense and only a part of the sound information can be perceived consciously, the huge amount of acoustic input that reaches the ear must be filtered during its processing along the auditory pathway. One way of structuring the sound input is retaining it in form of sound objects, which are formed by stimuli that have a certain regularity in common (for a review see Winkler *et al.*, 2009). This regularity is stored in a sensory memory trace and predictions about forthcoming auditory events are made. Subsequent incoming sound information is compared to these predictions and mismatches are detected in an automatic manner (Bendixen *et al.*, 2009; for a review see Bendixen *et al.*, 2012). Mismatching stimuli are often of high importance and therefore they are detected pre-attentively and can trigger an involuntary attention switch towards them (Escera *et al.*, 2000; Escera & Corral, 2007; Sussman, 2007). This attention switch is essential for an adequate reaction to meaningful auditory stimuli in everyday life and particularly in dangerous situations.

In 1978, Näätänen and colleagues discovered a human auditory-event related potential which reflects this process of detecting mismatching sounds (Näätänen *et al.*, 1978). In their experiment a so-called oddball paradigm was presented to participants, who listened passively or actively to the sound sequence, while their electroencephalogram (EEG) was measured. The oddball paradigm is a simple sound sequence, which is composed of unchanging repetitive standard sounds and rare, randomly occurring, deviating sounds, which differ in one or several sound properties from the standard stimuli. When the researchers compared the auditory evoked potentials (AEPs) in response to the standard and the deviant sounds, they found that the violation of the sound regularity by the deviant sound triggered a negativity in the AEPs. The potential difference of the standard and deviant AEPs, peaking usually at 150 to 250 ms from stimulus onset, was termed “mismatch negativity” (MMN; Näätänen *et al.*, 2007). Ever since, MMN has been extensively studied and is applied as a marker to investigate cognitive functions and dysfunctions (Näätänen & Escera, 2000; Kujala *et al.*, 2007; Näätänen *et al.*, 2011a; Näätänen *et al.*, 2012).

Recently, it was discovered that the violation of a sound regularity is reflected at earlier latencies than those of the MMN by means of modulations of the human middle latency response (MLR) of the AEP (for reviews see Grimm & Escera, 2011; Escera *et al.*, 2013). This was an important finding, as it indicates that the detection of deviant sounds is a faster and more basic property of the auditory system than originally thought. Thereupon many questions about the characteristics of this deviance-related MLR activity arose. Finding answers to these questions will be an important step in exploring the functioning of the auditory novelty system and an essential contribution to the knowledge base of the auditory system. Understanding the basic functions of the auditory system in turn is fundamental for studying more sophisticated auditory functions, like for example music and speech perception (Tervaniemi & Huotilainen, 2003; Pulvermüller & Shtyrov, 2006; Rohrmeier & Koelsch, 2012). Moreover, it could facilitate the investigation and the treatment of auditory dysfunctions as well as neurological disorders, like schizophrenia and contribute to the development of medical devices, like hearing aids, cochlea implants and auditory brain-computer interfaces (Näätänen *et al.*, 2012).

THE AUDITORY PATHWAY

In the following only the most important neural projections and relay stations of the ascending auditory pathway are described. Auditory stimuli are transformed from mechanical energy into electrical neuronal codes by the sensory cells in the cochleae (Møller, 2006). From the cochlear nerves on both sides of the brain, the signal is projected to the cochlear nuclei and from there to the superior olivary complex, where information from both ears is integrated for the first time. Via the lateral lemniscus, the most important fiber track of the classical ascending auditory pathway, information is relayed to the inferior colliculi (ICs) of the opposite sides, where all ascending auditory information of the midbrain is channeled (Møller, 2006). The next relay station is the medial geniculate body (MGB) of the thalamus in the midbrain (Møller, 2006). The thalamus forms the conjunction to the primary auditory cortices, situated in the Heschl's gyri of the superior temporal gyri, as well as to some other auditory cortical areas (Møller, 2006). From the primary auditory cortices, fiber tracts project to the secondary and belt regions of the auditory cortices as well as to the association cortices, where auditory information is integrated with information from other senses and from further brain areas (Møller, 2006). The auditory nuclei and regions of the two brain hemispheres are connected at several levels of the auditory pathway (Møller, 2006; Bamiou *et al.*, 2007). Moreover, in addition to the ascending auditory projections, there are abundant descending projections, extending from the auditory cortex (AC) to the cochlear hair cells (Suga *et al.*, 2002; Møller, 2006).

THE ELECTROENCEPHALOGRAM AND THE AUDITORY EVENT-RELATED POTENTIALS

The first human EEG was recorded by Hans Berger in the 1920s in Jena, Germany (Sanei & Chambers, 2007; Picton, 2011). For recording the EEG from the scalp, highly-sensitive electrodes consisting of an electrically conducting metal, such as a silver/silver-chloride pellet, are attached individually or in a cap to the scalp (Picton, 2011). A conducting connection, usually a saline jelly is necessary for good connectivity between the electrode and the scalp (Picton, 2011). The brain potentials, which are recorded in the EEG, arise from current flows during post-synaptic potentials or action potentials (Burkard *et al.*, 2007; Sanei & Chambers, 2007). They are attenuated by the different layers of the human head including the scalp, the skull and the brain (Sanei & Chambers, 2007). Therefore, with scalp electrodes, an EEG signal is only measurable, when large populations of hundreds or thousands of neurons are activated (Picton, 2011). Moreover, the neural activity has to be synchronous and the structures that generate it have to be aligned in parallel (Burkard *et al.*, 2007). Still, the EEG potentials are tiny and must therefore be amplified 10000 to 1000000 times to the level of Volts, and filtered to attenuate frequencies which obscure the signal of interest (Picton, 2011). For measuring AEPs, the electrodes can be placed over the temporal lobes, where the auditory cortices are located, but are commonly placed near the vertex of the head, because at this position temporal lobe activity from both brain hemispheres as well as attention-related activity from frontal brain areas can be picked-up (Burkard *et al.*, 2007). Since AEPs are usually smaller than the background activity, averaging hundreds of AEPs in response to the same auditory stimulus is required to cancel out the background noise (Picton, 2011). AEPs with cortical sources are larger than AEPs with subcortical sources, since the cortex is closer to the scalp, is a larger structure than the subcortical auditory nuclei, and the dipoles are much better aligned (Burkard *et al.*, 2007).

AEPs which are generated by neural activity in the auditory brainstem are called the auditory brainstem response (ABR) and are the earliest auditory evoked potentials that can be extracted from the EEG. There are two types of ABRs, the transient-evoked ABRs, and the steady-state frequency following potentials (Picton, 2011; Pratt, 2012). Jewett, Romano and Williston described human transient-evoked ABRs for the first time systematically (Jewett *et al.*, 1970; Jewett & Williston, 1971). They consist of a series of 6 or 7 positive waveforms, generated in the first 10 ms after stimulus onset and about 1 ms apart from each other (Pratt, 2012). They are labeled by the Roman numerals I to VII, as introduced by Jewett and Williston (1971). ABRs are the smallest AEPs, with amplitudes in the order of tenths of a microvolt (Pratt, 2012), but normally smaller than 0.5 microvolt (Møller, 2006). The largest component is wave V (Picton, 2011), which has generators in the contralateral distal lateral lemniscus and the inferior colliculus (Stone *et al.*, 2009). For extracting the ABR from the auditory evoked potential, a frequency filter is necessary. The ABR has a high frequency and therefore a low-pass filter of between 2000 and 3000 Hz and a high-pass filter of between 5 and 30 Hz are typically applied (Picton, 2011). Non-pathological factors, which influence the transient-evoked ABR are, amongst others, the subject’s body temperature, gender and age. Besides, stimulus factors, like frequency composition, intensity, envelope and presentation rate, have an influence on the ABR (Pratt, 2012). With increasing stimulus intensity, the ABR peak latency shortens and high-frequency stimuli as well as stimuli with a short rise time evoke ABRs with larger amplitudes and shorter latencies. Attention does not seem to influence the ABR and even during sleep the ABR does not change significantly (Picton, 2011).

AEPs evoked after 10 to 50 ms from sound stimulus onset are called the middle latency response (Burkard *et al.*, 2007). They where first described by Dan Geisler in 1958 and in the late 1960s and 1970s intensively studied by Robert Goldstein and colleagues at the University of Wisconsin (Hall, 2007). The major components of the MLR are the Na, Pa, Nb and Pb waves, the latter also called P50 (Hall, 2007). The most prominent wave is Pa and occurs with high level stimulation normally at about 25 ms after stimulus onset (Hall, 2007). The amplitude of the Pa wave is in normal adult subjects on average approximately 1 µV (Hall, 2007). Pb, which is highly variable between subjects, occurs at about 50 ms after stimulus onset (Hall, 2007). Factors like the subject's state of arousal and age, the stimulus rate, the filter settings and others have influence on the latency and amplitude of the MLR waves (Hall, 2007). Clinical applications of the MLR are, for example, the assessment of cochlear implant performance, the measurement of "sensory gating" in patients with neuropsychiatric disorders, the evaluation of depth of anesthesia during surgery, the assessment of frequency sensitivity in older children and adults and the documentation of auditory dysfunction above the level of the auditory brainstem (Hall, 2007). The main neural generators of the MLR are the core areas of the AC, but the exact sources of the single waves are not totally clear (Burkard *et al.*, 2007). For the Na wave, they are believed to be located subcortically in the thalamus or in thalamocortical projections (Burkard *et al.*, 2007). The Pa Wave probably has ascending subcortical as well as primary and possibly secondary AC contributions (Yvert *et al.*, 2001; Burkard *et al.*, 2007). Sources of the Nb and Pb wave are supposed to lie in the secondary cortex (Yvert *et al.*, 2001; Hall, 2007). A high-pass filter of approximately 10 Hz should be applied for showing the MLR waves (Hall, 2007).

Following the MLR, the long-latency AEPs are evoked. They have sources in multiple different cortex areas, but mainly in AC (Picton, 2011). Much more than the earlier AEPs, they are affected by psychological expectancy of the perceiver (Picton, 2011). The most important exogenous AEPs of the long-latency range are the N1 wave, which has a latency of approximately 100 ms, P2 wave, with a latency of approximately 180 ms, and the N2 wave, with a latency of about 250 ms. In addition, the above described MMN component can be elicited, which results when subtracting the AEP elicited by a standard stimulus of a regular sound sequence from the AEP elicited by a deviating sound stimulus, which violates the standard regularity. MMN can be manifested in form of an enhancement of the later part of the N1 wave, as a separate N2 wave, or as an attenuation of the P2 wave (Picton, 2011). Maximal MMN amplitudes can be recorded over the fronto-central areas of the scalp and when the signal is referenced to the nose, MMN usually reverses polarity at the mastoid sites, below the Sylvian Fissure (Kujala *et al.*, 2007; Näätänen *et al.*, 2007). Its cerebral sources are located bilaterally in the supratemporal cortex and in prefrontal cortex, with the latter possibly underlying the attention switch to a novel stimulus (Alho, 1995; Rinne *et al.*, 2000; Deouell, 2007; Maess *et al.*, 2007). MMN arises at approximately 150-250 ms from sound change onset and its peak latency gets shorter with increasing change magnitude (Sams *et al.*, 1985; Näätänen *et al.*, 1989a; Näätänen *et al.*, 1989b; Amenedo & Escera, 2000). Another important characteristic of MMN is that it is elicited even when the subject does not pay attention to the sounds (Kujala *et al.*, 2007).

THE AUDITORY NOVELTY SYSTEM

MMN can most easily be elicited by presenting a so-called "oddball" sequence to the participant (Näätänen *et al.*, 1978). As already mentioned, it consists of a sequence of repetitive standard sounds, which is interspersed randomly and rarely by deviant sounds, which are normally presented with a probability of 0.1 to 0.25. For the elicitation of MMN simple sounds, like pure tones, or more complex sounds, like chords or speech sounds, can be used (e.g. Aaltonen *et al.*, 1987; Alho *et al.*, 1996; for a review see Näätänen *et al.*, 2007). In the simplest version of the oddball paradigm, deviant sounds differ in only one auditory feature from the standard sounds, for example, in frequency (Näätänen *et al.*, 1978), intensity (Näätänen *et al.*, 1989a), location (Paavilainen *et al.*, 1989) or duration (Näätänen *et al.*, 1989b). Deviants, which differ in two or more auditory features form the standard sounds, like double or triple deviants, elicit a larger MMN than single deviants (Wolff & Schröger, 2001). Besides detecting deviants in an oddball paradigm, the auditory novelty system is capable to encode more complex auditory regularities and their violations, what is demonstrated by the presence of MMN (for a review see Näätänen *et al.*, 2007; Näätänen *et al.*, 2010). Picton et al. (2000) classified the different types of auditory regularities into five kinds of invariance:

I. Simple invariance (simple oddball paradigm): standard stimuli are all the same in every possible feature, like frequency, duration etc. Deviant stimuli differ in any discriminable manner from the standard stimuli. Examples for studies are given above.

II. Complex invariance: None of the standard stimuli are identical, but they are all the same regarding at least one auditory feature. For example, they all have the same frequency, but different intensities, durations etc. Deviant stimuli differ in respect to the identical feature of the standard stimuli (e.g., Gomes *et al.*, 1995).

III. Hypercomplex invariance: standard stimuli (two or more) have a distinct combination of multiple stimulus features. For example, one standard is presented with 500 Hz and 60 dB SPL and the other standard with 600 Hz and 50 dB SPL. Deviants combine the features of the different standard stimuli, so that none of the individual features is new, but its combination is. That is, in this example, 500 Hz and 50 dB SPL or 600 Hz and 60 dB SPL (e.g., Gomes *et al.*, 1997; Takegata *et al.*, 1999).

IV. Pattern invariance: The standard stimulus is a sound pattern consisting of a stimulus sequence, which contains up to eight tones that differ in any feature or several features from each other. Deviant stimuli violate this sound pattern, e.g. in terms of a stimulus repetition (e.g., Schröger *et al.*, 1992).

V. Abstract invariance: Standard stimuli are related to each other, based on an abstract rule. For example, pairs of tones, in which the second tone is always higher in frequency than the first one. Deviant stimuli violate this abstract rule as the second tone of the tone pair is lower in frequency than the first tone (e.g., Saarinen *et al.*, 1992; Tervaniemi *et al.*, 1994; Bendixen *et al.*, 2008).

In addition to these paradigms there exists the multi-feature paradigm, which was developed by Näätänen and colleagues (Näätänen *et al.*, 2004). It is similar to a simple oddball paradigm, and has the advantage that several types of deviants can be presented at the same time. Every second stimulus (or less) is a deviant stimulus, but the standard trace is nevertheless formed, since the deviants act as standard stimuli regarding their non-deviating features. This paradigm is much faster than the traditional oddball paradigm and is therefore especially useful for clinical or infant studies.

Also the N1 wave is related to changes in the auditory world. It is a change detector, which is enhanced, when the acoustic properties of a sound change. Thus, in an auditory regularity, N1 enhancement to deviant stimuli is based on a decreased neural response to the repeated standard sounds in contrast to a stronger response, including fresh populations of neurons, when a deviating sound stimulus is presented (Butler, 1968; Budd *et al.*, 1998; for a review on the N1 adaptation hypothesis see May & Tiitinen, 2010). Since N1 can overlap with MMN, it is important to disentangle repetition positivity to regular standard sounds from the detection process of the changing auditory stimuli (MMN). Therefore a control condition should be included into the experimental design (Schröger & Wolff, 1996; Jacobsen *et al.*, 2003; for repetition positivity see Haenschel *et al.*, 2005; Costa-Faidella *et al.*, 2011). In an optimum way, in this condition, there should be several different, equiprobable sound stimuli presented with the same probability as the deviant stimulus of the oddball condition, so that there are no standard or deviant stimuli. Furthermore, control stimuli should differ from each other to the same degree as standard and deviant stimuli of the oddball condition. By comparing the AEPs in response to the deviant stimuli of the oddball condition with the corresponding, physically identical, control stimuli, it can be assured that the resulting MMN is not due to release from neural refractoriness (Schröger & Wolff, 1996; Jacobsen & Schröger, 2001; Jacobsen *et al.*, 2003).

In the nineties, first studies provided evidence for MMN-like responses in the thalamus of the guinea pig, that is, in a subcortical auditory structure (Kraus *et al.*, 1994a; Kraus *et al.*, 1994b; King *et al.*, 1995). More recent intracerebral recordings in the rat, mice and cat revealed that probabilities are encoded even at single neuron level in the MBG and also in the IC and the AC (e.g. Ulanovsky *et al.*, 2003 - cat primary AC; Pérez-González *et al.*, 2005 - rat IC; Anderson *et al.*, 2009 - mouse MGB). These so-called "novelty neurons", showed decreased firing rate to repetitive sounds and restored firing rate to deviant sounds of an oddball paradigm, a phenomenon called stimulus-specific adaptation (SSA; for a recent review see Escera & Malmierca, 2013). Since SSA and MMN show similar behavior in many regards, it was hypothesized that SSA could be the cellular correlate of the MMN (Ulanovsky *et al.*, 2003; Escera & Malmierca, in press). However, the stimulus onset of the majority of novelty neurons has latencies of only 10-20 ms, what is much shorter than the onset latencies of the human MMN (Pérez-González *et al.*, 2005; Anderson *et al.*, 2009). Moreover, novelty neurons have not only been found in AC but also in the subcortical MGB and IC, whereas MMN has exclusively cortical sources. In contrast, earlier human AEPs, which involve lower hierarchical structures than those of MMN could represent a more direct correlate of SSA and might help to link the fast and slow novelty detection processes (Escera *et al.*, 2013).

In 2006, a study on the human MLR to location deviants of an oddball paradigm, showed that the detection of location deviants is reflected by an enhancement of the Na wave of the human MLR at ca. 25 ms from stimulus onset (Sonnadara *et al.*, 2006). Grimm and colleagues found further evidence for traces of deviance detection at the level of the MLR. They conducted a frequency oddball study and showed that the Nb wave at 40 ms from stimulus onset was stronger in response to deviant stimuli than to standard stimuli (Grimm *et al.*, 2011). Importantly, in both studies a reversed oddball condition was applied, where standard and deviant stimuli had swapped frequencies, or locations, respectively. By using such a reversed condition, standard and deviant stimuli with the same physical properties could be compared, and thus it could be ruled out that the differences in the MLR, which is sensitive to changes of physical stimulus properties, might be based on the physical aspects of the standard and deviant stimuli. As explained above for MMN, also an enhanced MLR to deviants could be attributed to release from neural refractoriness and activation of fresh neural populations instead of true deviance detection. To probe this, Grimm and colleagues (2011) also applied a control condition in the frequency oddball study, similar to the control paradigm used in MMN studies (Schröger & Wolff, 1996; Jacobsen *et al.*, 2003). Their results confirmed an enhancement of the Nb wave in response to deviant compared to control stimuli and provided thus evidence for "true" novelty detection reflected at the level of the MLR. A second study by Grimm et al. suggests that also location deviants in a controlled oddball paradigm modulate the MLR in form of an enhanced Na wave at approximately 20 ms from stimulus onset, corroborating the findings by Sonnadara and colleagues (Grimm *et al.*, 2012). In fact, these deviance-related modulations of the MLR are rather small, but they are significant and represent a very early trace of deviance-detection in the human AEP. Their early latencies and sources in core regions of the AC suggest that they could be a more direct AEP correlate of SSA than MMN. Until now a deviance-related enhancement of the MLR has only been shown for deviants of simple oddball paradigms, which represent a simple auditory regularity (for a recent review see Escera *et al.*, 2013). In contrast, MMN is also sensitive to deviations from more complex auditory regularities.

Evidence for auditory regularity encoding from the brainstem up to the cerebral cortex, suggests that the detection of auditory deviants is a pervasive property of the auditory system, extending from auditory brainstem up to higher areas of the cerebral cortex. Considering that the more downstream in the brain, the more abstract problems are solved, we hypothesize that the novelty system works in a hierarchical order, with low-level auditory brain areas encoding simple regularity violations and higher-order auditory brain areas encoding more complex regularity violations (see also Winkler *et al.*, 2009; Grimm & Escera, 2011; Escera *et al.*, 2013; Escera & Malmierca, 2013).

OBJECTIVES

The objective of this doctoral thesis was to examine the role of the MLR in the auditory novelty detection process. More concretely, and based on the hypothesis that the auditory novelty system works in a hierarchical manner (Winkler *et al.*, 2009; Grimm & Escera, 2011; Escera & Malmierca, 2013), the aim was to study the level of regularity complexity being encoded at the level of the MLR. To this end, the MLR in response to auditory novelty paradigms with different degrees of difficulty should be recorded. At the same time MMN should be analyzed, in order to have a direct comparison of the MLR and the long-latency AEPs to standards, deviants and if possible control stimuli.

1) The first study was the object of testing whether intensity deviants of an oddball paradigm would evoke any modulations of the MLR. Additionally, a control condition was applied in

order to control for a refractoriness-based effect. There are many studies showing that louder as well as softer intensity deviants elicited MMN (e.g. Jacobsen *et al.*, 2003) and, from animal studies, there is evidence that deviation in intensity is encoded at cellular level (e.g. Ulanovsky *et al.*, 2003). We used click sounds, since frequency did not play a role in this paradigm. Therefore, in addition to the MLR and MMN, the ABR was recorded. In a study by Slabu et al. (2010) on frequency deviants the ABR was analyzed, but did not show any novelty-related modulations and we wanted to probe if this holds true also for intensity deviants.

2) The second study aimed at testing whether deviance from a hypercomplex invariance is encoded at the level of the MLR. By the time there was, to the author's knowledge, no study on deviance-related MLR modulations to stimuli of a more complex auditory invariance than the oddball paradigm. The auditory sequence which should be applied was a feature-conjunction paradigm with two standards. Knowing that frequency and location deviants of an oddball paradigm are detected at the level of the MLR, we considered it constructive to use different frequency-location combinations. To compare the outcome with the deviance-related MLR modulations by stimuli of a simple regularity violation, in addition an oddball paradigm with frequency deviants was conducted. By studying the MLR in response to deviants and standards of a feature-conjunction paradigm we sought discovering whether this complex yet not abstract regularity would be encoded at the level of the MLR.

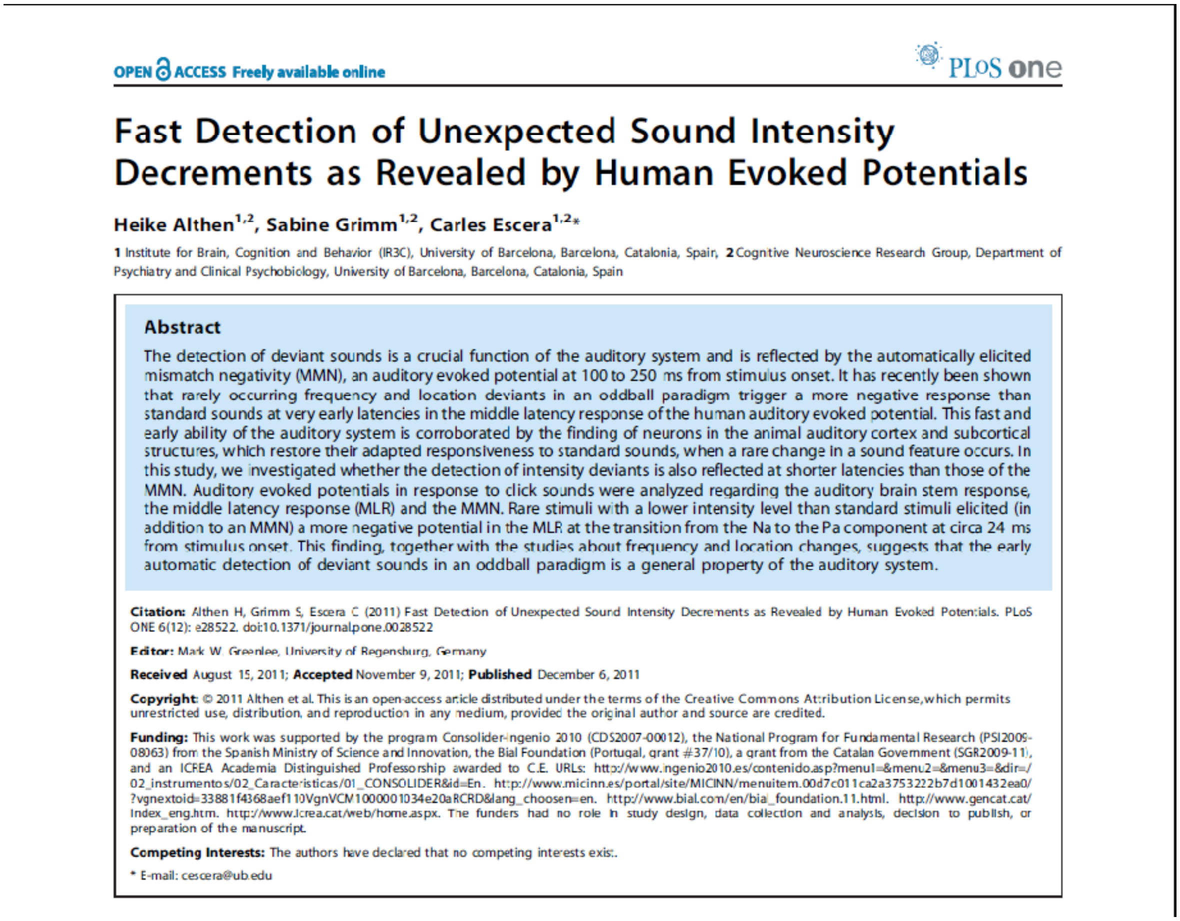
3) With the third study, run in the "Cognitive Brain Research Unit" of University of Helsinki, the MLR modulations in response to double and single feature deviants were compared. In order to obtain MLRs to single and double deviants, recorded in the same experimental session, we used the multi-feature paradigm, which has been developed by researchers of the "Cognitive Brain Research Unit" (Näätänen *et al.*, 2004). As explained above, the multi-feature paradigm is time-saving and since the length of MLR experiments is an important limiting factor, we were moreover interested in whether in future studies the multi-feature paradigm could be used as an alternative to the oddball paradigm.

STUDY I

Althen H, Grimm S, Escera C (2011) Fast Detection of Unexpected Sound Intensity Decrements as revealed by Human Evoked Potentials. *PLoS One 6(12)*: e28522. doi:10.1371/journal.pone.0028522

Webpage:

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0028522



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PLoS one

Fast Detection of Unexpected Sound Intensity Decrements as Revealed by Human Evoked Potentials

Heike Althen[1,2], **Sabine Grimm**[1,2], **Carles Escera**[1,2]*

1 Institute for Brain, Cognition and Behavior (IR3C), University of Barcelona, Barcelona, Catalonia, Spain, **2** Cogntive Neuroscience Research Group, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Barcelona, Catalonia, Spain

Abstract

The detection of deviant sounds is a crucial function of the auditory system and is reflected by the automatically elicited mismatch negativity (MMN), an auditory evoked potential at 100 to 250 ms from stimulus onset. It has recently been shown that rarely occurring frequency and location deviants in an oddball paradigm trigger a more negative response than standard sounds at very early latencies in the middle latency response of the human auditory evoked potential. This fast and early ability of the auditory system is corroborated by the finding of neurons in the animal auditory cortex and subcortical structures, which restore their adapted responsiveness to standard sounds, when a rare change in a sound feature occurs. In this study, we investigated whether the detection of intensity deviants is also reflected at shorter latencies than those of the MMN. Auditory evoked potentials in response to click sounds were analyzed regarding the auditory brain stem response, the middle latency response (MLR) and the MMN. Rare stimuli with a lower intensity level than standard stimuli elicited (in addition to an MMN) a more negative potential in the MLR at the transition from the Na to the Pa component at circa 24 ms from stimulus onset. This finding, together with the studies about frequency and location changes, suggests that the early automatic detection of deviant sounds in an oddball paradigm is a general property of the auditory system.

Citation: Althen H, Grimm S, Escera C (2011) Fast Detection of Unexpected Sound Intensity Decrements as Revealed by Human Evoked Potentials. PLoS ONE 6(12): e28522. doi:10.1371/journal.pone.0028522

Editor: Mark W. Greenlee, University of Regensburg, Germany

Received August 15, 2011; **Accepted** November 9, 2011; **Published** December 6, 2011

Funding: This work was supported by the program Consolider-Ingenio 2010 (CDS2007-00012), the National Program for Fundamental Research (PSI2009-08063) from the Spanish Ministry of Science and Innovation, the Bial Foundation (Portugal, grant #37/10), a grant from the Catalan Government (SGR2009-11), and an ICREA Academia Distinguished Professorship awarded to C.E. URLs: http://www.ingenio2010.es/contenido.asp?menu1=&menu2=&menu3=&dir=/02_instrumentos/02_Caracteristicas/01_CONSOLIDER&id=En. http://www.micinn.es/portal/site/MICINN/menuitem.00d7c011ca2a3753222b7d1001432ea0/?vgnextoid=33881f4368aef110VgnVCM1000001034e20aRCRD&lang_choosen=en. http://www.bial.com/en/bial_foundation.11.html. http://www.gencat.cat/index_eng.htm. http://www.icrea.cat/web/home.aspx. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: cescera@ub.edu

STUDY II

Althen H, Grimm S, Escera C (2013) Simple and Complex Acoustic Regularities are encoded at Different Levels of the Auditory Hierarchy. *European Journal of Neuroscience*. doi: 10.1111/ejn.12346

Webpage:

http://onlinelibrary.wiley.com/doi/10.1111/ejn.12346/abstract

EJN EUROPEAN JOURNAL OF NEUROSCIENCE

European Journal of Neuroscience, Vol. 38, pp. 3448–3455, 2013 doi:10.1111/ejn.12346

NEUROSYSTEMS

Simple and complex acoustic regularities are encoded at different levels of the auditory hierarchy

Heike Althen,[1,2] Sabine Grimm[1,2] and Carles Escera[1,2]

[1]Institute for Brain, Cognition and Behavior (IR3C), University of Barcelona, Catalonia, Spain

[2]Cognitive Neuroscience Research Group, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Catalonia, Spain

Keywords: auditory deviance detection, auditory evoked potentials, auditory novelty system, middle-latency response, mismatch negativity

Abstract

The detection of auditory stimuli that deviate from a simple or complex auditory regularity is reflected by the mismatch negativity component of the human auditory evoked potential. Moreover, simple deviants of an oddball paradigm modulate the preceding middle-latency response of the auditory evoked potential. For the frequency oddball paradigms it has been shown that the Nb wave, at approximately 40 ms from stimulus onset, is enhanced in response to deviant compared with standard stimuli. In this study we tested whether the detection of auditory deviants in a (frequency-location) feature-conjunction paradigm is reflected by modulations of the Na, Pa or Nb wave of healthy human participants. In addition, a frequency oddball paradigm was applied to directly contrast the results of a simple and a complex invariance. Feature-conjunction deviants did not elicit any modulations of the tested middle-latency waves. Deviants of the frequency oddball paradigm, by contrast, elicited an enhancement of the Nb wave, confirming the outcome of precedent studies. In both conditions a significant mismatch negativity component was elicited, which showed larger amplitudes and shorter latencies in the oddball condition than in the feature-conjunction condition. These findings corroborate the idea that simple auditory regularities are encoded upstream of those of more complex auditory features and are in line with the idea of a hierarchically working auditory novelty system.

STUDY III

Althen H, Huotilainen M, Grimm S, Escera C. Double Deviants in a Multi-feature Paradigm elicit Larger MLRs than Single Deviants. *In preparation*

Double deviants in a multi-feature paradigm elicit larger MLRs than single deviants.

Heike Althen[1,2], Minna Huotilainen[3,4,], Sabine Grimm[1,2] and Carles Escera[1,2]

[1]Institute for Brain, Cognition and Behavior (IR3C), University of Barcelona, Spain

[2]Cognitive Neuroscience Research Group, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Spain

[3]Finnish Institute of Occupational Health, Helsinki, Finland

[4]Cognitive Brain Research Unit, Institute for Behavioural Sciences, University of Helsinki, Finland

Correspondence:

Prof. C. Escera, as above.

E-mail: escera@ub.edu

Abstract

Recent studies on auditory deviance detection have shown that single-feature deviants of an oddball paradigm elicit enhancements of the human middle-latency response (MLR) at 20 to 50 ms from deviance onset. In the present study, we examined the MLR and the mismatch negativity (MMN) to frequency, intensity and double-feature deviants presented in an optimum-2 condition of the multi-feature paradigm. Furthermore the MMN in response to double deviants was compared to the MMN in response to double deviants of an oddball paradigm without single-feature deviants. In the multi-feature paradigm, double deviants elicited significant enhancements of the Nb and Pb MLR waves compared with the Nb and Pb waves in response to standard stimuli. These enhancements equalled approximately the sum of the enhancements elicited by the single deviants. In contrast, MMN to double deviants did not show such additivity. MMNs elicited by double deviants in the multi-feature and the oddball paradigm showed no significant difference in amplitude or latency. We conclude that double deviants elicit stronger enhancements of the MLR than single deviants and that the optimum-2 condition of the multi-feature paradigm can be used to record deviance-related modulations of MLR. Moreover, our results suggest that MMN elicited by double deviants of the multi-feature paradigm is not affected by the fact that single deviants with matching auditory features are presented in the same sound sequence.

DISCUSSION

In the present PhD thesis three EEG experiments were conducted in young healthy adults. The aim was to examine the MLRs to stimuli of auditory sequences with different levels of underlying regularity. In the first study an oddball paradigm with lower intensity deviants and a control condition were applied (Althen *et al.*, 2011). Intensity deviants elicited a slight negativity at the transition from the Na to the Pa wave, in comparison to the response elicited by physically identical standard stimuli. In addition, an MMN was elicited. Wave V of the ABR to the different stimulus types showed no differences. In the second study the MLRs to standard and deviant stimuli with different feature conjunctions were examined (Althen *et al.*, 2013). Two types of standard stimuli, each with a distinct combination of frequency and location, and two types of deviant stimuli, each with the frequency of one standard stimulus, and the location of the other, were presented. In addition, an oddball paradigm was presented, in which the sequence design was comparable to the conjunction paradigm, i.e. standards could occur from different locations. The Nb wave of the MLR was enhanced in response to frequency deviants compared to standard stimuli of the oddball paradigm. However, comparison of the MLRs to feature-conjunction deviants and standards revealed no differences. An MMN was elicited in both paradigms. In the third study the application of the optimum-2 version of the multi-feature paradigm for MLR studies and the MLR in response to double deviants were probed (for optimum-2 version see Näätänen *et al.*, 2004; Althen *et al.*, in preparation). Frequency and intensity single deviants as well as frequency-intensity double deviants were presented in a multi-feature paradigm, where on average every fourth stimulus was a deviant. Furthermore, a short oddball paradigm with only double deviants was presented. Double deviants of the multi-feature paradigm elicited a stronger enhancement of the MLR than the single deviants, and moreover this amplification proved to be additive. Comparison of MMNs in response to double deviants presented in the oddball and in the multi-feature paradigm showed no differences in amplitude or latency.

The first study was designed in order to examine whether intensity deviants would elicit an enhancement of the MLR or even of the ABR. To the author's knowledge, this is the first study reporting a deviance-related enhancement of the MLR elicited by intensity deviants of a simple oddball paradigm. The enhanced MLR at 24 ms from stimulus onset, together with the modulation found for location deviants, are among the earliest auditory deviance-related modulations observed in the human AEP (Sonnadara *et al.*, 2006; Althen *et al.*, 2011; Cornella *et al.*, 2012; Grimm *et al.*, 2012). Yet, the MLR to intensity deviants was not enhanced in comparison to the MLR elicited by the same physical stimuli of the control condition. However, it should be noted that the intensity deviants were presented with a softer intensity than the standard stimuli, which rules out that the enhanced MLR to deviants is due to stronger sensory input. Moreover, it is possible that the applied control condition in fact “overcontrolled” so that the true deviance detection processes could therefore not be revealed (see Althen *et al.*, 2011). Furthermore, in this experiment the same pattern was found for MMN. Still, it cannot be concluded that at the early latencies of the MLR a true change detection process for the intensity deviants occurred.

This new finding on deviance-related activity in the MLR complements the examination of oddball paradigms with single-feature deviants for the most basic sound features. The numerous studies which have been conducted on this topic in the last years suggest that depending on the sound feature which is deviating from the standard sound, enhancements at different MLR waves are elicited. The earliest deviance-related modulations were found for location deviants, which elicited enhancements of the Na wave compared to standard and control stimuli at about 20 ms from stimulus onset. After this was shown by Sonnadara et al. (2006) the finding was confirmed by two studies from our lab (Cornella *et al.*, 2012; Grimm *et al.*, 2012). As explained above, from the first study of the present PhD thesis, there is evidence that intensity deviants enhanced the MLR at latencies of 24 ms at the Na/Pa slope (Althen *et al.*, 2011). The similarity in latency for the MLR modulations in response to intensity and location deviants suggests that common brain sources are involved for the encoding of deviance in these two features. This is supported by the fact that sound intensity is a main cue used to estimate the distance of a sound source (Warren, 2008). In the second study of the present PhD thesis as well as in several precedent studies, it has been shown that a larger Nb wave is elicited in response to rare frequency changes compared to stimuli featuring a frequently occurring standard frequency (Grimm *et al.*, 2011; Alho *et al.*, 2012; Leung *et al.*, 2012; Recasens *et al.*, 2012; Althen *et al.*, 2013). Moreover, these MLR modulations represent true deviance detection as it was proved by Grimm and colleagues (2011), who applied a condition controlling for refractoriness-based effects (Schröger & Wolff, 1996; Jacobsen *et al.*, 2003). In these studies about frequency deviants, different test frequencies, stimulation paradigms and recording techniques were applied. The frequencies of the deviant stimuli ranged from 200 to 3730 Hz. The stimulation paradigms applied, were a simple oddball (Grimm *et al.*, 2011; Recasens *et al.*, 2012), a blocked frequency (Alho *et al.*, 2012) and a multi-feature paradigm (Leung *et al.*, 2012). Also in the second study of the present PhD thesis a frequency oddball paradigm was applied, but with two kinds of standards and deviants, as stimuli could occur either from the right or the left side of the subject. Thus, in this paradigm, there was variation regarding the stimulus location (Althen *et al.*, 2013). In sum, the results from these studies give evidence that the Nb enhancement to frequency deviants holds true for low pitched to moderately high pitched tones and suggest that a certain variability in the regularity trace can be tolerated. Frequency deviants modulated the MLR at later latencies and at a different MLR wave than intensity deviants, which suggests that different neural sources underlie the processes of deviance detection for these two auditory features. This is supported by studies in the rat, suggesting that sound frequency and intensity activate spatially distinct areas of the AC (Sally & Kelly, 1988; Takahashi *et al.*, 2004; see Astikainen *et al.*, 2006).

In the study on frequency deviants by Recasens and colleagues, field potentials extracted from the magnetoencephalogram were examined and the cerebral sources of the deviance-related activity in the magnetic MLR and the later magnetic MMN were modeled (Recasens *et al.*, 2012). The source reconstruction analysis of the data suggests that the deviance-related activity in the magnetic MLR had sources in AC and that these sources were spatially different for the magnetic MLR and the magnetic MMN. More precisely, the sources of the enhancements at the magnetic Nb wave triggered by frequency deviants were located in the vicinity of the right primary auditory cortex, whereas the sources of magnetic MMN were located in the right superior temporal gyrus - lateral and posterior to the sources of magnetic Nb. To the author's knowledge, the exact cerebral sources of deviance-related MLR activity for other feature deviants, has not been examined yet. Since the sources of the Na and the Pa wave are supposed to lie in primary AC (Burkard *et al.*, 2007) and the MLR modulations in response to intensity deviants occurred earlier than the modulations in response to frequency deviants, the cerebral sources of MLR modulations elicited by intensity deviants may also lie in primary AC, but upstream to the sources reported for frequency deviants.

In addition to the MLR elicited by deviance in the most basic auditory features described above, there is also evidence that deviance in pitch and temporal regularity is encoded at the level of the MLR. Pitch deviants, in form of band-pass-filtered broadband noise stimuli presented in an oddball paradigm, elicited an enhancement of the Pa wave (Slabu *et al.*, 2010). Another study aimed at testing whether the novelty-related modulations of the Nb wave to pure tone deviants also holds true for missing-fundamental pitch changes (Alho *et al.*, 2012). An enhancement of the Nb wave in response to the first changing stimulus after a block of repetitive standard stimuli was reported and the authors presumed that pitch processing presumably takes place at or near the primary auditory cortex. The results of a study on temporal regularity deviants in an oddball paradigm, by Leung and colleagues suggest that deviance in stimulus onset asynchrony (SOA) is reflected by an increased Pa and Nb amplitude (Leung *et al.*, 2013). A study, on even more complex sounds than harmonics showed a contrary effect on the MLR. Cornella and colleagues presented repetitive short descending frequency-modulated sweeps as standard and deviant stimuli in oddball paradigms including ascending frequency-modulated sweeps, and found that the Pa wave was larger in response to standards than to deviants (Cornella *et al.*, 2013). This is an important finding, since it is opposite to the results of the other studies on oddball deviants, which revealed that deviants trigged an enhancement of the MLR. Furthermore, it could indicate that at the level of the primary AC there is sensitivity for stimuli as complex as frequency-modulated sweeps, since its repetition is encoded, but the detection of a deviation from the standard trace might need a higher-order mechanism (see also Cornella *et al.*, 2013). In line with the findings by Cornella and colleagues, Slabu and colleagues showed that some aspects of the brainstem frequency-following response (FFR) to consonant-vowel /ba/-stimuli, were enhanced when they were presented as standard stimuli compared to when they were presented as deviant stimuli (Slabu *et al.*, 2012). Importantly, the main generators of FFR are supposed to be located subcortically in the ascending fibers of the lateral lemniscus towards the inferior colliculus and thus upstream to the sources of the MLR (Picton, 2011). Other recent studies on the FFR to repetitive sounds confirm these findings (Chandrasekaran *et al.*, 2009; Skoe & Kraus, 2010b).

Concerning the brainstem response there is further evidence from the first study of the present PhD thesis that the transient ABR to short clicks presented as standards and as lower intensity deviants does not show any differences at Wave V, with latencies of 7 to 9 ms from stimulus onset (Althen *et al.*, 2011). Similarly, in a study on pitch deviants by Slabu and colleagues, no differences for Wave V in response to standard and deviant stimuli were found (Slabu *et al.*, 2010). These negative finding for traces of regularity encoding at the level of the very early transient ABR indicate that in the distal lateral lemniscus and the inferior colliculus no encoding of stimulus probabilities takes place yet or that it is at least not reflected in the transient ABR (Stone *et al.*, 2009). In contrast, the FFR, which is an ongoing potential reflecting subcortical sustained, phase-locked activity elicited by the incoming stimulus and which probably can be modulated through the influence of descending fibers from cortical areas, seems to track the encoding of stimulus repetition (Skoe & Kraus, 2010a; Picton, 2011). Also electrophysiological recordings in rodents, by means of single cell responses, multi-unit responses and evoked local field potentials in the inferior colliculi have shown that, already at this early subcortical level, stimulus probabilities are encoded (Pérez-González *et al.*, 2005; Malmierca *et al.*, 2009; Zhao *et al.*, 2011; Ayala *et al.*, 2012; Duque *et al.*, 2012; Patel *et al.*, 2012; Pérez-González *et al.*, 2012; Anderson & Malmierca, 2013; for a review see Ayala & Malmierca, 2013). However, SSA to the standard stimuli, that is, a decreased response to standard stimuli and restored firing rate to deviant stimuli presented in oddball paradigms, was found. Moreover, SSA has been observed in the IC of the bat (Thomas *et al.*, 2012). That study suggests that only non-specialized neurons, which are not specialized, e.g., in directional frequency modulated sweeps, as used for communication, showed SSA. This could be linked to the finding by Cornella et al. (2013), stating that directional frequency modulated sweeps presented as deviants, did not elicit an enhanced MLR in humans, but in contrast, enhanced the responses to standard stimuli. Concerning the underlying mechanisms of SSA in the IC, there is a study by Pérez-González et al. (2012) which suggests that GABA(A)-mediated inhibition modulates SSA in the IC. Also in the MGB of the thalamus, which is the last important subcortical auditory nucleus, there are neurons, which adapt in a stimulus-specific manner, demonstrating decreased spiking rates in response to repetitive standard stimuli, and a restored response to frequency deviants, similar to neurons in the IC (Anderson *et al.*, 2009; Antunes *et al.*, 2010; Antunes & Malmierca, 2011; Bäuerle *et al.*, 2011; Richardson *et al.*, 2013). At the lowest level of the auditory pathway, that is in the cochlear nuclei of the brainstem, no SSA to sounds stimuli presented in an oddball paradigm has been observed in rodents (Ayala *et al.*, 2012). In sum, while in animal IC and MGB stronger cellular responses to deviants than to repetitive standard stimuli have been recorded, the transient ABR of the human AEP, with sources in or around the IC did not show any traces for regularity encoding (Slabu *et al.*, 2010; Althen *et al.*, 2011). As pointed out by Escera and colleagues (2013), an explanation could be that Wave V, as suggested by its short latencies, is generated in the ascending lemniscal portions of the IC, whereas SSA in animals was described predominantly for non-lemniscal parts of the IC. Another possible explanation for this discrepancy in the results on animals and humans is that the rodent and the human auditory system are not directly comparable. On the one hand, auditory evoked potentials in rodents can show shorter latencies than the human auditory evoked potentials, e.g. the N1 or MMN-like component (Sambeth *et al.*, 2003; Astikainen *et al.*, 2011). On the other hand, since in the rodent brain the auditory cortex is less developed than in humans, the subcortical processing of sound input might assume more complex processes than in humans. Furthermore, animals are normally anesthetized during the experiments, what can lead to alterations in the response properties of the neurons. What is more, neural activity in auditory nuclei does not always generate large AEPs in humans. Dendrites of the auditory regions in the human thalamus, for example, are oriented rather randomly, and consequently no large far-field potentials are produced (Burkard *et al.*, 2007).

As explained above, the suggested sources for the deviance-related activity at Nb wave in a frequency oddball paradigm, lie partially in the primary AC (Recasens *et al.*, 2012). However, for the sound features intensity and location, deviance-related activity of the Na and Pa wave have been observed and the sources of these waves are suggested to be located subcortically in the thalamus, in thalamocortical projections, or in the AC (Yvert *et al.*, 2001; Burkard *et al.*, 2007). In the studies on SSA in the rodent thalamus, typically deviance in the frequency domain was examined and there is, to the author's knowledge, no study showing a direct cellular correlate for the detection of intensity deviants in the thalamus or other subcortical structures in mammals. Therefore, the early deviance-related activity in response to intensity deviants found in the first study of the present thesis (Althen *et al.*, 2011), cannot be compared directly to the findings on SSA in the thalamus of mammals. However, it has been suggested by Reches and Gutfreund (2008) that neurons in the optic tectum of the barn owl, which is the avian homolog of the superior colliculus in mammals, are sensitive to sound intensity change. Moreover, in the primary AC of rodents, SSA to standard stimuli and restored responses to intensity deviants of an oddball paradigm were found (Ulanovsky *et al.*, 2003; Farley *et al.*, 2010). This could be the basic principle for the observed modulations of the MLR to intensity deviants in humans. As for intensity deviants, SSA to frequency standards and deviants has been described for neurons in the auditory cortex of rodents, cat and the monkey (Ulanovsky *et al.*, 2003; Ulanovsky *et al.*, 2004; Szymanski *et al.*, 2009; von der Behrens *et al.*, 2009; Farley *et al.*, 2010; Taaseh *et al.*, 2011; Fishman & Steinschneider, 2012; Yaron *et al.*, 2012). Especially interesting is a study by Fishman and Steinschneider, who recorded responses to standard and deviant stimuli of an oddball paradigm as well as to control stimuli from the awake monkey's primary AC (Fishman & Steinschneider, 2012). They report that field potentials, current source density components, multiunit activity, and induced high-gamma band responses were larger for deviant stimuli than for standards stimuli of the oddball paradigm.

In the second study of the present thesis a feature-conjunction paradigm was applied. The results showed that frequency-location deviants elicited no significant modulations of the MLR, although frequency deviants of an oddball paradigm with otherwise similar experimental design elicited an MLR enhancement at the Nb wave (Althen *et al.*, 2013). However, an MMN was elicited in both paradigms. This suggests that the encoding of frequency-location combinations or at least, the presentation probabilities of frequency-location combinations require neural sources downstream to the sources of the MLR. Consequently, one can also speculate that the latencies of the deviance-detection process for frequency-location combinations exceeds at least 50 ms. Other studies on more complex auditory regularities, yielded similar results. In a study on repetition deviants by Cornella and colleagues (2012) no deviance-related modulations of the MLR were observed. Another very recent study by Recasens and colleagues (submitted), examined the MLR and MMN to local rule violations versus global rule violations. "Local deviant" refers to low-probability stimuli, which differ in frequency from the repetitive tones of a four-tone sequence (A-A-A-B) and "global deviant" refers to infrequent repetitions of the last frequent stimulus in this sequence, which works as an established standard pattern (AAAB-AAAB-AAAaB). MMNm was obtained to global and to local deviants, while at the level of the MLR a deviance-related effect at the Nbm (45-55 ms) and the Pbm (60-75 ms) was only observed for local deviants. This suggests that distinct neuronal sources in the auditory cortex were active when detecting local and global regularity violations and that the encoding of the four-tone sequence as a standard pattern, which is necessary to detect the global deviants, does not take place at the early latencies and neuronal sources underlying the MLR.

According to the classification of invariance by Picton et al. (2000), explained in the Introduction, the feature-conjunction paradigm represents a hypercomplex invariance and a tone repetition paradigm represents a pattern invariance. The studies by Althen, Cornella, Recasens and colleagues strongly suggest that deviance in a hypercomplex and pattern invariance is not yet tracked at the level of the MLR (Cornella *et al.*, 2012; Althen *et al.*, 2013; Recasens *et al.*, submitted). At later latencies, MMN was elicited in all three studies and there is more evidence by many other studies that the violation of a hypercomplex or pattern invariance is indicated by MMN (e.g. Schröger *et al.*, 1992; Gomes *et al.*, 1997). Even in animals MMN-like responses to feature-conjunction deviants have been recorded (Astikainen *et al.*, 2006). To the author's knowledge, it has not been examined yet, whether stimuli which violate an abstract invariance elicit modulations of the MLR. However, it is improbable that an abstract invariance, which displays an invariance as complex as the hypercomplex or the pattern invariance, would be tracked at latencies as early as the latencies of the MLR. A complex invariance, where none of the standard stimuli are identical, but all are the same regarding at least one feature, has, to author's knowledge, not been tested neither. In the third study of the present thesis the multi-feature paradigm was applied (Althen *et al.*, in preparation). In this paradigm, three types of deviants were presented, so that there was a certain variation in the stimuli which formed the standard trace. The results showed that frequency-intensity double deviants elicited a significant enhancement of the Nb and Pb wave of the MLR compared to the MLR to standard stimuli. Also a study by Leung and colleagues (2012), who applied the original version of the multi-feature paradigm, suggests that frequency deviants elicit an enhanced Nb wave. In this paradigm, every second stimulus was a deviant, and four types of deviants were presented. That is, the standard trace was highly variable. The outcome of these two studies, point to a toleration of feature variation in the standard trace at the level of the MLR. Nevertheless, it would be interesting to record the MLR to stimuli of a complex invariance in a future study, in order to examine the exact extent of this tolerance for variance in the standard trace.

In the third study of the present thesis the MLR to frequency-intensity double deviants was tested (Althen *et al.*, in preparation). Double deviants elicited an enhancement of two MLR waves, the Nb and the Pb wave. It has been shown in several precedent studies that deviance in frequency triggers an enhancement of the Nb wave (see above). An additional enhancement of the magnetic Pb wave has also been reported by Recasens and colleagues (submitted). Moreover, in the second study of the present thesis higher amplitudes of the Pb wave were observed in response to frequency deviants compared to standard stimuli (even though this was not explicitly statistically tested in the respective publication). Thus, regarding the frequency domain, the enhancements of the Nb and Pb waves in response to the double deviants go in line with the results of precedent studies. However, due to the rather big frequency difference of standard and deviant stimuli and given that the auditory system has a tonotopic organization (Malmierca *et al.*, 2008), this Pb modulation may be partly due to release from neural refractoriness. Regarding the intensity domain, there is evidence from the first study of the present thesis that single intensity deviants elicit an enhancement of the Na/Pa slope of the MRL (Althen *et al.*, 2011). Strikingly, the deviance-related modulations found in the double-deviant study, started 20 ms later than in the study on intensity deviants. This could be based upon several facts. First, in the intensity study, the used stimuli were clicks, while in the double-deviant study pure-tones were used and it is probable that the clicks were processed faster than the pure tones. Secondly, it is expectable that the standard trace in the multi-feature paradigm was not formed as firmly as in the oddball paradigm. Furthermore, the enhancement of the Nb and Pb wave elicited by frequency-intensity deviants was twofold as high in amplitude as the enhancement at the same MLR waves, elicited by the single deviants. This could imply that deviance in two auditory features instead of one feature doubles the perceptibility at the level of the MLR. It would be interesting to investigate in future studies if this holds also true for other auditory feature combinations. Since it has been suggested by this and other studies that the frequency-intensity double MMN is not additive, it seems that at earlier latencies, reflected by the MLR, the two features frequency and intensity are encoded more independently from each other than at later latencies, reflected by the MMN.

When recording the MLR there are some general limitations, which will be discussed in this paragraph. One major point is that a high number of recordings is needed to obtained a sufficiently good signal-to-noise ratio of the MLR. Since an experimental session cannot exceed a length, which is comfortable for the participant, auditory designs with long SOAs and low deviant probabilities are critical. Another important point is that a clear MLR can only be recorded in response to short sounds. Moreover, as the amplitudes of MLRs are small, a moderate to high presentation intensity is often applied. Studies, which suggest that subcortical SSA in animals is greater to stimuli presented at moderate intensities than at loud intensities, could indicate that stronger deviance-related modulations of the MLR might be obtained if softer stimulation was feasible (Duque *et al.*, 2012; Richardson *et al.*, 2013). What is more, when recording MLR to stimuli of moderate to high intensities, it must always be taken into account that there is the potential risk of confound with the post-auricular muscle response, which has latencies similar to the latencies of the MLR (Burkard *et al.*, 2007). Moreover, it is very important to compare standard, deviant and control stimuli with the same physical properties, because the MLR latencies and amplitudes change with sound characteristics like frequency, amplitude or location. In the studies of the present thesis we tried to consider all these points when designing and analyzing the experiments. However, the restrictions in the sequence design probably have contributed to the fact that the deviance-related activities which we observed in the first and second study were numerically rather small and for the single deviants of the third study not even significant. It is likely that with lower deviant probabilities stronger effects would have been observed, but with regard to the high trial number which had to be recorded, we chose the given probabilities. Furthermore, it must be taken into account that filtering the EEG data can potentially introduce distortions and shifts in the latencies of the deviance-related effects (Widmann & Schröger, 2012). However, based on simulations conducted by colleagues of our lab, we assume that the non-causal filters used in the studies of the present thesis, introduce less distortions into the MLR data, than causal filters would do. What is more, the signal-to-noise level of the MLRs recorded in the third study was not optimal. Electrical noise in the EEG signal, which blurs the MLR, can be attributed, amongst others, to potentials evoked by muscle activity, which have similar frequencies as the MLR, or to artifacts from the 50 Hz electrical currents of the electrical power system (Picton, 2011).

The results of the present PhD thesis corroborate the notion that important initial processes of detecting deviants in simple acoustic regularities are mirrored in the MLR. Based on the studies of the present thesis and the studies outlined in this discussion, one can say that the encoding of sound probabilities is a pervasive property of the auditory system, which has its first origins in subcortical auditory structures, as shown by animal SSA in the inferior colliculi and the MGB as well as by FFR studies in humans (Malmierca *et al.*, 2009; Antunes *et al.*, 2010; Slabu *et al.*, 2012; for a review see Escera & Malmierca, 2013). In animals, subcortical SSA was predominantly observed in nonlemniscal regions (Pérez-González *et al.*, 2005; Malmierca *et al.*, 2009; Antunes *et al.*, 2010; Zhao *et al.*, 2011; Duque *et al.*, 2012; Ayala *et al.*, 2013), which receive strong cortifugal input from the AC (Winer *et al.*, 1998; Winer, 2005; Malmierca & Ryugo, 2011). In contrast to this stands the finding that SSA is pervasive in primary AC and that the primary AC is the first lemniscal station (Ulanovsky *et al.*, 2003; Antunes & Malmierca, 2011). Therefore it was hypothesized that SSA found in the subcortical regions is based on cortifugal projections from the auditory cortex (Ulanovsky *et al.*, 2003; Nelken & Ulanovsky, 2007). However, a study by Anderson and Malmierca, where SSA in the IC was examined with and without cortical deactivation, suggests that SSA in the IC generally does not depend on efferent cortical projections (Anderson & Malmierca, 2013). Moreover, Antunes and Malmierca tested whether SSA in the MGB depends on the functioning of the AC, by means of deactivating the AC with cooling (Antunes & Malmierca, 2011). Their results suggest that SSA in the MGB is modulated, but not abolished by deactivation of the AC (Anderson & Malmierca, 2013). However, it must be taken into account that the experimental animals in both studies where anesthetized, which could have led to suppression of the cortical input (Richardson *et al.*, 2013). The notion that SSA is generated subcortically is also supported by the fact that the maximal differences between standard and deviant responses in the IC occur in the onset portion of the responses (e.g. Malmierca *et al.*, 2009; Duque *et al.*, 2012; Escera & Malmierca, 2013).

It has been proposed that SSA to stimulus probabilities observed in animal auditory subcortical and cortical structures could be the single neuron correlate to the deviance-related activity in the human AEP due to its similar characteristics to MMN regarding, e.g. stimulus SOA or frequency contrast of deviant and standard stimuli (Ulanovsky *et al.*, 2003; Escera & Malmierca, 2013). The latencies of neurons which showed SSA in subcortical and cortical auditory structures were as short as 20-30 ms, but for some neurons they extended to up to 250 ms (Ulanovsky *et al.*, 2003; Pérez-González *et al.*, 2005; Antunes *et al.*, 2010). Since the deviance-related modulations in the MLR, with short latencies of 20 to 50 ms, occur earlier than MMN and have brain sources upstream to those of MMN, it is probable that they reflect the onset portion of the cellular SSA more directly than MMN. Regarding the exact characteristics of the deviance-related activity in the MLR related to SOA or the frequency contrast of the oddball sequence, no conclusions can be drawn yet. Due to the small effect size of the deviance-related activity in the MLR, it still is a technical challenge to design stimulus sequences on this question. However, there is one major difference between the deviance-related effects of the human MLR and SSA on cellular level recorded in animals. The enhancements of the MLR by frequency and location deviants are supposed to reflect true deviance detection, since the responses to the deviants are stronger than the responses to the control stimuli (Grimm *et al.*, 2011; Grimm *et al.*, 2012). In contrast, for SSA in animals there is no clear evidence that deviants elicit stronger responses than control stimuli of a control condition, like used in the studies by Grimm et al. On the one hand, results of a study by Taaseh et al. on this issue, suggest that enhanced responses to deviants in rat AC are at least partially due to true deviance-detection and not only based on adaptation to the standard stimuli (Taaseh *et al.*, 2011). On the one hand, recordings from primary AC of the awake rat and the awake Macaque, where a frequency oddball and a control paradigm were applied, showed that responses to the control and the deviant stimuli were similar, which indicates that enhanced responses to deviant compared to standard stimuli are based on adaptation to standard stimuli instead of on true deviant detection (Farley *et al.*, 2010; Fishman & Steinschneider, 2012). Consequently, it might be that deviance-related modulations of the human MLR reflect a more advanced stage of regularity encoding, that is to say, a stage, which goes beyond the pure detection of stimulus repetition. In the MMN, an even higher stage of deviance-detection is revealed, since MMN is sensitive to deviance from complex and abstract regularities. This confirms the theory that the detection of auditory deviants happens in a hierarchical order. In humans, at the level of the brainstem, simple regularities are likely encoded by an increased synchronization for the repeated standard stimulus. In the MLR, with sources in core AC areas, deviance from a simple regularity is encoded by an enhanced response to the deviants, but deviance from more complex regularities is not reflected yet. This suggests that at the level of the MLR the formation of a sensory memory, but yet no "primitive intelligence" is reflected (Näätänen *et al.*, 2001; Näätänen *et al.*, 2010). The encoding of complex regularities seems to be restricted to higher-order auditory and other cortex areas, which underlie the MMN (see also Winkler *et al.*, 2009; Grimm & Escera, 2011; Escera & Malmierca, 2013).

In future research it would be interesting to study active paradigms in order to examine if the deviance-related MLR responses are modulated by attention, since there is evidence that MMN is modulated by attention, although it is widely regarded as reflecting a preattentive auditory process (Sussman, 2007). Furthermore, the MLR in response to auditory regularities and its violations could be examined in patient groups, since some patient groups, like schizophrenics show altered MMN (Näätänen *et al.*, 2011b). As it has been shown that already in newborns MMN-like responses are elicited (Näätänen *et al.*, 2011b), it could further be tested if also deviance-related MLR responses can be recorded in newborns.

CONCLUSIONS

The goal of the present PhD thesis was to investigate the role of the MLR in auditory deviance detection and to study the level of regularity complexity being encoded at the level of the MLR. The ABR, MLR and MMN were recorded in response to regular and deviating stimuli, presented in three auditory paradigms with different levels of invariance, in order to have a direct comparison of early, subcortical, early cortical and later cortical traces of deviance detection.

1) The results of the first study suggest that intensity deviants are encoded by an enhancement of the MLR at the slope from the Na to the Pa wave at approximately 24 ms from stimulus onset. A "true" deviance detection in terms of a stronger response to deviants than to control stimuli could not be confirmed. In addition, an MMN was elicited. In contrast, in the ABR no traces for regularity encoding were observed.
2) The outcome of the feature-conjunction study suggests that frequency-location deviants are not tracked at the level of the MLR. Comparisons of the Na, Pa and Nb waves elicited by standard and deviant stimuli showed no significant differences. However, in the oddball condition, a larger Nb component was elicited in response to frequency deviants than in response to standard stimuli. In contrast, an MMN was elicited in the feature-conjunction as well as in the oddball condition. This indicates that auditory regularities as complex as the feature-conjunction paradigm require brain sources downstream to the sources underlying the MLR.
3) In the third study, the Nb and Pb waves recorded in response to double deviants were significantly larger than in response to standard stimuli of the multi-feature condition, whereas for single deviants no significant enhancement was found. Moreover, the enhancement elicited by the double deviants was as large as the sum of the enhancements elicited by the single deviants. An MMN was elicited by all three deviant types. Since double deviants elicited a significant MLR modulation, the optimum-2 version of the multi-feature paradigm generally seems to be applicable as an alternative to the oddball paradigm.

We conclude that the early deviance detection at the level of the MLR holds only true for auditory regularities as simple as the oddball or the multi-feature paradigm (applied in study one and three), where formation of the standard trace does not require feature-combining or extraction of an abstract rule. Summarizing the results of the present thesis and of precedent studies, it was shown that simple deviation in intensity, frequency, location, pitch and SOA is tracked by modulations of the MLR. Furthermore, the results of the present thesis on the MLR to frequency-intensity double deviants suggest that deviations in the auditory features frequency and intensity are processed independently from each other. Based on evidence from the present thesis and other related studies, we conclude that the regularity encoding and deviance detection of stimuli presented in more complex auditory paradigms than the simple oddball or the multi-feature paradigm requires higher-order brain mechanisms than those reflected in the MLR, as indicated by the elicitation of the long-latency MMN. This goes in line with the hypothesis of a hierarchically working auditory novelty system.

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ANNEX: SPANISH SUMMARY

Introducción

Nuestro ambiente acústico es rico en sonidos: voces, música o el simple sonido del tintineo de un vaso en una ruidosa fiesta. Éstos tienen diferentes orígenes, frecuencias, intensidades y otros aspectos auditivos divergentes. Dado que la audición es un sentido no dirigido y sólo una parte de la información puede ser percibida conscientemente, la enorme cantidad de "input" acústico que llega al oído debe ser filtrado durante su procesamiento a lo largo de la vía auditiva. Una forma de estructuración de este "input" de sonido es retenerlo en forma de objetos de sonido, que se forman gracias a que los estímulos tienen una cierta regularidad en común (para una revisión véase Winkler *et al.*, 2009). Estas regularidades auditivas se almacenan en forma de trazas en la memoria sensorial y nos permiten crear predicciones acerca de los objetos auditivos futuros. Los sonidos entrantes se comparan con las predicciones y cualquier desajuste del "input" entrante con éstas se detecta de manera automática (Bendixen *et al.*, 2009; para una revisión véase Bendixen *et al.*, 2012). Estímulos desajustados son, a menudo, de gran importancia por lo que se detectan sin siquiera prestarles atención y pueden provocar un cambio de atención involuntario hacia ellos (Escera *et al.*, 2000; Escera & Corral, 2007; Sussman, 2007). Esta reorientación de la atención es esencial para una reacción adecuada hacia estímulos auditivos significativos en nuestra vida cotidiana y en particular en situaciones peligrosas.

En 1978, Näätänen y sus colaboradores descubrieron un potencial evocado auditivo humano que refleja este proceso de detección de sonidos desviados (Näätänen *et al.*, 1978). En su experimento, denominado paradigma "oddball", se presentó una secuencia de sonidos que los participantes escucharon de manera activa y pasiva, durante la cual se registró su electroencefalograma (EEG). El paradigma "oddball" es una secuencia de sonidos sencilla, que se compone de sonidos repetitivos estándar que no cambian y sonidos desviados que ocurren con poca frecuencia y al azar y que difieren en una o varias propiedades acústicas de los estímulos estándar. Cuando los investigadores compararon los potenciales evocados auditivos (ingl. auditory evoked potentials; AEPs) en respuesta a los estímulos estándar y a los sonidos desviados, encontraron que la violación de la regularidad auditiva por los sonidos desviados provocaba una negatividad en los AEPs. La diferencia de potencial en los AEPs estándar y desviados se denominó "el potencial de disparidad" (ingl. mismatch negativity; MMN; Näätänen *et al.*, 2007). En dependencia al paradigma que se aplica, la MMN alcanza su pico entre los 150 y los 250 ms desde el inicio del estímulo (Näätänen *et al.*, 2007). Desde su descubrimiento, la MMN se ha estudiado ampliamente y se aplica como un marcador psicofisiológico para investigar tanto funciones como disfunciones cognitivas (para revisiones vease Näätänen & Escera, 2000; Kujala *et al.*, 2007; Näätänen *et al.*, 2011; Näätänen *et al.*, 2012).

Recientemente, se descubrió que la violación de una regularidad acústica también se refleja en latencias más tempranas que las de la MMN por medio de modulaciones de la respuesta de latencia media humana (ingl. middle latency response; MLR) del AEP (para revisiones véase Grimm & Escera, 2011; Escera *et al.*, 2013). Esto fue un hallazgo importante, ya que indica que la detección de sonidos desviados es una propiedad del sistema auditivo más rápida y más básica de lo que se pensaba originariamente. En consecuencia, muchas preguntas han surgido acerca de las características de esta actividad de la MLR. La búsqueda de respuestas a estas preguntas será un paso importante en la exploración del funcionamiento del sistema de la novedad auditiva y una contribución esencial a la base de conocimientos sobre el sistema auditivo. Comprender las funciones básicas del sistema auditivo, a su vez, es fundamental para el estudio de funciones auditivas más sofisticadas como, por ejemplo, la percepción de la música y el habla (Tervaniemi & Huotilainen, 2003; Pulvermüller & Shtyrov, 2006; Rohrmeier & Koelsch, 2012). Además, podría facilitar la investigación y el tratamiento de disfunciones auditivas y trastornos neurológicos como la esquizofrenia, así como contribuir al desarrollo de dispositivos médicos como audífonos, implantes de cóclea e interfaces cerebro-ordenador auditivas (Näätänen *et al.*, 2012).

Objetivos

El objetivo de esta tesis doctoral es analizar el papel de la MLR en el proceso de detección de la novedad auditiva. Más concretamente, y en base a la hipótesis de que el sistema de la novedad auditivo funciona de una manera jerárquica, el objetivo es estudiar el nivel de complejidad de las regularidades codificadas durante la MLR (Winkler *et al.*, 2009; Grimm & Escera, 2011; Escera & Malmierca, 2013). Para este fin, se registraron las MLRs en respuesta a paradigmas de la novedad auditivas con diferentes grados de complejidad. Al mismo tiempo la MMN fue analizada con el fin de obtener una comparación directa entre la MLR y las AEPs de larga latencia de estímulos estándar, desviados y, cuando fuera posible, estímulos de control.

1) El objetivo del primer estudio fue comprobar si estímulos desviados en intensidad, en un paradigma “oddball”, evocarían incrementos en la MLR. Además de la MLR se registró la MMN y la respuesta del tronco auditivo (ingl. auditory brainstem response; ABR).
2) La secuencia auditiva que se aplicó en el segundo estudio es un paradigma “feature-conjunction” con dos estándares con diferentes combinaciones de frecuencia y ubicación. Además, se presentó un paradigma “oddball” con estímulos desviados en frecuencia.
3) En el tercer estudio, que se ejecutó en la “Cognitive Brain Research Unit” de la Universidad de Helsinki, comparamos las modulaciones de la MLR en respuesta a estímulos desviados en dos características y en una sola característica presentados en el paradigma “multi-feature”.

Resúmenes de los estudios (Traducciones de los abstracts de los artículos originales)

Resumen Althen et al. 2011

La detección de un sonido desviado es una función decisiva del sistema auditivo y está reflejada en el Potencial Evocado auditivo de Disparidad, generado automáticamente entre los 100 y 250 ms después del inicio del estímulo novedoso. Recientemente se ha demostrado que estímulos dispares en frecuencia y localización, que ocurren raramente en un paradigma "oddball", provocan una respuesta con un potencial eléctrico más negativo que los sonidos estándar en latencias muy tempranas de la respuesta de latencia media del potencial evocado auditivo humano. Esta pronta capacidad del sistema auditivo está corroborada por el hallazgo en animales de neuronas, tanto en la corteza auditiva como en estructuras subcorticales, capaces de restablecer su sensibilidad de respuesta, previamente adaptada frente a sonidos estándar, cuando ocurre un cambio infrecuente en una característica de sonido. En este estudio investigamos si la detección de estímulos dispares en intensidad se refleja también en latencias más tempranas que las del Potencial de Disparidad. Los potenciales evocados auditivos en respuesta a sonidos de tipo "clic" fueron analizados en las latencias propias de la respuesta auditiva del tronco encefálico, la respuesta de latencia media y del Potencial Evocado de la Disparidad. Los estímulos dispares con una intensidad menor que la de los estímulos estándar provocaron, además de un Potencial Evocado de Disparidad, un potencial eléctrico más negativo en la respuesta de latencia media en torno a la transición entre el componente Na y el componente Pa, aproximadamente unos 24 ms después del inicio del estímulo dispar. Este hallazgo, juntos con estudios sobre cambios en frecuencia y localización, sugiere que la detección temprana y automática de sonidos dispares en un paradigma "oddball" es una propiedad general del sistema auditivo.

Resumen Althen et al. 2013

La detección de estímulos auditivos que se desvían de una regularidad auditiva simple o compleja está reflejada en el Potencial Evocado auditivo humano de Disparidad. Además, las desviaciones simples en un paradigma "oddball" modulan la respuesta precursora de latencia media del potencial evocado auditivo. En los paradigmas "oddball" de frecuencia se ha mostrado que la onda Nb, evocada aproximadamente a los 40 ms del inicio del estímulo, aumenta su potencial en respuesta ante estímulos desviados en comparación con estímulos estándar. En este estudio comprobamos si la detección de estímulos auditivos desviados en un paradigma de características combinadas (frecuencia-localización) se refleja en las modulaciones de las ondas Na, Pa o Nb de participantes humanos sanos. Asimismo, se empleó un paradigma “oddball” de frecuencia para contrastar directamente los resultados de una desviación simple y de una desviación compleja. Los estímulos dispares con características combinadas no provocaron ninguna modulación de las ondas de latencia media, mientras que los estímulos dispares del paradigma “oddball” de frecuencia provocaron un aumento de la onda Nb, confirmando así los resultados de estudios previos. En ambas condiciones se generó un Potencial de Disparidad significativo. Este mostró una mayor amplitud así como una latencia de respuesta más corta en la condición “oddball” que en la condición de características combinadas. Estos resultados corroboran la idea de que las regularidades auditivas simples están codificadas en niveles inferiores de procesamiento, en comparación con aquellas de características auditivas más complejas, y están en sintonía con la idea de que el sistema auditivo de novedad funciona de forma jerárquica.

Resumen Althen et al. en preparación

Estudios recientes sobre la detección de la desviación auditiva han demostrado que sonidos desviados de un paradigma “oddball”, que solo se desvían en una característica auditiva, provocan aumentos del potencial evocado de latencia media auditiva humana entre los 20 y 50 ms después del inicio de la desviación. En el presente estudio hemos examinado el potencial evocado de latencia media auditivo y el Potencial Evocado auditivo de Disparidad en respuesta a desviaciones en frecuencia, intensidad y doble desviación en la condición óptima-2 del paradigma “multi-feature”. Además, el Potencial Evocado auditivo de Disparidad en respuesta a desviaciones dobles se comparó con el Potencial Evocado auditivo de Disparidad en respuesta a estímulos desviados dobles de un paradigma “oddball” en el que no se presentaron estímulos desviados en una sola característica auditiva. En el paradigma “multi-feature”, estímulos desviados dobles provocaron aumentos significativos de las ondas Nb y Pb del potencial evocado de latencia media en comparación con las ondas Nb y Pb en respuesta a los estímulos estándar. Estos aumentos igualaron aproximadamente la suma de los aumentos provocados por los estímulos desviados en una sola característica auditiva. Por el contrario, el Potencial Evocado auditivo de Disparidad provocado por los estímulos desviados dobles no mostró tal efecto acumulado. Potenciales Evocados auditivos de Disparidad provocados por estímulos desviados dobles en el paradigma “multi-feature” y en el paradigma “oddball” no mostraron diferencias significativas en su amplitud o latencia. Llegamos a la conclusión de que estímulos desviados dobles provocan un aumento del potencial evocado de latencia media más fuerte que estímulos desviados en una sola característica auditiva y que la condición óptima-2 del paradigma “multi-feature” se puede utilizar para medir modulaciones del potencial evocado de latencia media relacionados con la desviación. Por otra parte, el Potencial Evocado auditivo de

Disparidad provocado por estímulos desviados dobles del paradigma “multi-feature” no parece verse afectado por el hecho de que los estímulos desviados en una sola característica, con características auditivas coincidentes, se presentan en la misma secuencia de sonidos.

Resultados

Los estímulos desviados en intensidad que fueron presentados en el primer experimento suscitaron una negatividad en la transición de la onda Na a la onda Pa de la MLR, en comparación con la respuesta provocada por estímulos estándar físicamente idénticos. Además, se obtuvo una MMN. La onda V de la ABR en respuesta a los diferentes tipos de estímulo no mostró diferencias. En el segundo estudio, la onda Nb de la MLR aumentó en respuesta a estímulos desviados en frecuencia, en comparación con los estímulos estándar del paradigma “oddball”. Sin embargo, la comparación de la MLR en respuesta a los estímulos desviados y estándares del paradigma “feature-conjunction” no reveló diferencias. Una MMN se obtuvo en los dos paradigmas. En el tercer estudio, estímulos desviados en frecuencia e intensidad provocaron un aumento significativo de la MLR que parecía de tipo aditivo, en comparación con el aumento provocado por los estímulos desviados en solo una característica.

Discusión

Los resultados de Recasens y colaboradores sobre los campos magnéticos evocados por estímulos desviados en frecuencia presentados en un paradigma “oddball” sugieren que las modulaciones en la MLR magnética provocadas por la desviación de la regularidad tenían sus fuentes en la corteza auditiva y que estas fuentes fueron anatómicamente diferentes para la MLR magnética y la MMN magnética (Recasens *et al.*, 2012). Al suponerse que las fuentes de las ondas Na y Pa de la MLR se encuentran en la corteza primaria (Burkard *et al.*, 2007) y que las modulaciones de la MLR provocadas por estímulos desviados en intensidad se produjeron antes que las modulaciones provocadas por estímulos desviados en frecuencia, las fuentes cerebrales de las modulaciones de la MLR provocadas por estímulos desviados en intensidad deberían encontrarse también en la corteza auditiva primaria, pero en un nivel mas básico que las fuentes reportadas para los estímulos desviados en frecuencia.

Los resultados del segundo estudio sugieren que la codificación de una combinación de frecuencia y ubicación o, por lo menos, de las probabilidades de presentación de combinaciones de frecuencia y ubicación requieren fuentes neuronales de un nivel superior al nivel de las fuentes de la MLR (Althen *et al.*, 2013). En consecuencia, se puede especular que las latencias del proceso de detección de desviación de combinaciones de frecuencia y ubicación superan al menos 50 ms. Otros estudios sobre regularidades auditivas más complejas dieron resultados similares. En un estudio sobre estímulus desviados por repetición de Cornella y colaboradores no se observaron modulaciones de la MLR relacionados a la desviación (Cornella *et al.*, 2012). Otro estudio muy reciente de Recasens y colaboradores (Recasens *et al.*, submitted), examinó la MLR y la MMN en respuesta a violaciones de reglas locales frente a violaciones de reglas globales y no se encontró ninguna modulación de la MLR en respuesta a violaciones de las reglas globales, que requieren codificación de un corto patrón de tonos.

En el tercer estudio, el aumento de las ondas Nb y Pb provocado por estímulos desviados dobles en frecuencia e intensidad era el doble de alto en amplitud que el aumento provocado en las mismas ondas de MLR por los estímulos desviados individuales solo en frecuencia o intensidad (Althen *et al.*, in preparation). Esto podría implicar que la desviación en dos características auditivas en lugar de en una característica duplica la perceptibilidad al nivel de la MLR. Sería interesante investigar en futuros estudios si esto es también cierto para otras combinaciones de características auditivas. Dado que se ha sugerido por este y otros estudios que la MMN en respuesta a estímulos desviados dobles en frecuencia e intensidad no iguala la suma de los aumentos provocados por los estímulos desviados individuales parece que, en latencias más tempranas y en regiones más básicas de la corteza auditiva, las dos características, frecuencia e intensidad, se codifican de manera más independiente que en latencias más tardanas y en regiones más altas de la corteza auditiva. Esto está apoyado por el hecho de que en regiones más altas de la corteza auditiva se lleva a cabo más integración de características auditivas.

Medidas intracerebrales recientes en la rata, el ratón y el gato revelaron que las probabilidades de estímulos están codificados incluso al nivel de neuronas individuales en el tálamo, el colliculo inferior y en la corteza auditiva (Ulanovsky *et al.*, 2003; Pérez-González *et al.*, 2005; Anderson *et al.*, 2009). Estas llamadas "neuronas de novedad" mostraron disminución de la ratio de disparo en respuesta a sonidos repetitivos y una ratio de disparo restaurada a los sonidos desviados de un paradigma "oddball", un fenómeno conocido como adaptación estímulo-específica (para una revisión reciente véase Escera & Malmierca, 2013).

Se ha propuesto que la adaptación estímulo-específica podría ser el correlato celular de la actividad relacionada con la desviación observada en los AEPs humanos debido a sus características similares a la MMN con respecto a, por ejemplo, el intervalo de presentación de estímulos o contraste de frecuencia de los estímulos desviados y estándares (Ulanovsky *et al.*, 2003; Escera & Malmierca, 2013). Las latencias de las neuronas que mostraron adaptación estímulo-específica en las estructuras auditivas subcorticales y corticales fueron tan cortas como de 10 a 20 ms, pero para algunas neuronas se extendieron a un máximo de 250 ms (Pérez-González *et al.*, 2005; Antunes *et* *al.*, 2010). Como las modulaciones de la MLR provocadas por desviación tienen latencias cortas de 20 a 50 ms, se producen antes que la MMN y disponen de fuentes cerebrales de un nivel más bajo que la MMN, es probable que reflejen la primera parte de la adaptación estímulo-específica más directamente que la MMN.

Conclusiones

Llegamos a la conclusión de que la detección de desviación temprana en el nivel de la MLR es sólo cierta para regularidades auditivas tan simples como el paradigma “oddball” o el paradigma “multi-feature”, donde la formación de la traza estándar no requiere la combinación de características auditivas o la extracción de una regla abstracta. Resumiendo los resultados de la presente tesis y de estudios precedentes, se ha demostrado que la desviación simple en intensidad, frecuencia, lugar de origen, altura del tono e intervalo entre los estímulos está indicada por modulaciones de la MLR. Por otra parte, los resultados de la presente tesis sobre la MLR en respuesta a desviados dobles, en frecuencia e intensidad, sugieren que la desviación en dos características auditivas provoca un aumento de la MLR de tamaño doble al aumento provocado por la desviación en una sola característica auditiva, que apunta a un procesamiento independiente de la desviación en las características. Basada en pruebas por la presente tesis y otros estudios relacionados, se concluye que la codificación de regularidad y de la detección de desviación de estímulos presentados en paradigmas auditivos más complejos que el paradigma “oddball” o el paradigma “multi-feature” requiere mecanismos cerebrales de orden superior de los que se refleja en la MLR, como se indica por la provocación del potencial de larga latencia MMN. Esto va en línea con la hipótesis de que el sistema de la novedad auditiva trabaja de forma jerárquica.

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