Regularity encoding in the auditory brain as revealed by human evoked potentials

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SUMMARY

Acoustic regularity encoding has been associated with a decrease of the neural response to repeated stimulation underlying the representation of auditory objects in the brain. The present thesis encloses two studies that sought to assess the neural correlates of acoustic regularity encoding in the human auditory system, by means of analyzing auditory evoked potentials.

Study I was conducted at the Cognitive Neuroscience Research Group, at the Faculty of Psychology of the University of Barcelona (Barcelona, Catalonia, Spain), under the direct supervision of Dr. Carles Escera. This study aimed to explore the dynamics of adaptation of the auditory evoked potentials to probabilistic stimuli embedded in a complex sequence of sounds. The main outcome of this study was the demonstration that the amplitude of auditory evoked potentials adapts to the complex history of stimulation with different time constants concurrently: it adapts faster to local and slower to global probabilities of stimulation. This study also showed that auditory evoked potential amplitudes correlate with stimulus expectancy as defined by a combination of local and global stimulus probabilities.

Study II was conducted at the Institute of Child Health (ICH), at the University College of London (UCL; London, United Kingdom), under the direct supervision of Dr. Torsten Baldeweg. This study aimed to explore the influence of timing predictability in the neural adaptation to probabilistic stimuli. The main outcome of this study was the demonstration that timing predictability enhances the repetition-related modulation of the auditory evoked potentials amplitude, being essential for repetition effects at early stages of the auditory processing hierarchy.

LIST OF ORIGINAL PUBLICATIONS

STUDY I

Costa-Faidella, J., Grimm, S., Slabu, L., Díaz-Santaella, F. & Escera, C. (2011). Multiple time scales of adaptation in the auditory system as revealed by human evoked potentials. *Psychophysiology, 48*(6), 774-783.

STUDY II

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This work has been carried out at the Cognitive Neuroscience Research Group (Centre of Excellence established by the Generalitat de Catalunya, 2009SGR11) at the Department of Psychiatry and Clinical Psychobiology, Faculty of Psychology, University of Barcelona (UB; Barcelona, Catalonia, Spain), lead by Dr. Carles Escera, and partly at the Institute of Child Health (ICH), University College of London (UCL; London, United Kingdom) lead by Dr. Torsten Baldeweg. This work has been supported by the Spanish Ministry of Science and Innovation (pre-doctoral fellowship FPU (AP2007-01084) and grants PSI 2008-00968-E; PSI2009-08063; EUI2009-04086; Consolider-Ingenio2010 CSD2007-00012) and the ICREA Academia Distinguished Professorship awarded to Carles Escera.

ABBREVIATIONS

AEP	Auditory Evoked Potential
ASA	Auditory Scene Analysis
DEV	Deviant
EEG	Electroencephalography
LLR	Long Latency Range (of the AEP)
MLR	Middle Latency Range (of the AEP)
MMN	Mismatch Negativity
NMDA	*N*-methyl *D*-aspartate (Glutamate receptor)
RP	Repetition Positivity
SSA	Stimulus Specific Adaptation
STD	Standard

CONTENTS

Introduction

INTRODUCTION

"Imagine that you are on the edge of a lake and a friend challenges you to play a game. The game is this: Your friend digs two narrow channels up from the side of the lake. Each is a few feet long and a few inches wide and they are spaced a few feet apart. Halfway of each one, your friend stretches a handkerchief and fastens it to the sides of the channel. As waves reach the side of the lake they travel up the channels and cause the two handkerchiefs to go into motion. You are allowed to look only at the handkerchiefs and from their motions to answer a series of questions: How many boats are there on the lake and where are they? Which is the most powerful one? Which one is closer? Is the wind blowing? Has any large object been dropped suddenly into the lake?" (Bregman, 1990, p. 5-6).

Auditory scene analysis: the cocktail party problem

The game proposed by Bregman (1990) is an analogy to the problem that our auditory system faces every day. The water of the lake represents the surrounding air. The two channels are our ear canals, and the handkerchiefs our eardrums. It seems impossible to be successful in playing such a game the way it is posed; yet, we are not surprised of our hearing's ability to know how many people are talking in a room, which one talks louder, which one is closer, or if there is a loudspeaker crying our favorite song. The problem of partitioning the mixed air vibrations reaching our eardrums into auditory streams (i.e., perceptually bound collections of sounds that together constitute an event) was termed Auditory Scene Analysis (ASA) by Bregman in his comprehensive

review (1990). The same problem was previously referred to as the cocktail party problem (Cherry, 1953), in reference to our common experience of being in a crowded party with dozens of people talking concurrently, glasses clinking, music playing, but still being able to focus our attention and understand what our interlocutor is telling us.

Figure 1. A typical cocktail party. The listener must follow the conversation of interest despite many concurrent sound sources. (Image from Breakfast at Tiffany's: Paramount Pictures).

The cocktail party problem, or ASA, has generated extensive research, both in psychophysics (Van Noorden, 1975; Bregman 1990) and in the search of its neuronal mechanisms (Bidet-Caulet & Bertrand, 2009; Carlyon, 2004; Shamma et al., 2011). However, it is beyond the scope of this introduction to review all the proposed mechanisms solving concurrent and sequential integration and segregation of sound features into auditory streams. This PhD thesis is focused on the notion that "regularity representations play an essential role in parsing the complex acoustic input into discrete object representations and in providing

continuity for perception by maintaining a cognitive model of the auditory environment" (Winkler et al., 2009). That is, auditory streams are based on encoded sound regularities.

Auditory object formation by acoustic regularity encoding

Auditory streams can be thought of perceptual auditory objects. An auditory object is a perceptual entity that depends on the brain mechanisms available to represent and analyze sensory information (Griffiths & Warren, 2004). Because acoustic information is extracted analyzing the evolution of sound pressure waves in time, memory processes must operate in order to generate an auditory object representation. These memory mechanisms, which will be reviewed in the following sections, operate over a range of timescales and auditory processing stages, supporting the representation of auditory objects.

The need of an object representation in memory in order to identify incoming sounds was already stated by Bregman (1990) in his schema-based processing model: sound identification depends on achieving a match between incoming auditory information and an object concept that is stored in semantic memory. Although Bregman referred to long-term stored memory representations, or the listener's *a priori* knowledge of the sound source, new theories of perception state that *priors* can be generated online, by encoding the information of the environment that reaches our sensory systems in sensory memory (Friston, 2005; Winkler et al., 2009). The encoding of the regular aspects of the sensory input would enable the generation of predictive models of the incoming sensory input. Importantly, as natural environments are highly complex and dynamic,

the reliability of the predictions based on the given regularity representation resolves the competition between alternative sound groupings (Winkler et al., 2009).

Very strong evidence for the role of regularity encoding in the formation of auditory objects comes from a recent study by McDermott and colleagues (2011). In this study, the authors found that synthesized noise sounds with naturalistic properties could be segregated and identified if they occurred repeatedly across different mixtures of other sounds. Importantly, the sounds were generated in a way that bottom-up cues and top-down knowledge could not be used to perform the identification task, and demonstrated as well that identification was not possible by listening only once to the sound mixture. The authors concluded that repeating sources induce temporal regularities in the mixed auditory input, which are detected and used by the auditory system to recover sound sources.

Summarizing, the representation of regularities, which are predictive of the sound that a source is likely to emit, can underpin the formation of an identifiable perceptual unit as well as its separation from other units (Winkler et al, 2009).

Indirect evidence of acoustic regularity encoding by indexing regularity violations: the mismatch negativity auditory evoked potential

The neuronal representation of acoustic regularities has extensively been studied in humans using an indirect approach: we can ascertain that the brain has encoded an acoustic regularity if we are able to observe differential brain

activity to an acoustic event that violates it. The most studied neuronal correlate of regularity violation in the scientific literature, which has generated more than 1500 studies since its description, comes from the human electrophysiology research field: the mismatch negativity (MMN) auditory evoked potential (AEP; Escera, 2007; Näätänen, 2007; Näätänen et al., 1978). This brain response is usually obtained with a passive (i.e., without overt attention) auditory *oddball* paradigm, comparing activity elicited by a frequently repeated stimulus (standard) to that elicited by an interspersed rare stimulus containing a feature variation (deviant). In that way, MMN can be obtained for violations of simple feature rules, as for example in the case of frequency, location, or intensity deviants, but it is also elicited for sounds violating more complex regularities (e.g., phonetic contrasts, abstract regularities defining the relationship between sounds, etc.; for an overview, see Picton, et al. 2000). Thereby, an MMN response is generated at 100–250 ms from deviance onset by sources located bilaterally in the supratemporal brain region in the vicinity of the auditory cortex (Alho, 1995; Maess, et al., 2007; Näätänen & Alho, 1995). Additional prefrontal contributions have been reported as well in several studies (for an overview; see Deouell, 2007).

An important aspect of the MMN is, related to the encoding of acoustic regularity and the strength of the sensory-memory trace, that its amplitude increases with lowering deviant probability (Imada et al., 1993; Javitt et al., 1998) or lengthening the local sequence of stimulation (Giese-Davis et al., 1993; Sams et al., 1983). In other words, the more infrequent the acoustic event that deviates from the established regularity is, being as such both in terms of global or sequential probability, the larger the neural response to it. Crucially,

NMDA receptor function is essential in the generation of the MMN (Javitt et al., 1996; Näätänen et al., 2011; Umbricht et al., 2000). This establishes a neurochemical link between MMN and sensory-memory trace formation, which is dependent on short-term synaptic plasticity.

Although the MMN is usually obtained by the procedure described above (deviant minus standard difference waveforms), this traditional procedure poses a problem: the effects of regularity encoding cannot be disentangled from those indexing *true* regularity violation. In other words, by the subtraction procedure we are adding to the MMN the contribution of the refractory effects that repetition exerts on the AEP, which are expressed as an amplitude reduction of AEPs like the N1 (repetition effects in the AEP will be reviewed at section 1.5.). Thus, part of the MMN amplitude is due to changes in the amplitude of the standard AEP. To overcome this issue in the search of a *true* deviance index, Schröger and colleagues (1996) introduced a control manipulation in which the deviant stimulus from the oddball block is compared to a physically identical sound occurring with the same probability as the deviant, but in a context of different randomly presented equiprobable stimuli. Hence, the differential response is ensured not to be due to the differences in stimulus probability and associated differences in the state of refractoriness of neural populations, but is reflecting *true* deviance detection based on a regularity representation stored in auditory sensory memory. This type of *true* MMN has been shown for location (Schröger & Wolff, 1996), pitch (Jacobsen & Schröger, 2001), intensity (Jacobsen et al., 2003) and duration (Jacobsen & Schröger, 2003) deviant stimuli. Global and local deviant probability effects have not been studied up to date on *true* MMN.

In addition to MMN as a marker of regularity violations, recent studies from our laboratory have shown correlates of deviance detection at much earlier latencies than those of the MMN, which typically peaks between 100-250 ms post-deviance onset. These early responses have been found in the middle latency range of the AEP (MLR) peaking around ~40 ms post-deviance onset, appearing also in controlled paradigms such as those described above, thus suggesting that *true* signals of regularity violation can be found at the level of primary auditory cortex (Grimm et al., 2011a; 2011b; Slabu et al., 2010). Such evidence is supportive of a multi-stage deviance detection system in the auditory modality (Grimm & Escera, 2011). Future studies will be important to establish links between the degree of complexity of the acoustic regularity and the stage in the auditory pathway where this regularity can be encoded successfully.

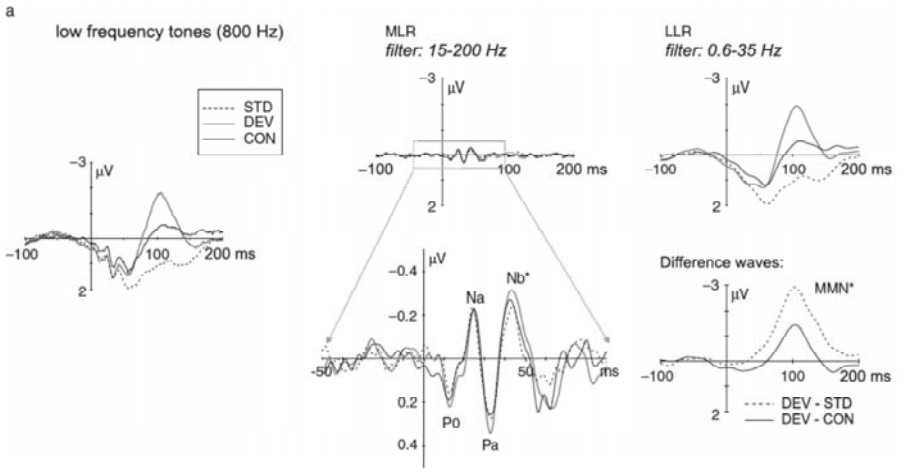


Figure 2. An example of AEP to pure tones in an oddball paradigm and in the controlled paradigm (pitch deviance detection). On the left panel, unfiltered responses to repeated tones (STD; dotted line), deviant tones (DEV; grey solid line) and control tones (CON; black solid line). On the mid panel, the same responses filtered to obtain the MLR AEP. It can be seen that the Nb MLR AEP (~40ms) elicited to deviant tones is larger than that elicited to standard and control tones, thus indexing *true* deviance detection at the level of the primary auditory cortex. On the right panel, top, same responses filtered to obtain the long latency range (LLR) AEP; bottom, difference waveforms reveal the traditional MMN (dotted line) and the *true* MMN (black solid line). These responses also show *true* deviance detection, but at the traditional longer latencies (~100ms), probably at the level of the secondary auditory cortex. (Reprinted from Grimm, et al., 2011).

Summarizing, the MMN, and its recently found earlier homologues, constitute an index reflecting that the brain has encoded an acoustic regularity, which, as previously stated, is crucial in the formation of an auditory object. However, these are but indirect measures of regularity encoding as what they signal, properly speaking, is the violation of an established regularity, and not the sensory-memory trace *per se*.

Direct evidence of acoustic regularity encoding in the non-human auditory system: stimulus-specific adaptation in single-cell recording studies

Direct evidence of the encoding of acoustic regularities comes from neuronal adaptation studies using single-neuron and multiunit electrophysiological recordings in non-human animals. In a very relevant paper, Ulanovsky and colleagues (2003) described a type of neuronal adaptation in the primary auditory cortex of the anesthetized cat, which could not be explained in terms of refractoriness (i.e., neuronal fatigue; neurons get "tired" of firing to a stimulus and thus their response gets suppressed by changes in ion concentrations that reduce excitability; reviewed in Nelken & Ulanovsky, 2007). They used the term stimulus specific adaptation (SSA) to refer to this type of responses, in which single-neurons ceased their firing to a repeated pure tone but recovered their responses to a low-probability pure tone of a different frequency. Importantly, SSA was found applying the oddball paradigm, extensively used in human AEP studies (see previous section), to single-neuron recordings, and the obtained responses were found to share many properties with the MMN: both MMN and the differential firing rate to standard and deviant stimuli in single-neurons exist in anesthetized cats; both are localized to auditory cortex; their magnitudes are monotonically related to the frequency difference between the two tones used in the oddball paradigm (Δf); their magnitude is inversely related to the probability of the deviant stimulus; their latency is inversely proportional to Δf; their latencies are longer than those to standard stimuli; both increase with the number of repeated stimuli in a local sequence of stimulation; both decrease with the length of the inter-stimulus interval; both are stronger in the presence of

one compared to many standards; both show a one-trial effect (i.e., a partial reset of the sensory-memory trace due to the presentation of a stimulus violating the established regularity in the previous trial; Sams, et al., 1984); and both exist to amplitude deviants as well (Nelken & Ulanovsky, 2007). Despite the great similarities between MMN and SSA, there is a remarkable difference in timing between the firing onset to a deviant stimulus in single-neurons showing SSA (~20ms; Pérez-González et al., 2005) and the peak latency of the MMN (~100-250ms), which is contradicting the view that the former directly accounts for the latter (von der Behrens et al., 2009). Therefore, the activity of the "novelty neurons" can be interpreted as a change detection process in the primary auditory cortex lying upstream of MMN generation. Interestingly, the early deviance detection signals at the MLR of the AEP reviewed in the previous section could be the human counterpart of these responses in non-human animal single-neurons (Grimm et al., 2011a; 2011b; Slabu et al., 2010). Furthermore, SSA has been replicated in many studies spanning different levels in the anatomical hierarchy of the auditory system: primary auditory cortex (Farley et al., 2010; Ulanovsky et al., 2003; 2004), medial geniculate body of the thalamus (Anderson et al., 2009; Antunes et al., 2010) and inferior colliculus (Malmierca et al., 2009; Pérez-González et al., 2005; Reches & Gutfreund, 2008; Zhao et al., 2011).

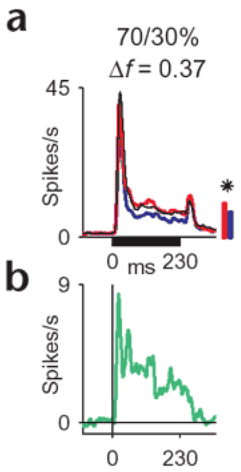


Figure 3.A. Single unit responses of neurons in primary auditory cortex of the cat to the same p tone in different contexts: repeated stimulus (7 probability; blue trace), deviant stimulus (3 probability; red trace), and equiprobable (50-5(stimulus (black trace). **B.** Subtraction of the fi rates to repeated from deviant stimulus. This fig clearly shows the SSA phenomenon, a direct ma of regularity encoding in the auditory brain. (Ada from Ulanovsky et al., 2003).

All this body of evidence suggests that there are subsets of neurons al anatomical auditory pathway that can encode acoustic stimulus stat crucial step in the formation of auditory objects. Furthermore, the enc stimulus statistics by single-neurons has been shown to act in multi scales simultaneously, a property that may aid to capture the complexity auditory stimulation. Using a modification of the oddball paradigm ap single-neurons in the primary auditory cortex, Ulanovsky and colleague showed that SSA is faster for short than long-term stimulus history (i.e., l global probabilities). Their paradigm, which consisted in a fixed sequence embedding different local and global stimulus probabilities, r that single-neuron responses adapted in time-scales ranging from millis to several seconds concurrently. In addition, local and global s

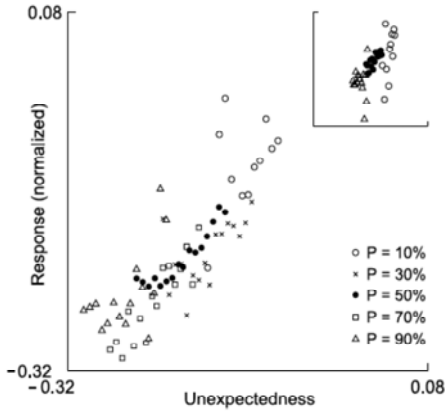


Figure 4. Fitting a linear model of stimu unexpectedness to neuronal responses of primary auditory cortex of the cat. Each represents the mean population response to fifth-order local sequence, with symbol sh representing the global probability of stimulus. The inset represents data using a sma frequency difference between the two to (Reprinted from Ulanovsky et al., 2004).

To summarize, the encoding of stimulus probabilities by single-neurons alo the auditory pathway in a wide temporal range would enable the audito system to generate expectations of the incoming stimulation, which are cruc in the formation of auditory objects that typically have their features distribut over time (Nelken et al., 2003; Nelken & Bar-Yosef, 2008).

Direct evidence of acoustic regularity encoding in the human auditc system: the repetition positivity auditory evoked potential

Up to now, we reviewed evidence for the encoding of acoustic regularities in t human auditory system by means of recording AEP to violations of t established regularities. But, as seen in the previous section, direct markers regularity encoding in multiple-time scales exist at the level of single-neurons the non-human animal auditory system. Are there such direct markers

the AEP can occur very fast (Baldeweg et al., 2004; Cowan et al., 1993). One appropriate paradigm to study sequential repetition effects in the AEP is termed *roving standard* paradigm. It consists in a train of repeated sounds, with variable number of repetitions, followed by another train of repeated sounds that differ in any sound feature from the previous. The inter-train interval is usually the same as the inter-stimulus interval, constituting an uninterrupted sound sequence. This way, an MMN can be obtained to the first tone presentation in the sequence as it acts as a deviant compared to the previous sequence, but with repetition it turns into a standard stimulus. Hence, this paradigm allows tracking the repetition-related changes in the neuronal response to an acoustic stimulus.

Using roving standard stimulation, Baldeweg and colleagues showed in several studies that tone repetition modulates the long-latency AEP components in a conjoined and reliable way: an increase of the P50, decrease of the N1 and increase of the P2 AEPs, all riding on a slow positive wave, which they called the Repetition Positivity (RP; Baldeweg et al., 1999; Baldeweg et al., 2006; Haenschel et al., 2005). The RP behaves in a very similar way to the SSA reviewed in the previous section: both occur without overt attention to sounds, are stimulus-specific and develop rapidly (Baldeweg, 2007). The onset of RP in the latency of P50 (~70 ms) implicates the primary auditory cortex in its generation, based on a latency comparison with intracranial generators of human AEP (Liegeois-Chauvel et al., 1991). This, with all caution in comparing different neural scales, makes the RP a possible human electrophysiological counterpart of SSA and a signal of sensory-memory trace formation in the human auditory system. In sum, the RP can be taken as a direct

electrophysiological correlate of acoustic regularity encoding in humans that can be explored using the appropriate stimulation paradigms.

Another classical example of a paradigm used to study repetition effects in the AEP is the *paired-click paradigm*, in which a sound (tone, click, etc.) is presented in pairs with a shorter inter-stimulus interval within than between pairs. This paradigm has been extensively applied in sensory-gating studies revealing important differences between healthy individuals and those presenting psychopathological disorders such as schizophrenia (sensory gating is defined as a predominantly preattentional inhibitory filter mechanism that could protect the integrity of higher-order functions from sensory information overload). In short, the P50 AEP gets reduced to sound repetition in healthy but not in impaired individuals (Freedman et al., 1987). The reduction of P50 to the repeated sound in the *paired-click paradigm* contrasts with its enhancement in the *roving standard paradigm*. This difference might be explained by the biphasic behavior of early cortical responses to repetition: their amplitude gets reduced to the first repetition of a sound, but shows a rebound to further repetitions (Garrido et al., 2009). Hence, this paradigm will not be further discussed here, as it is not suitable to study the sequential repetition effects constituting the focus of interest of this PhD thesis.

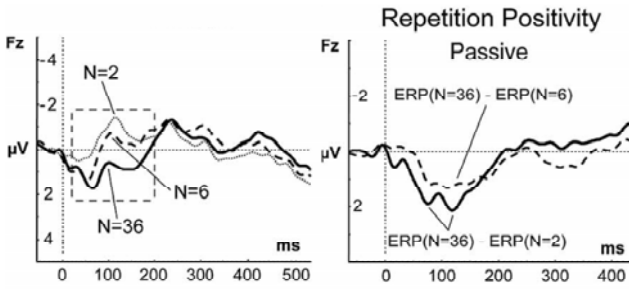


Figure 5. The RP. The left panel shows the AEP to the standard tones in a roving standard paradigm (dotted line, after 2 stimulus presentations; dashed line, after 6; solid line, after 36). The increase of the P50 (~70ms), decrease of N1 (~100ms) and increase of P2 (~170ms) riding on a slow wave can be better seen in the right panel, where the AEP to the 2nd (solid line) and 6th (dashed line) tone repetition was subtracted from the AEP to the 36th stimulus repetition. (Adapted from Haenschel et al., 2005).

Acoustic regularity encoding in the auditory system: stimulus probability and… what about stimulation timing?

As reviewed in the previous sections, a large body of evidence supports the encoding of acoustic regularity in the auditory system, constituting the basis for the generation of predictive models of the environment aiding auditory object formation. Interestingly, most of the experimental evidence and theoretical interpretations are based on one aspect of the acoustic regularity only: stimulus probability. In other words, neuronal adaptation as the mechanism to encode acoustic regularity has been mainly studied by modifying the expectation that a sound will occur based on how many times this same sound has been presented before. The conclusion is simple: the more probable a stimulus is, the more expected, and thus the stronger the neuronal adaptation to it, indexing the encoding of its probability. However, in natural environments, guiding our

actions towards auditory objects involves the prediction of the object itself, but also the anticipation, in time, of the appearance of this object in the scene. That is, prediction entails two crucial aspects of regularity: "*what*" do we expect and "*when*" do we expect it to happen. Whereas the former aspect has been extensively studied as reviewed above, the latter has surprisingly been neglected: all evidence for neuronal adaptation to stimulus probability has always been obtained using *isochronous* stimulation. This does not mean that *random* timing stimulation has not been used ever, still, up to now there are no studies exploring the interaction between stimulus probability and timing in neuronal adaptation (further references than those reviewed above can be found at Study II of this PhD thesis). In line with the theoretical framework followed in this PhD thesis, neuronal adaptation to predictable stimuli in terms of probability and timing should be greater than that to predictable stimuli merely in terms of probability, if neuronal adaptation is to reflect regularity encoding in a broad sense.

Summary

Natural acoustic environments are highly complex and dynamic. As multiple sound sources emit sounds simultaneously, the auditory system needs to parse the acoustic information reaching the ears as mixed sound pressure waves into meaningful auditory objects to which behavior can be directed. Because sounds from the same source contain acoustic regularities, the auditory system can track them and generate sensory-memory traces that can be used as predictive models to individuate such sources into auditory objects. The encoding of

acoustic regularities has been traditionally studied by means of the MMN AEP, while this is but an indirect measure, as it is elicited to the violation of an established regularity. Direct evidence supporting the encoding of acoustic regularities has been found in the form of SSA to stimulus probabilities in single-cell recordings of the non-human animal auditory pathway. A human correlate of sensory-memory trace formation can be found as well as a reliable pattern of changes in the AEP with stimulus repetition, the RP, when studied with the appropriate stimulation paradigms. Whereas SSA has been shown to operate in multiple time-scales, thus supporting the encoding of the complex past history of auditory stimulation, and correlates with the modeled expectedness of a sound, no such property has been observed in the human auditory system. This gap in the literature constitutes the motivation of the first study of this PhD thesis. Furthermore, studies regarding sensory-memory trace formation by tracking changes in neuronal activity to repeated stimuli, reflected by SSA in non-human animal single-cell recordings or by RP of the human AEP, have usually used isochronous stimulation. Hence, the second study of this PhD thesis is focused in exploring the influence of timing regularity in the formation of a sensory-memory trace by neuronal adaptation.

Aim of the studies

AIM OF THE STUDIES

The specific objectives of the present studies can be formulated as follows:

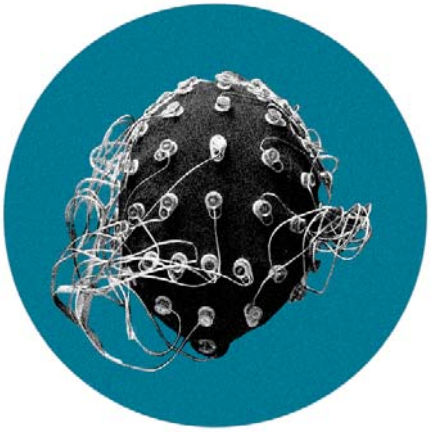
STUDY I

The first aim is to examine, by means of AEP recordings in healthy human participants, the dynamics of adaptation of *true* MMN and RP to sounds embedded in a sequence containing local and global aspects of auditory stimulation history. The main hypothesis states that *true* MMN and RP will reveal the encoding of stimulus probabilities in several time-scales concurrently, showing shorter adaptation time constants to short than long-term history of stimulation. If demonstrated, that would parallel the behavior of single neurons exhibiting SSA in the non-human animal primary auditory cortex.

The second aim is to fit a simple linear model of auditory stimulus expectancy to the recorded electrophysiological responses. The main hypothesis states that the amplitude of the AEP will correlate with stimulus expectancy, being more negative to unexpected stimuli (towards an MMN response type) and more positive to expected stimuli (towards a RP response type).

STUDY II

The main objective of this study is to explore the influence of timing predictability in the neuronal changes associated to repeated stimulation by means of AEP recordings in healthy human participants. The main hypothesis states that, if the amplitude of the RP indexes the strength of a sensory-memory trace to acoustic regularity, repeated stimulation with predictable timing should elicit larger RP amplitudes than repeated stimulation with unpredictable timing.



Study I: multiple time scales of adaptation in the auditory system as revealed by human evoked potentials

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Multiple time scales of adaptation in the auditory system as revealed by human evoked potentials

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Abstract

Single neurons in the primary auditory cortex of the cat show faster adaptation time constants to short- than long-term stimulus history. This ability to encode the complex past auditory stimulation in multiple time scales would enable the auditory system to generate expectations of the incoming stimuli. Here, we tested whether large neural populations exhibit this ability as well, by recording human auditory evoked potentials (AEP) to pure tones in a sequence embedding short- and long-term aspects of stimulus history. Our results yielded dynamic amplitude modulations of the P2 AEP to stimulus repetition spanning from milliseconds to tens of seconds concurrently, as well as amplitude modulations of the mismatch negativity AEP to regularity violations. A simple linear model of expectancy accounting for both short- and long-term stimulus history described our results, paralleling the behavior of neurons in the primary auditory cortex.

Descriptors: Sensory memory, Event-related potentials (ERP), Stimulus-specific adaptation (SSA), Mismatch negativity (MMN), Expectancy

Detecting unexpected sounds allows for prompt adaptive behavior to potentially relevant novel events. To accomplish that, the auditory system models the acoustic background forming sensory memory-traces, compares new input with inferences derived from the model, and elicits an error signal triggering an orienting attention mechanism whenever a sound mismatches the prediction (Escera & Corral, 2007; Winkler, 2007). A relevant question, then, is how the auditory system forms the sensory memory traces used to model acoustic scenes. Recent evidence coming from animal single-cell recordings suggests that the main mechanism lies in the ability to match the neuron's spiking rate to stimulus statistics in multiple time scales (Ulanovsky, Las, Farkas, & Nelken, 2004). In other words, neurons in the primary auditory cortex are sensitive to both local (short-term) and global (long-term) aspects of stimulus history simultaneously, a property that may aid us to capture the complexity of past auditory stimulation. Whether this neural mechanism generalizes to the activity elicited by large neural populations, as recorded in human electroencephalography (EEG), still remains to be determined.

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Deviance detection in the auditory modality has been studied using the *oddball* paradigm, where a repeated sound (termed *standard* stimulus) is occasionally replaced by a rare sound (termed *deviant* stimulus). Evidence for deviance detection in the human auditory system comes traditionally from the mismatch negativity (MMN) auditory evoked potential (AEP; Näätänen, Paavilainen, Rinne, & Alho, 2007), which is isolated as the differential brain response to the deviant stimulus as compared with that to the standard stimulus (Näätänen, Gaillard, & Mantysalo, 1978). Evidence at the single-neuron level comes from animal stimulus-specific adaptation (SSA) studies. SSA, that is, the reduction of spiking rate to standard stimuli while keeping robust responses to deviant stimuli, has been found in primary auditory cortex (PAC) neurons (Ulanovsky, Las, & Nelken, 2003; Ulanovsky et al., 2004) as well as in subcortical structures (Anderson, Christianson, & Linden, 2009; Antunes, Covey, & Malmierca, 2009; Malmierca, Cristaudo, Pérez-González, & Covey, 2009; Pérez-González, Malmierca, & Covey, 2005; Reches & Gutfreund, 2008).

A striking property of SSA is that it matches stimulus statistics in multiple time scales simultaneously, showing fast adaptation time constants to short stimulus sequences, and slower adaptation time constants to long stimulus sequences (Ulanovsky et al., 2004). The encoding of stimulus probabilities in a wide temporal range would enable the auditory system to generate expectations of the incoming stimulation, which are crucial in the formation of auditory objects that typically have their features distributed over time (Bregman, 1990; Nelken & Bar-Yosef,

PSYCHOPHYSIOLOGY

2008; Nelken, Fishbach, Las, Ulanovsky, & Farkas, 2003). Since SSA is a pervasive property of neurons along the auditory pathway, it is reasonable to expect a dynamic adaptation of human neural responses to repeated stimuli as measured with AEPs. Indeed, when the acoustic stimulation consists of trains of repetitive tones with tone frequency changing across trains (i.e., roving standard paradigm), the response to the standard stimulus changes gradually towards a positive deflection. This deflection, involving an increase of the P50 and P2 AEP amplitudes together with a decrease of the N1 AEP amplitude riding on a slow positive wave, has recently been isolated as the Repetition Positivity (RP; Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Baldeweg, Wong, & Stephan, 2006; Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005). Thus, RP has been proposed as the human AEP correlate of auditory sensory memory trace formation. Although several studies reported a fast development (Baldeweg et al., 2004, 2006; Haenschel et al., 2005) as well as a long-term persistence of the sensory memory-trace, from tens of seconds (Cowan, Winkler, Teder, & Näätänen, 1993; Ritter, Sussman, Molholm, & Foxe, 2002), up to minutes (Baldeweg, Williams, & Gruzelier, 1999) and even days (Atienza, Cantero, & Dominguez-Marin, 2002), no study has shown dynamic changes of AEPs to repetition in multiple time scales simultaneously.

Here we explored the dynamics of adaptation of MMN and RP in an oddball sequence that embedded short- and long-term stimulus history, testing the hypothesis that MMN and RP amplitudes would be modulated in multiple time scales simultaneously. A simple linear model defining expectancy as a combination of both local and global aspects of stimulation history was devised to describe our results.

Materials and Methods

Participants

Twenty healthy volunteers (9 male, aged 18–28 years, mean age 21.4 years; one left-handed) with no history of neurological, psychiatric, or hearing impairment and with normal or corrected-to-normal visual acuity participated in the experiment. Subjects gave informed consent and received monetary compensation for their participation. The study was approved by the Ethics Committee of the University of Barcelona, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Participants were asked to avoid smoking at least 1 h before the experimental session, as acute nicotine administration could affect RP amplitude (Baldeweg et al., 2006). All subjects underwent an audiometric test assessing the individual hearing level for tone frequencies used in the experimental blocks, equal to 401, 1409, and 3089 Hz. Subjects showed no hearing threshold differences of 15 dB or more between the left and the right ear. Data of one subject had to be excluded from the analysis due to poor signal-to-noise ratio (i.e., less than 50% of artifact-free epochs in one block).

Stimuli and Procedure

The auditory stimuli consisted of pure sinusoidal tones of 40 ms duration including a 5-ms rise and a 20-ms fall time. They were generated with the Neurosoft (El Paso, TX) sound program and delivered binaurally through headphones (Sennheiser HD-555, Wennebostel, Germany) by the Stim interface system (Neuro-Scan Labs, Sterling, VA). Tone intensity was individually adjusted to 55 dB sensation level (SL) with respect to the averaged hearing threshold for the three frequencies used in the audiometric test. The experiment used a switching frozen oddball sequence (Ulanovsky et al., 2004) embedding multiple temporal scales of stimulation history (Figure 1). In short, it consists of a repeating sequence of two stimuli differing in tone frequency appearing at fixed positions, designed in order to reveal short- and long-term adaptation effects. We defined these multiple time scales of stimulation, from the shortest to the longest, as follows: (1) "Repetition," consisting of consecutive trains of 2 (626 ms), 6 (1.9 s), and 12 (3.8 s) presentations of f1 stimulus (acting as the standard stimulus), each train followed by an f2 stimulus (acting as the rare or deviant stimulus); (2) "Run," consisting of two identical and consecutive presentations of a "Repetition" micro-sequence (Run1, Run2), so that trains of 2, 6, and 12 presentations of f1 stimulus in Run2 were comparable with those in Run1, having all Run1 stimulation history (6.3 s); and (3) "Switch," consisting of the repetition of the two "Runs" structure, but switching standard and deviant stimulus roles between f1 and f2 (SW1, SW2).

Note that the first stimulus of a "Switch" had, in fact, the role of a deviant stimulus in the previous micro-sequence but simultaneously that of the first standard stimulus in the present micro-sequence, resembling a roving standard paradigm (Baldeweg et al., 2004, 2006; Cowan et al., 1993; Haenschel et al., 2005). The Switch time scale allowed us to directly test the influence of adaptation to a tone repetition when this tone appears as a rare stimulus, by comparing f2 stimuli acting as deviants in SW1 with f1 stimuli acting as deviants in SW2, with f1 stimuli having all SW1 stimulation history as standards, i.e., 40 repetitions,

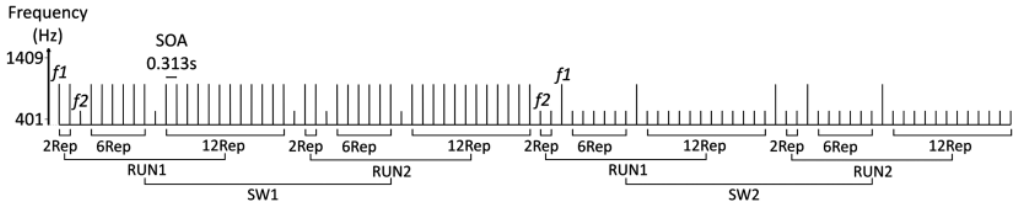

Figure 1. Schematic diagram of the stimulus sequence. A tone of frequency f1 was presented in a row of 2, 6, and 12 consecutive stimuli, each of which was followed by a tone of frequency f2. This micro sequence was presented in two successive runs, which we called Run1 and Run2. Both Runs formed the first half of the sequence, called Switch1, where f1 acted as a standard stimulus and f2 as a deviant stimulus. Switch2 had the same structure as Switch1, but frequency roles were switched so that f1 acted as a deviant stimulus and f2 as a standard stimulus. The frozen sequence was preceded and followed by equal sequences containing stimuli of a different pair of frequencies (ranging from 401 to 1409 Hz). SOA, Stimulus Onset Asynchrony.

~12.5 s. It could be argued that the fixed order of the 2-, 6-, and 12-stimulus long repetitive trains within the Runs confounds local with global effects. For instance, the 12th f1 stimulus in Run2 could be considered as the 40th f1 repetition in the last 45 sounds. However, as shown by Ulanovsky and colleagues (2004), the discharge rate of an auditory cortex neuron exhibiting SSA to a tone (f1) increases when it appears after a rare or deviant tone (f2), meaning that the latter partially erases the memory trace of the former (what has been called *one-trial* or *after-deviant* effect). Thus, our design is suitable to study local sequence effects, which are differently influenced by the global structure of the sequence.

To control for stimulus acoustic differences, tone frequencies f1 and f2 were chosen from a pool of six different frequencies (401, 619, 827, 1021, 1217, and 1409 Hz) in a way that all possible pairwise combinations were covered, resulting in 30 different frozen sequences of 90 stimuli each. Although the perceptual difference between higher tones was smaller than between lower tones, the pairwise combinations eliminated all possible artifacts in the N1/MMN elicited to deviant stimuli. In order to enable stimulus comparisons between this study and single neuron SSA studies, we provide the normalized frequency difference (Δf) between a pair of tones. Δf, defined as $(f2 - f1)/(f2 \times f1)^{1/2}$ according to single-cell recordings in animals (Ulanovsky et al., 2003), was 0.59 on average ($SD = 0.36$). Stimulus onset asynchrony (SOA) and inter-sequence interval were 313 ms. The 30 frozen sequences were delivered in a pseudo-random order forming one single experimental block, with the constraint that a particular sequence could not contain any of the two frequencies appearing in the previous one, so that every repetition of the sequence would be treated as "new" by the neural populations encoding the frequencies of both tones. Four single blocks were presented separated by pauses of approximately 5 min. In short, this complex design aimed to extract the auditory evoked responses to each stimulus in a sequence according to its position, regardless of the frequency of the tones that constitute it.

In order to control for deviant stimuli N1 refractoriness effects, we adapted the control condition developed by Schröger and Wolff (1996). In short, this control condition allows obtaining an AEP elicited by a stimulus with the same physical properties and probability as a deviant stimulus in an oddball sequence, embedded in a non-regular context. Thus, a "true" index of regularity violation can be extracted by comparing deviants against control stimuli. We presented two control blocks consisting of 60 frozen control sequences each. In these control sequences, control stimuli appeared in the same position and had the same particular frequencies as deviant stimuli in the oddball sequences. However, standard tones were replaced by random frequency tones (39 different frequencies, one per standard, ranging from 421 to 3089 Hz; average Δf between control tones and random tones, 0.82; $SD = 0.56$). It should be noted that the frequency range of the control stimuli and the average Δf exceed those of the oddball stimuli. This means that a control stimulus (of the same tone frequency as the oddball stimulus) will be preceded by a tone that is, on average, more different in frequency than the one in the oddball sequence. Thus, control stimuli were expected to elicit larger or equal N1 amplitudes than deviant stimuli, excluding N1 refractoriness effects. Because no frequency repetition existed, control sequences presented the same structure as one single oddball switch of 45 stimuli (i.e., half of the frozen oddball sequence).

Participants sat in a comfortable chair in a sound-attenuated and electrically shielded room. They were instructed to ignore the sounds and watch a silent movie with subtitles. The first block in the experiment was a control block, followed by the four experimental blocks and a final control block. The total duration of the six blocks was 90 min approximately.

Auditory Evoked Potentials Recording and Analysis

The EEG was continuously recorded with frequency limits of 0.05–100 Hz and digitized at a sampling rate of 500 Hz by a SynAmps amplifier (NeuroScan Inc., Herndon, VA). Pure tin electrodes were used for the EEG acquisition, 6 of which were mounted in a nylon cap (Electro-Cap International, Eaton, OH) at the standard locations F3, Fz, F4, C3, Cz, and C4 according to the international 10–20 system. Additionally, two electrodes were positioned over the left and the right mastoids (M1 and M2). Vertical and horizontal electrooculogram (EOG) were measured from monopolar electrodes placed, respectively, below (VEOG) and laterally (HEOG) to the right eye. The ground electrode was placed on the central forehead, and the common reference electrode was attached to the tip of the nose. All impedances were kept below 5 kΩ during the whole recording session. Data were bandpass-filtered off-line between 0.3 and 20 Hz and averaged for epochs of 413 ms duration including a prestimulus baseline of 100 ms. Epochs with a signal range exceeding 80 μV at any EEG or EOG channel were excluded from the average.

Epochs used in the analysis of the effects of multiple time scales of stimulation history on brain potentials were averaged separately for deviant stimuli after 2, 6, and 12 standard stimuli, for both "Runs" in both "Switches" (resulting in $3 \times 2 \times 2 = 12$ conditions), as well as for the standards preceding a deviant (12 conditions), and for control stimuli after 2, 6, and 12 random frequency stimuli for both "Runs" (6 conditions). After rejection, a mean of 110 epochs ($SD = 8.82$; 74 minimum) were averaged for each stimulus type, condition, and subject. In order to avoid possible deviant stimulus refractoriness effects, MMN difference waveforms were obtained by subtracting the brain potentials evoked by control stimuli from those evoked by deviant stimuli (Schröger & Wolff, 1996). Peak latencies of mismatch potentials were determined from the Fz electrode as the largest negative peak in the interval of 80–180 ms for all difference waves and subjects separately. MMN mean amplitudes were derived in a 20-ms time window centered on the mean peak latency of the grand-average waveforms for all the 12 conditions (135–155 ms). Repetition effects on standard stimuli were assessed at Fz electrode by means of RP mean amplitudes, measured in a latency window ranging from 50 to 250 ms following the sound onset, and also by retrieving the mean amplitude in the latency window of the P2 evoked to the repeated tone, which coincided with that of the MMN (135–155 ms). In order to determine the time course of adaptation of AEPs to standard stimuli, an exponential curve was fitted to the P2 mean amplitudes elicited to all f1 stimuli in Switch1 and all f2 stimuli in Switch2 (averaged separately according to their position), except for the second stimulus in Run1, which showed a deviant-like response. Epochs used to model brain potentials as a function of stimulus expectancy were averaged separately for all 90 stimuli appearing in the sequence according to their position.

Statistical Analysis

The effects on MMN peak latencies and mean amplitudes, as well as the effects on standard stimulus mean amplitudes in RP and MMN time windows (50–250 ms; 135–155 ms, respectively),

were evaluated with separate repeated measures analyses of variance (ANOVAs) including three factors: Switch (1, 2) × Run (1, 2) × Repetition (2, 6, 12). Subsequent repeated measures ANOVAs were performed to assess interaction effects. The Greenhouse-Geisser correction was applied when appropriate. To characterize the time course of AEPs adaptation to standard stimuli, we retrieved the mean amplitudes in the P2 time window from the averaged AEPs across subjects (in order to isolate better the obtained repetition effects, which inverted their polarity at the mastoid electrodes, Fz was re-referenced to M1) and performed a nonlinear least-square fit to find the best-fitting exponential function as follows: decay size × $(1 - e^{-t/\tau})$+asymptote.

Modeling Auditory Evoked Potentials as a Function of Stimulus Expectancy

A simple linear model was devised in order to account for brain potential modulations as a function of stimulus expectancy. Mean amplitudes of responses to all standard and deviant stimuli appearing in the sequence (90 stimuli; epochs averaged according to their position) were retrieved in the MMN/P2 latency window for all subjects at the Fz electrode re-referenced to M1. Assuming that negative brain potential values in that time window decrease with increasing number of repetitions/higher probability (Imada, Hari, Loveless, McEvoy, & Sams, 1993; Javitt, Grochowski, Shelley, & Ritter, 1998; Sams, Alho, & Näätänen, 1983), we defined stimulus expectancy as a linear combination of two independent factors: (1) the memory for the local stimulus history (M); and (2) the estimated probability of the stimulus (P). For M, we postulated that the local effect of preceding stimuli on the expectancy of the current stimulus is an exponentially decaying function of serial position (Squires, Wickens, Squires, & Donchin, 1976; Ulanovsky et al., 2004). In particular, the memory M for stimulus k (i.e., *f1* or *f2*) at position N as a function of the sequence of past stimuli S_i is assumed to be:

$$M_{kN} = \frac{1}{Z} \sum_{i=N-1}^{N-m} \alpha^{N-i} S_i$$

with S_i taking the value of 1 when the stimulus at position i equals k and 0 when the stimulus at position i is unequal to k (i.e., in order to model the memory for an *f1* stimulus we only take into account previous *f1* stimuli); m is the number of past stimuli conforming the local sequence (here, as in Squires et al., 1976; and Ulanovsky et al., 2004, $m = 5$) and the constant α determines the time course of memory decay ($0 \leq \alpha \leq 1$). Z is a normalization factor that takes the maximum value of M, so that $0 \leq M \leq 1$ (Ulanovsky et al., 2004), defined as:

$$Z = \sum_{i=1}^{m} \alpha^i$$

The second factor (P) was modelled taking into account how the "subjective probability" of a stimulus is represented and updated over time, rather than how it changes on average (Mars et al., 2008). It should be noted that all stimuli in the "frozen oddball sequence" were equiprobable. Thus, global probability could not be used as a factor as it has been done in previous studies using random oddball paradigms (Squires et al., 1976; Ulanovsky et al., 2004). Instead, we used the estimate probability (P) of a stimulus (f1 or f2) appearing in the sequence, which is continuously modified by the occurrence of new stimuli. Because the estimate probability p_k will be 0 if the stimulus k has not been previously presented, an *a priori* probability is needed in order to assume initially that all stimuli are equally likely to occur. This issue was solved by using a prior Dirichlet distribution (Mars et al., 2008). A uniform Dirichlet distribution is parameterized by a vector $\gamma = [\gamma_1, \ldots \gamma_k]$ of dimension equal to the number of possible elements, and written as $P(p|\gamma) = \mathrm{Dir}(p;\gamma_k)$. Choosing all elements of γ equal to one means to start with a sequence of equiprobable stimuli. In the present case, using six different frequencies in the experimental blocks results in an *a priori* probability for a stimulus of $1/6 \approx 0.17$. The subsequent distribution representing the estimated probabilities after j positions, X^j, is given by

$$P(p|X^j, \gamma) = Dir(p^j; n_k^j + \gamma_k)$$

where $n^j{}_k$ refers to the number of occurrences of stimulus k up to position j. This distribution takes again a Dirichlet form, parametrized by the vector with elements equal to $n^j{}_k + \gamma_k$. In short, this expression states that the estimated probability of finding a particular stimulus k in position j is determined by the sequence of stimuli presented and by the *a priori* probabilities (parametrized by γ). The expression that represents the probability of observing stimulus k in position j as a function of the estimated probabilities in position j-1 is

$$p(x^j = k|X^{j-1}, \gamma) = \frac{n_k^{j-1} + 1}{N^{j-1} + K} = \tilde{p}_k^j$$

where

$$N^{j-1} = \sum_{k=1}^{K} n_k^{j-1}$$

is the total number of stimuli preceding position j, which is equal to j-1, and K stands for the number of possible stimuli ($K = 6$). To sum up, the prediction of the probability of observing stimulus k on position j ($\tilde{p}_k^j$) depends on all preceding observations and a uniform prior.

Finally, stimulus expectancy was defined as a linear combination of the memory for the local stimulus history (M) and the estimate probability of the stimulus (P), as shown in the following expression: $A = aM + bP + c$, where a, b, and c are the parameters to be adjusted in a multiple linear regression analysis, and A is the predicted amplitude value of the brain potential. We modeled the amplitudes of all 90 stimuli averaged across subjects and for each subject individually.

Results

Grand-average waveforms evoked to standard (*gray*), deviant (*black*), and control (*dotted trace*) stimuli are illustrated for each condition in Figure 2, together with deviant-minus-control waveforms (Switch1, *black thick trace*; Switch2, *gray thick trace*). RP can be identified as a repetition-enhanced positive slow wave evoked to standard stimuli that develops drastically from 2 to 6 repetitions in Run1 (both Switches). Embedded in this RP, we can observe the emergence of the P2 potential increasing with the number of repetitions in a time range coinciding with that of the MMN, which increased as well the more standard stimuli preceded a deviant stimulus. Furthermore, a remarkable decrease in the amplitudes of the MMNs elicited to deviant stimuli in Switch2 can be seen in comparison to those elicited to deviant stimuli in Switch1.

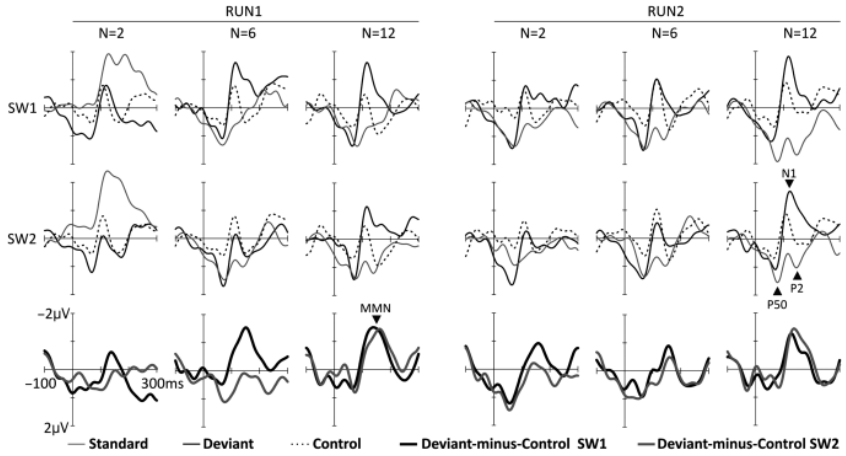

Figure 2. Grand-average waveforms for standard (*gray*), deviant (*black*), and control (*dotted trace*) stimuli after 2, 6, and 12 stimulus presentations in both Runs and Switches, together with deviant-minus-control difference waves (SW1, *black thick trace*; SW2, *gray thick trace*). The arrows point to the P50, N1, and P2 AEP components in the grand-average waveforms as well as to the MMN in the difference waveforms.

Effects of Multiple Time Scales of Stimulus History on Sensory Memory-Trace Formation

Sensory memory-trace formation to repeated stimuli, as indexed by amplitude changes of RP, was strengthened in a short-term time scale only to the first presentations of a given acoustic stimulus (Run1), thus showing a fast adaptation of the neural response that reached the maximum after 12 consecutive stimulus presentations (interaction between Run and Repetition factors, $F(2,36) = 16.895$, $p < .001$, $\eta^2 = 0.484$; a *post-hoc* repeated measures ANOVA revealed significant effects of Repetition in Run1, $F(2,36) = 26.430$, $\varepsilon = 0.665$, $p < .001$, $\eta^2 = 0.595$, but no significant effects were obtained in Run2, $\eta^2 = 0.076$). However, the P2 potential evoked to repeated sounds revealed a better sensitivity to multiple time scales of stimulus history than the RP, showing a marked increase with the number of repetitions in the first presentations of a given tone (Run1) together with a slighter increase in further presentations (Run2; interaction between Run and Repetition factors, $F(2,36) = 15.916$, $p < .001$, $\eta^2 = 0.469$; a *post-hoc* repeated measures ANOVA revealed significant effects of Repetition in Run1, $F(2,36) = 38.453$, $\varepsilon = 0.682$, $p < .001$, $\eta^2 = 0.681$, and in Run2, $F(2,36) = 3.285$, $p < 0.05$, $\eta^2 = 0.154$). Previous presentation of a tone as a deviant stimulus exerted no effect on brain potentials evoked to the same acoustic stimulus when occurring as a standard stimulus (no significant Switch effect in RP or P2). P2 mean amplitudes evoked to standard stimuli are shown in Figure 3. As no effects or interactions including the factor Switch were found, data were pooled across the two Switches for graphic purposes. When fitting exponential functions, the time course of adaptation of brain potentials to repeated stimuli was similar for standard stimuli in Switch1 ($\tau = 10.4$ s, with 95% confidence bounds; R^2 (*adjusted*) $= 0.536$) and Switch2 ($\tau = 8.2$ s, with 95% confidence bounds; R^2 (*adjusted*) $= 0.466$) (Figure 4; *black*, exponential curve fits for f1 (*white*) in Switch1 and f2 (*gray*) in Switch2).

Effects of Multiple Time Scales of Stimulus History on Deviance Detection

True memory-based deviance detection, as indexed by the amplitude of the MMN controlled for refractoriness effects, was enhanced in a short-term time scale as a function of the number of standard stimuli preceding the deviant stimulus (Repetition effect, $F(2,36) = 4.320$, $p < .05$, $\eta^2 = 0.194$; from 2 [$\sim$ 0.6s] to 12 stimulus presentations [$\sim$ 4s]). This enhancement was found together with a marked decrease of MMN when the same acoustic stimulus deviating from the local sequence was previously presented as a standard stimulus (Switch effect, $F(1,18) = 6.050$, $p < .05$, $\eta^2 = 0.252$), thus reflecting long-term effects of stimulation

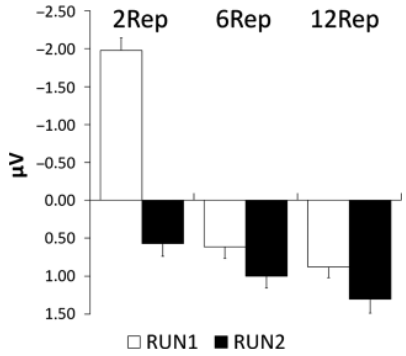

Figure 3. P2 mean amplitudes elicited to standard stimuli after 2, 6, and 12 stimulus repetitions for Run1 (*white*) and Run2 (*black*) for averaged Switches (135–155 ms time window; amplitudes in μV; error bars denote standard error of means). P2 mean amplitudes increased the more a standard stimulus was repeated, at both short- (Repetition) and long-term (Run) time scales.

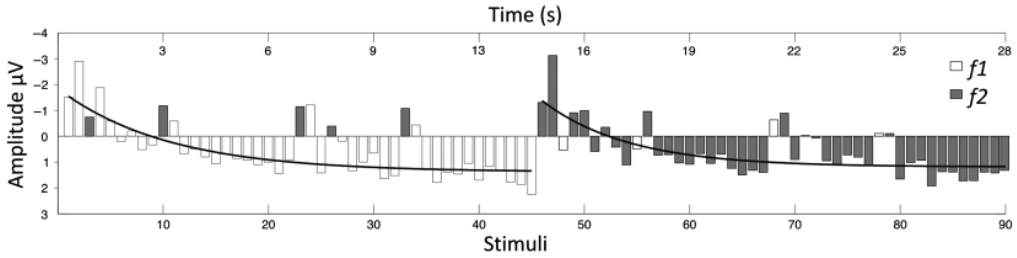

Figure 4. Amplitude of brain potentials in the MMN/P2 time window obtained for all 90 stimuli appearing in the sequence together with the exponential fits for f1 in Switch1 and f2 in Switch2 (amplitudes in μV; f1 stimulus, *white*; f2 stimulus, *gray*; exponential curve fit for Switch1and Switch2, *black*).

history (~10.33 seconds). No modulations were found for MMN peak latencies, with a mean across conditions of 145 ms following stimulus onset. MMN mean amplitudes are shown in Figure 5. As no effects or interactions including the factor Run were found, data were pooled across the two Runs for graphic purposes.

AEP Amplitude as a Function of Stimulus Expectancy

Brain potentials amplitudes evoked to all 90 stimuli appearing in the sequence in the MMN/P2 time range are illustrated in Figure 4. We first determined the memory decay constant α that maximized the linear relationship between brain potentials and the memory for the local stimulus history *M*. The obtained value was $\alpha = 0.786$, which determined a time constant of memory decay (i.e., time for the memory-trace to decay to the half of its value) of: $\tau_M = 1/(1- \alpha) \approx 4.67$ stimuli ≈ 1.46 s (Ulanovsky et al., 2004). The estimated probability of a stimulus (*P*) was calculated for each of the 90 stimuli in the sequence (see Materials and Methods). We then performed a multiple linear regression analysis that determined the equation relating the amplitude measures to *M* and *P* factors, resulting in the following expression: $A = 2.1081M + 1.3235P - 1.6683$. Brain potential observed amplitudes evoked to all 90 stimuli are plotted in Figure 6 as a function of stimulus expectancy. A positive correlation value of $R = 0.764$ and a significant model adjustment of R^2 (*adjusted*) = 0.579, $F(1,89) = 123.258$; $p < 10^{-17}$, indicated that brain potential amplitude in the MMN/P2 time window increased linearly as a function of stimulus expectancy. A stepwise method used to compute single-variable regressions revealed that each single parameter in the model could itself explain a significant amount of the variance in the data: *M*: R^2 (*adjusted*) = 0.515, $F(1,89) = 95.579$, $p < 10^{-14}$; *P*: R^2 (*adjusted*) = 0.251, $F(1,89) = 30.784$, $p < 10^{-6}$. Moreover, the linear model provided a significant fit for each individual subject as well: mean R^2 (*adjusted*) = 0.268; *SD* = 0.183; mean *p* values $< 10^{-18}$; *SD* = 0.05.

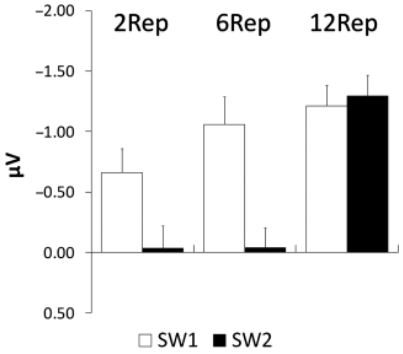

Figure 5. MMN mean amplitudes after 2, 6, and 12 standard stimuli in Switch1 (*white*) and Switch2 (*black*) for averaged Runs (135–155 ms time window; amplitudes in μV; error bars denote standard error of means). MMN was significantly affected by short- and long-term stimulus history simultaneously, increasing in amplitude the more a preceding standard stimulus was repeated (Repetition effect) and being suppressed when deviant stimuli featured a frequency previously presented as a standard stimulus (Switch effect).

Discussion

The present data shows dynamic amplitude modulations of AEP to simple sounds spanning multiple time scales concurrently, paralleling SSA properties. AEP amplitude modulations were seen as a linear increase of positivity in the time range of the P2 potential, coinciding with that of the MMN, as a function of

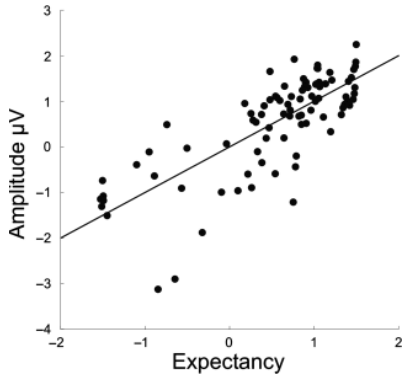

Figure 6. Brain potential observed amplitudes to all 90 stimuli appearing in the sequence plotted as a function of the predicted expectancy score (amplitudes in μV; expectancy values in arbitrary units). Note the linear increase of the AEP amplitude in the MMN/P2 time window as a function of stimulus expectancy.

stimulus expectancy. Thus, our results suggest that adaptation in multiple time scales is a basic property of the auditory system expanding from the single-neuron scale to a wider range of neural populations.

Multiple Time Scales of Adaptation in the Human Auditory System

Previous studies examining the effect of stimulus history on human auditory sensory memory reported a fast development (Baldeweg et al., 2004, 2006; Haenschel et al., 2005) as well as a long-term persistence of the sensory memory-trace, from tens of seconds (Cowan et al., 1993; Ritter et al., 2002), up to minutes (Baldeweg et al., 1999) and even days (Atienza et al., 2002).

Here we used a design from a single-neuron recording study (Ulanovsky et al., 2004) allowing us to reveal that human AEPs to repeated stimuli adapt in multiple time scales simultaneously. Specifically, we showed a fast adaptation time constant to the local sequence preceding the stimulus ($\tau_M \sim 1.5$ s) concurrently with a slower adaptation time constant involving a longer history of stimulation ($\tau \sim 10$ s). This adaptation lasted $\sim$10 s, as seen by the decrease of the neural response to a deviant stimulus that has been preceded by several repetitions of the same acoustic stimulus (i.e., switch effect). This slow recovery coincides with the estimate duration of sensory memory as seen by AEPs (Bottcher-Gandor & Ullsperger, 1992) and behavioral studies (Cowan, 1984), and contrasts to the simultaneous fast recovery seen in the response to post-deviant stimuli, which show a partial reset of the sensory-memory trace ($\sim$0.3 s, one-trial effect; Sams, Alho, & Näätänen, 1984). Unfortunately, longer time scales in the range of minutes as those obtained in SSA by Ulanovsky and colleagues (2004) couldn't be explored in this study because of the use of a roving standard paradigm across the oddball sequences. However, interestingly, the adaptation to the local sequence of stimulation developed in a similar time range to that reported in PAC neurons of the cat (Ulanovsky et al., 2004).

Additionally, we succeeded to predict amplitude modulations of AEPs as a function of stimulus expectancy with a simple linear model accounting for both local and global aspects of stimulation history. Previous research linked stimulus predictability to amplitude and latency modulations of the P300 component of the cognitive evoked potentials, while subjects performed some task related to auditory or visual stimuli (Fogelson et al., 2009; Mars et al., 2008; Squires et al., 1976). The P300 has been related to the evaluation of inferences about the environment as a function of the context (Squires et al., 1976), attention switching (Escera, Alho, Schröger, & Winkler, 2000) and learning of surprising events (Donchin, 1981). Interestingly, similar models could explain our results in human AEPs to unattended sounds as well as neuronal firing patterns in the PAC of anesthetized animals (Ulanovsky et al., 2004), suggesting that inference based on updating probabilities is a basic property of the auditory system not necessarily under the influence of top-down processes.

Repetition Effects on Auditory Evoked Potentials

Modulations of the AEP correlated with stimulus repetition were observed as a frontocentral positive waveform, between 50 and 250 ms post-stimulus, which we identified as RP (Baldeweg et al., 2004, 2006; Haenschel et al., 2005). It has been argued that RP does not consist of a unitary phenomenon but rather a combined modulation of P50, N1, and P2 potentials (Haenschel et al., 2005). In fact, our results showed better sensitivity to stimulation history when the amplitude of the AEP to standard stimuli was measured in the P2 potential, which largely coincides with the time range of the MMN AEP elicited to regularity violations ($\sim$145 ms post-stimulus). Other studies reported P2 enhancements in time scales of minutes (Baldeweg et al., 1999) or days (Atienza et al., 2002), as well as N1 habituation (Butler, Spreng, & Keidel, 1969; Näätänen et al., 1988; Picton, Woods, & Proulx, 1978) to repeated stimuli. P50 enhancements have also been reported to repetitions embedded in constantly changing acoustic backgrounds (Dyson, Alain, & He, 2005). However, repetition usually diminishes P50 and P2 potentials (Boutros et al., 1995; Javitt, 2000; Lijffijt et al., 2009; Lu, Williamson, & Kaufman, 1992), meaning that refractoriness effects should in turn diminish RP. These differences between studies could arise from the use of different experimental paradigms, such as oddball, roving standard, or paired-click paradigms, as well as from differences in data analysis. Indeed, P50 studies usually exclude the contribution of low frequency-band activity included in MMN and RP studies (from 0.1 to 10 Hz). Hence, we tested additionally whether P50 enhancements with repetition could be due to slow wave contributions by re-analyzing our data with the appropriate filter settings (10 to 49 Hz; see Appendix I). We found a reduction in the P50 amplitude (70 ms post-stimulus) evoked to standard stimuli compared to deviant stimuli that was not modulated across conditions, and no differences between the P50 evoked to deviant and control stimuli were found. These results agree with previous research showing that P50 habituation fully develops within one repetition (Rosburg et al., 2004) and support the notion that the habituation of early AEPs to repetition possibly indexes the formation of stimulus feature traces and not an integrated stimulus representation (Näätänen & Winkler, 1999). It also highlights the importance of low frequency bands in the development of RP, previously related to an oscillatory inference generation mechanism involving the encoding of temporal contingencies (Bendixen, Schröger, & Winkler, 2009; Clementz, Barber, & Dzau, 2002; Näätänen, 1992). We suggest that the development of this positive slow wave reflects the entrainment of neural populations encoding a certain frequency with rhythmical stimulation (Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008; Will & Berg, 2007). This could explain why the RP starts well before stimulus onset, why it is not present in control stimuli, and why the response to the second stimulus at the beginning of each Switch presents a prominent negative response (by interpreting deviant stimuli as breaking the entrainment, which takes several tone repetitions to be reinstated). However, this hypothesis needs further testing in future experiments properly designed to perform time-frequency analyses of the EEG data.

Neural Mechanisms of Deviance Detection in the Auditory System

Since its discovery, the MMN has been considered an index of primitive intelligence in the auditory cortex (Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001). Two main hypotheses compete for the interpretation of its underlying neural mechanisms: the *regularity violation hypothesis*, stating that MMN is generated by the mismatch between new input and predictions of future sensory events driven by a subset of extrapolatory sensory neurons (Näätänen, 1992); and the *N1 adaptation hypothesis*, proposing that MMN emerges when comparing an N1 response to a deviant stimulus with a refractory N1 response to a repeated stimulus (Jääskeläinen et al., 2004), both arising from the activity of tonotopically organized

afferent sensory neurons subject to adaptation and lateral inhibition (May et al., 1999; May & Tiitinen, 2010; for an extensive discussion about the concepts of neural adaptation and habituation in single-cell recordings and AEPs, please refer to Nelken & Ulanovsky, 2007). Our results, as well as those arising from studies using similar control stimuli (Jacobsen & Schröger, 2001, 2003; Jacobsen, Horenkamp, & Schröger, 2003; Jacobsen, Schröger, Horenkamp, & Winkler, 2003; Schröger & Wolff, 1996), are in agreement with the position advanced by Näätänen (1992) by showing that the time course of the controlled MMN extends beyond that of the N1 potential. Moreover, we found an enhancement of the controlled MMN amplitude with the local sequence of stimulation, a result at odds with that reported by Haenschel and colleagues (2005), where MMN amplitude increments with repetition were entirely due to changes in the standard AEP. While other studies reported MMN amplitude increments with the local sequence of stimulation (Giese-Davis, Miller, & Knight, 1993; Sams et al., 1983) or lower deviant probabilities (Imada et al., 1993; Javitt et al., 1998), the nature of the MMN repetition effect is still controversial. For instance, none of these studies separated the differential contributions of the standard AEP repetition effect from those of the deviant; studies focused on the RP using roving standard paradigms report significant increments of the deviant negativity as well as standard positivity (Baldeweg et al., 2004, 2006), whereas Haenschel and colleagues (2005) only report increments in the standard positivity; and a study by Horváth, Winkler, and Bendixen (2008), which separated local sequences naturally occurring in an oddball paradigm with two equiprobable stimuli, only reported amplitude increments of the N1/MMN AEP elicited to deviant stimuli. A possible explanation for the differences between these studies is the fact that different stimulation paradigms lead to different results: roving, standard paradigms seem to enhance the changes to the standard AEP while oddball paradigms don't. In the present study, our findings suggest that, in addition to the adaptation to repetition in multiple time scales simultaneously, the system's excitability strengthens for stimuli differing from the repeated stimulus (Näätänen, 1992). Interestingly, an increase of the response to deviant stimuli in comparison to equiprobable control stimuli has also been shown in PAC neurons of the cat (Ulanovsky et al., 2003).

An intriguing finding observed here is the fact that MMN is reduced to deviant stimuli formed by a sound with a long history of stimulation. Simple adaptation cannot account for this reduction because it is reverted by local sequence effects and reinstated with only one presentation of the stimulus (Ritter et al., 2002), as seen by local (Repetition) but not global (Run) sequence effects in Switch2. We suggest that the adaptation of a subset of neurons in the auditory system, which encode stimulus probabilities in multiple time scales and thus enable the system to generate expectations of the incoming stimulation, may account for the P2 enhancement as a gradual decrease of the MMN response. This explanation fits well with the predictive coding approach, which attempts to interpret sensory systems as predictive machines trying to infer and learn the causes of sensory data by minimizing prediction error (i.e., surprise), adjusting top-down predictions to bottom-up inputs in every hierarchical level through synaptic plasticity (Friston, 2005). Importantly, this perspective integrates both the *regularity violation* and the *adaptation* MMN generation hypotheses (Garrido, Kilner, Kiebel, & Friston, 2009), interpreting MMN as an index of prediction error (Baldeweg, 2006, 2007).

In summary, we have demonstrated that large neural populations exhibit the ability to match neural activity to stimulus statistics in multiple time scales, paralleling the behavior of PAC neurons. This wide range of adaptation time constants could be useful for supporting representations of auditory objects that typically have their features distributed over time (Nelken et al., 2003). Thus, the present results may help to establish a crucial bridge between human and animal research towards unraveling the neural mechanisms underlying acoustic background encoding.

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APPENDIX I: ASSESSING REPETITION RELATED EFFECTS IN THE P50 AEP RANGE

Here we tested whether the repetition related enhancement observed at the initial part of the Repetition Positivity (RP), corresponding to the latency range of the P50 AEP, could be due to the contribution of low frequency bands (0.1 to 10 Hz), usually included in RP studies (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Baldeweg, Wong, & Stephan, 2006; Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005). After re-analyzing our data with the appropriate P50 AEP filter (bandpass filter, 10 to 49 Hz, Blackman window, applied off-line to the continuous EEG data; Jerger, Biggins, & Fein, 1992), we identified the P50 AEP as the largest positive peak in the interval of 40–100 ms following the sound onset, for all subjects ($n = 19$) in all conditions (deviant stimuli after 2, 6, and 12 standard stimuli, for both "Runs" in both "Switches," resulting in $3 \times 2 \times 2 = 12$ conditions; standards preceding a deviant, resulting in 12 conditions; and control stimuli after 2, 6, and 12 random frequency stimuli for both "Runs," resulting in 6 conditions). P50 AEP mean amplitudes were derived at Cz electrode in a 20-ms time window centered on the mean peak latency of the grand-average waveforms, for all conditions and subjects (60–80 ms). An ANOVA with the factors Stimulus (Deviant, Standard) × Switch (1,2) × Run (1,2) × Repetition (2,6,12) yielded a significant main effect of Stimulus. This was due to P50 AEP mean amplitude being larger for deviant stimuli than for standard stimuli: $F(1,18) = 21.821$; $p < .0005$; $\eta^2 = 0.548$. No other effects or interactions were found. Furthermore, two separate ANOVAs with the factors Stimulus (Deviant, Control) × Run (1,2) × Repetition (2,6,12) revealed that the amplitude of the P50 potential evoked to deviant stimuli did not differ from that evoked to control stimuli, as no effects or interactions were found for any Switch. Grand-average waveforms for Deviant (*black*), Standard (*gray*), and Control (*dotted*) stimuli are plotted in Figure 7. Data were pooled across conditions for graphic purposes, as no effects or interactions were found with any factor but Stimulus. The present results agree with previous findings relating P50 AEP amplitude decrements with stimulus repetition (Boutros et al., 1995; Lijffijt et al., 2009), and highlight the importance of the contribution of low frequency bands (0.1 to 10 Hz) in the development of the RP to repeated stimuli.

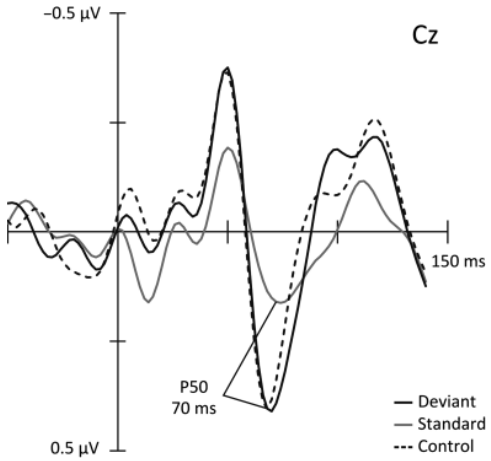

Figure 7. Grand-average waveforms for Deviant (*black*), Standard (*gray*), and Control (*dotted*) stimuli, averaged across conditions, after band-pass filtering the continuous data with the appropriate settings to highlight the P50 AEP (10 to 49 Hz). P50 amplitudes were retrieved in a 20-ms time window centered on the P50 mean peak latency (60–80 ms). Deviant events evoked a larger P50 AEP than Standard events but not than control events.

Study II: interactions between "what" and "when" in the auditory system: temporal predictability enhances repetition suppression

Dear Mr. Costa-Faidella:

Here is a copy of the decision letter for manuscript "Interactions between "what" and "when" in the auditory system: temporal predictability enhances repetition suppression." by Jordi Costa-Faidella, Torsten Baldeweg, Sabine Grimm, and Carles Escera [Paper #JN-RM-2599-11R2], which you were a Contributing Author.

Sincerely,

Earl Miller
Senior Editor
Journal of Neuroscience

Subject: Decision on Journal of Neuroscience JN-RM-2599-11R2

24th Oct 2011

Dear Dr. Escera:

I am pleased to inform you that your revised paper, "Interactions between "what" and "when" in the auditory system: temporal predictability enhances repetition suppression.," is considered suitable for publication in the Journal of Neuroscience in its present form.

Your manuscript will now pass through a series of pre-production checks at our Central Office. Soon, you will probably receive correspondence from the Central Office about issues such as figure sizes and color, length of the paper, and various forms that need to be completed. Once your paper is completely ready, you will receive email notification that it has been forwarded to the publisher.

Publication fees are $950 per regular article or $475 per Brief Communication. In four to five business days, unless corrections are needed to your manuscript, you will receive a payment form by e-mail. Please follow the instructions on the form to make your payment; proofs will be sent 4-6 weeks after the payment is made. Article proofs will not be sent to you until the publication fee has been received. Please contact the Central Office with any payment questions by e-mail: jn@sfn.org.

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On behalf of the Editorial Board, I thank you for submitting this paper to The Journal of Neuroscience.

Yours sincerely,

Earl Miller
Senior Editor
Journal of Neuroscience

Interactions between "what" and "when" in the auditory system: temporal predictability enhances repetition suppression.

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Keywords: sensory memory; adaptation; auditory evoked potentials (AEP); mismatch negativity (MMN); repetition positivity (RP); timing.

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ABSTRACT

Neural activity in the auditory system decreases with repeated stimulation, matching stimulus probability in multiple time-scales. This phenomenon, known as stimulus specific adaptation (SSA), is interpreted as a neural mechanism of regularity encoding aiding auditory object formation. However, despite the overwhelming literature covering from single-cell to scalp auditory evoked potential (AEP) recordings, stimulation timing has received little interest. Here we investigated whether timing predictability enhances the experience-dependent modulation of neural activity associated to stimulus probability encoding. We used human electrophysiological recordings in healthy participants that were exposed to passive listening of sound sequences. Pure tones of different frequencies were delivered in successive trains of a variable number of repetitions, enabling the study of sequential repetition effects in the AEP. In the predictable timing condition, tones were delivered with isochronous inter-stimulus intervals, whereas in the unpredictable timing condition inter-stimulus intervals varied randomly. Our results show that unpredictable stimulus timing abolishes the early part of the repetition positivity (RP), an AEP indexing auditory sensory memory trace formation, while leaving the later part (about >200ms) unaffected. This suggests that timing predictability aids the propagation of repetition effects upstream the auditory pathway, most likely from association auditory cortex (including the planum temporale) towards primary auditory cortex (Heschl's gyrus) and beyond, as judged by the timing of AEP latencies. This outcome claims for attention to stimulation timing in future experiments regarding sensory memory trace formation in AEP measures and stimulus probability encoding in animal models.

INTRODUCTION

The auditory system extracts stimulus probabilities from the acoustic scene serving the prediction of future events (Winkler et al., 2009): *what* do we expect on the basis of *"what"* we have heard before. Yet, guiding our actions in changing environments also involves anticipating *"when"* events will occur. Although the neural mechanisms of stimulus probability encoding have been the focus of much research, their interaction with stimulus timing is little understood.

Several studies showed that activity along sensory pathways is reduced with stimulus probability, a phenomenon supporting the neural representation of stimuli known as *repetition suppression* (Desimone, 1996). In the auditory system repetition suppression spans multiple spatial- and time-scales, as revealed by animal single-cell recordings exhibiting *stimulus specific adaptation* (SSA) in cortical and subcortical structures (Anderson et al., 2009; Antunes et al., 2010; Farley et al., 2010; Malmierca et al., 2009; Perez-Gonzalez et al., 2005; Reches & Gutfreund, 2008; Ulanovsky et al., 2003; Ulanovsky et al., 2004; Zhao et al., 2011), human long- and middle-latency auditory

evoked potentials (AEP; Costa-Faidella et al., 2011; Haenschel et al., 2005; Grimm et al., 2011; Slabu et al., 2010), and fMRI studies (Mutschler et al., 2010). However, none of the abovementioned studies explored the influence of timing regularity on repetition suppression, a subject only tapped scarcely in human electrophysiology literature leading to controversial findings. For example, whether single repeated tones in periodic vs. aperiodic sequences elicit a smaller N1-P2 complex of the AEP is still unclear (Rothman et al., 1970; Nelson et al., 1969; Nelson & Lassman, 1977). Similarly, periodicity in an AEP *oddball* paradigm can yield N1 decrements (Harada et al., 2005), P50 decrements (Moberget et al., 2008), and contradictory effects on pre-attentive deviance detection (Takegata & Morotomi, 1999; Schwartze et al., 2011). Divergences might arise from using inappropriate stimulation paradigms: because AEP repetition effects occur rapidly, using different stimuli with variable number of repetitions might prove more instructive (e.g., *roving standard paradigm*; Baldeweg et al., 2004; Cowan et al., 1993).

Considering that recent perception theories contemplate repetition suppression as a neural correlate of the precision with which future sensory events can be predicted (i.e. suppression of prediction error) based on past stimulation history (Friston, 2005; Winkler et al., 2009), it is of high interest to assess the relevance of timing predictability in neural adaptation. The present study seeks to provide human electrophysiological evidence showing that temporal predictability enhances the experience-dependent modulation of neural activity associated with probabilistic stimuli.

Here we recorded human AEP to pure tones arranged in a passive roving standard paradigm delivered with isochronous or random time intervals. We aimed to obtain a combined modulation of AEPs generated along the auditory pathway (P50, N1, P2), conforming the repetition positivity (RP), an AEP reflecting auditory sensory memory trace formation (Haenschel et al., 2005). If repetition suppression is enhanced by stimulus predictability, repetition effects should be greater in isochronous sound sequences. Furthermore, violating probability-based expectancies involving predictable time information should elicit stronger error signals, as indexed by the mismatch negativity (MMN; Näätänen, 2007).

MATERIALS AND METHODS

Participants

Seventeen healthy volunteers (6 male, aged 23-49years, mean age 29.18 years; all right-handed) with no history of neurological, psychiatric or hearing impairment and with normal or corrected-to-normal visual acuity participated in the experiment. All volunteers gave informed consent before their participation. Data from two participants had to be excluded from the analysis due to a poor signal-to-noise ratio in one case (i.e., less than 50% of artifact-free epochs in one block), and due to a muscle artifact time-locked to the onset of the acoustic stimuli in the other case (picked up by the electrodes located at the mastoid positions). Ethical approval was obtained from the local ethical committee, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Stimuli and procedure

The auditory stimuli consisted of pure sinusoidal tones of 50 ms duration, including 5 ms rise and fall times, generated with Audacity® (version 1.3, http://audacity.sourceforge.net/) free software. The tones were delivered binaurally through headphones by the Presentation® software (Version 0.70, www.neurobs.com). Each subject adjusted the loudness of the tones to a comfortable level, which was maintained throughout the recording session (average loudness, ~80 dB SPL). This experiment used a modified version of the roving standard frequency paradigm as described in (Baldeweg et al., 2004). Here, trains of 3, 6 and 12 equal tones were randomly delivered without inter-train pauses, with tone frequency varying across trains (Fig.1). In such a stimulus arrangement, the first tone of a train acts as a low-probability stimulus compared to those of the previous train (deviant stimulus), whereas the last tone of a train acts as a high-probability stimulus inside that train (standard stimulus). This paradigm allowed us to derive two types of measures on the amount of change in the AEPs as a function of stimulus repetition: a direct measure of the adaptation to repetition, indexing sensory-memory trace formation (Haenschel et al., 2005), by comparing the AEPs to the last tone in a train of 3, 6 and 12 stimuli; and a measure of the neural activity related to deviance detection, by means of the MMN, as obtained by subtracting the activity evoked to the standard stimulus from that evoked to the deviant

stimulus (Näätänen et al., 1978). The reason for choosing trains of 3 rather than 2 stimulus presentations as used in previous studies with roving standard paradigms (Baldeweg et al., 2004; Baldeweg et al., 2006; Haenschel et al., 2005) was to avoid the possibility of a residual MMN to either the preceding train of standards or to the deviant stimulus in the neural response to the repeated tone (Sams et al., 1983). Twenty-five different frequencies were used, ranging from 880 to 2921 Hz, with a frequency ratio between adjacent tones of 0.05 according to the following formula: $\Delta f=(f2-f1)/(f2 \times f1)^{1/2}$ (Ulanovsky et al., 2003). In order to avoid N1 refractoriness effects across trains, the tone frequency of a particular train did not appear in any of the ten subsequent trains.

In the "predictable timing" condition, the stimulus onset asynchrony (SOA) and the inter-train interval (ITI) were set to 708 ms. In the "unpredictable timing" condition, the SOA varied pseudo-randomly between 364 and 1062 ms in seven steps of 118 ms, equiprobably presented with the constraint that the SOA previous to the last stimulus in a train as well as the ITI were always 708 ms (pointed by asterisks in Fig.1B). This constrain was adopted to avoid potential baseline confounds in the AEP analysis due to carryover effects from the AEP to the previous stimulus. In total, 150 trains of 3, 6 and 12 tone repetitions were delivered per condition (900 trains overall). Participants sat in a comfortable chair in a sound-attenuated and electrically shielded room. They were instructed to ignore the sounds and watch a silent movie with subtitles. The auditory stimuli were arranged in three blocks of "predictable timing" and three of "unpredictable timing" conditions, delivered at random, with resting pauses in between. The total duration of the experiment was 80 minutes approximately, plus one hour of EEG recording preparation.

Auditory evoked potentials recording and analysis

The electroencephalogram (EEG) was continuously recorded with frequency limits of 0.05-100 Hz and digitized at a sampling rate of 1000 Hz by a SynAmps amplifier (NeuroScan Inc., El Paso, Texas, USA). Ag/AgCl electrodes were used for the EEG acquisition, 18 of which were mounted in a nylon cap (Quik-Cap; Compumedics, Abbotsford, VIC, Australia) at the standard locations Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8 and Oz according to the international 10-20 system. Additionally, two electrodes were positioned over the left and the right mastoids (M1 and M2). Vertical and horizontal electrooculogram (EOG) were measured from monopolar electrodes placed below (VEOG) and laterally (HEOG) to the right eye. The ground electrode was placed at Fpz and the common reference electrode was placed at Cpz. All impedances were kept below 5 kΩ during the whole recording session.

Data analysis was performed offline using EEGlab v.7 software (Delorme & Makeig, 2004) running under Matlab v7.6 (Mathworks, Natick, MA). Continuous EEG data was resampled to 250 Hz and periods contaminated by non-stereotyped muscle artifacts were rejected by visual inspection. Independent Component Analysis decomposition was applied using the Infomax algorithm, removing blink-related independent components on the basis of their scalp topography and continuous activity (Jung et al., 2000). EOG artifact corrected data was re-referenced to linked mastoids and filtered from 0.2 to 30 Hz. Epochs of 600 ms, starting -100 ms before stimulus onset and baseline corrected from -100 to 0 ms, were extracted and averaged for each experimental condition separately (12 conditions; standard and deviant stimuli x predictable/unpredictable timing x 3, 6, 12 tone repetition trains; 150 epochs per condition). Prior to averaging, epochs exceeding an amplitude threshold of ±100 μV were rejected (mean of overall rejected epochs = 22; SD = 14.9). MMN difference waveforms were obtained subtracting the activity elicited to the last stimulus in a train (i.e., standard stimulus: 3rd, 6th or 12th) from that elicited to the first stimulus of the subsequent train (i.e. deviant stimulus). For illustration purposes, RP difference waveforms were obtained by subtracting the activity elicited to the 3rd standard stimulus from that elicited to the 12th standard stimulus. To examine the early onset of AEP repetition effects, we computed the mean amplitude in the 60 to 80 ms time window around the P50 peak at Fz electrode for all standard and deviant AEPs. N1 peak amplitudes were retrieved from all standard and deviant AEPs by detecting the minimum amplitude values in the 80 to 180 ms time window at Fz. Similarly, P2 peak amplitudes were retrieved from all standard AEPs by detecting the maximum amplitude values in the 120 to 280 ms time window at Fz. P2 values were not retrieved from deviant stimuli due to a possible overlap with the ongoing MMN and P300 AEP components taking place in the response to improbable stimuli

(deviants). Finally, in order to compare the differential activity between standard and deviant stimuli around the MMN range, we retrieved the mean amplitudes for both stimulus types in a 30 ms time window centered at the individual MMN peak at Fz electrode (detected as the minimum value in the difference waveforms in the 80 to 250 ms time window).

Statistical analysis

Timing predictability and repetition effects and their interactions were assessed by means of repeated measures ANOVAs with the factors Stimulus (standard vs. deviant), Timing predictability (predictable vs. unpredictable) and Repetition (3, 6, 12) for all P50, N1 and MMN (time range) measures specified above. Effects on P2 values were computed with repeated measures ANOVAs with the factors Timing predictability (predictable vs. unpredictable) and Repetition (3, 6, 12). Subsequent repeated measures ANOVAs were performed to assess interaction effects. Linear trends are reported when applicable. The Greenhouse-Geisser correction was applied when the assumption of sphericity was violated. Significant ANOVA effects (alpha level = 0.05) are reported with the partial η^2 effect size measure.

In order to ascertain that stimulus probability and timing predictability affected the studied AEP (P50, N1, P2) and that the expected modulations were not due to other neural processes summing up at the scalp with those components, we computed a topographical measure of global dissimilarity (DISS; Murray et al., 2008). DISS is an index of configuration differences between two electric fields, independent of their strength. This test provides a statistical means of determining if the brain networks activated by two conditions differ. DISS equals the square root of the mean of the squared differences between the potentials measured at each electrode (average re-referenced; note that the relative form of the scalp topography is reference-independent), each of which is first scaled to unitary strength by dividing by the instantaneous global field power (GFP; the root mean square across the average-referenced electrode values at a given instant in time). DISS can range from 0 (topographic homogeneity) to 2 (topographic inversion). Because DISS is a single measure of the distance between two vectors, a non-parametric statistical test has to be conducted, and only pairwise comparisons are allowed with this method. We computed all possible pairwise comparisons between the scalp topographies obtained with the abovementioned measures for the P50, N1, and P2 AEPs, as follows: 1) data was average-referenced; 2) single-subject maps were re-assigned to different experimental conditions (i.e. permutations of the data); 3) grand-average AEPs were recalculated; 4) a DISS value was recalculated for the new grand-average AEP. Five thousand permutations of the data were used to obtain the empirical distribution, and the alpha level to determine whether the observed DISS between two conditions was significantly different compared to the distribution was set to 0.05.

RESULTS

Grand average waveforms evoked to standard and deviant stimuli after 3 (*blue trace*), 6 (*red trace*) and 12 (*green trace*) stimulus presentations for both predictable and unpredictable timing conditions are illustrated in Fig.2A, together with deviant minus standard difference waveforms (Fz electrode). As expected, tones in both conditions elicited the typical AEP waveforms with distinct P50, N1 and P2 components, and the subtraction of the waveforms to low from high probability tones revealed a prominent MMN. Below, we describe in detail the influence of stimulus probability and timing predictability in these AEP components.

Interactions between timing predictability and stimulus repetition effects on brain potentials

Early effects at the P50 range (~70 ms)

The P50 component of the AEP to standard and deviant stimuli indexed changes of early brain activity to tone repetition that depended on timing predictability (Timing predictability x Repetition interaction: $F(2,28) = 3.536$; $P = 0.043$; $\eta^2 = 0.202$). Whereas in the predictable timing condition the P50 mean amplitude evoked to standard and deviant stimuli was similar and increased as a function of repetition (Stimulus Type, $F(1,14) = 0.640$; $P = 0.437$; Stimulus Type x Repetition interaction, $F(2,28) = 0.184$; $P = 0.833$; Repetition effect for standard and deviant stimuli, $F(2,28) = 8.685$; $P = 0.001$; $\eta^2 = 0.383$; linear trend: $F(1,14) = 22.601$; $P = 0.0003$; $\eta^2 = 0.617$), it showed no significant changes in the unpredictable timing condition (Stimulus Type, $F(1,14) = 0.954$; $P = 0.345$; Stimulus Type x Repetition interaction, $F(2,28) = 1.901$;

P = 0.168; Repetition effect for standard and deviant stimuli, $F(2,28)$ = 0.066; P = 0.936). The topographical distribution of the P50 AEP remained stable across stimulus types and repetitions and did not depend on timing predictability, according to a global dissimilarity analysis (DISS; Murray et al., 2008) on every possible pairwise comparison. Stimulus-repetition-related changes in P50 mean amplitude elicited to deviant and standard stimuli in both predictable and unpredictable conditions are illustrated in Fig.2B.

Effects at the N1 range (~110 ms)

When analyzing the peak amplitudes of the N1 component of the AEP, larger amplitudes were found for deviant than standard stimuli (Stimulus type main effect, $F(1,14)$ = 18.308; P = 0.001; η^2 = 0.567). This main effect interacted with repetition (Stimulus type x Repetition interaction, $F(2,28)$ = 5.066; P = 0.009; η^2 = 0.285). Thus, when analyzing the N1 peak amplitude separately for deviant stimuli, no significant effects were found (Timing predictability, $F(1,14)$ = 0.916; P = 0.355; Repetition, $F(2,28)$ = 0.940; P = 0.403; Timing predictability x Repetition interaction, $F(2,28)$ = 0.027; P = 0.974), but the repetition effect interacted with timing predictability for standard stimuli (Timing predictability x Repetition interaction, $F(2,28)$ = 4.786; P = 0.016; η^2 = 0.255). This repetition effect was present in the predictable timing condition (Repetition main effect, $F(2,28)$ = 11.123; ε = 0.706; P = 0.001; η^2 = 0.443; linear trend, $F(1,14)$ = 14.633; P = 0.002; η^2 = 0.511) but not in the unpredictable timing condition ($F(2,28)$ = 0.846; P = 0.440). The topographical distribution of the N1 AEP remained stable across stimulus types and repetitions and did not depend on timing predictability, according to a DISS analysis on every possible pairwise comparison. N1 peak amplitudes retrieved from standard and deviant stimuli in both predictable and unpredictable timing conditions are plotted as a function of stimulus repetition in Fig.2C.

Effects at the P2 range (~170 ms)

The analysis of the peak amplitude of the P2 component of the auditory AEP to standard stimuli yielded an increase with repetition regardless of timing predictability, as shown by a significant effect of stimulus repetition without an interaction with timing predictability (Interaction, $F(2,28)$ = 2.334; P = 0.116; Repetition main effect, $F(2,28)$ = 4.899; ε = 0.706; P = 0.028; η^2 = 0.259; linear trend, $F(1,14)$ = 6.108; P = 0.027; η^2 = 0.304). The topographical distribution of the P2 AEP remained stable across stimulus repetitions and did not depend on timing predictability, according to a DISS analysis on every possible pairwise comparison. These changes in P2 peak amplitude with stimulus repetition in both predictable and unpredictable timing conditions are illustrated in Fig.2D.

In addition to the above mentioned analyses, the effect of stimulus repetition on the standard stimuli AEPs and its interaction with stimulus timing can be better seen in Fig.3A where, for illustration purposes, we subtracted the activity elicited to the 3rd from that elicited to the 12th tone in a train, a procedure commonly used to obtain the RP (Haenschel et al., 2005). The figure shows that the RP develops with stimulus repetition at much earlier latencies in the predictable timing (*blue trace*) than in the unpredictable timing (*red trace*) condition, an effect highlighted by the color arrows in the figure, marking the time windows of the P50 (*blue arrow*, ~70 ms), and P2 (*red arrow*, ~170 ms) components found in the standard stimuli AEPs. The typically fronto-central scalp potential distribution of the RP (Haenschel et al., 2005) is plotted in Fig.3B at the abovementioned time windows. This figure shows the lack of repetition effects in the AEP to standard stimuli over the whole scalp, until the P2 time range, in the unpredictable timing condition.

Interactions between timing predictability and stimulus repetition effects in auditory deviance detection

Auditory deviance detection was influenced both by stimulus repetition and timing predictability, as shown by an analysis on the separate contributions of deviant and standard stimuli to the MMN AEP (Fig.2E). Repetition effects were modulated by stimulus type and timing predictability (triple interaction between Stimulus type x Timing predictability x Repetition, $F(2,28)$ = 3.396; P = 0.048; η^2 = 0.195), being present mainly for standard stimuli and larger in the predictable than in the unpredictable timing conditions. Subsequent analyses showed that in the predictable timing condition, as expected, deviant stimuli elicited overall more negative amplitudes in the MMN time window than standard stimuli (Stimulus type main effect, $F(1,14)$ = 83.758; P = 2.8 * 10^{-7}; η^2 = 0.857), although repetition effects were only present in the responses to the latter (Stimulus type x Repetition interaction, $F(2,28)$ = 10.875; P = 0.0003; η^2 = 0.437;

Repetition effects on deviant stimuli, $F(2,28) = 0.159$; $P = 0.853$; Repetition effects on standard stimuli, $F(2,28) = 9.109$; $P = 0.001$; $\eta^2 = 0.394$; linear trend, $F(1,14) = 15.093$; $P = 0.002$; $\eta^2 = 0.519$). In the unpredictable timing condition, deviant stimuli elicited as well overall more negative amplitudes in the MMN time window than standard stimuli (Stimulus type main effect, $F(1,14) = 79.480$; $P = 3.8 * 10^{-7}$; $\eta^2 = 0.850$), and an interaction between Stimulus type and Repetition was also present ($F(2,28) = 3.977$; $P = 0.030$; $\eta^2 = 0.221$), indicating that repetition effects had opposite directions for deviant (increasing negativity) than standard (increasing positivity) stimuli. However, repetition effects per se did not reach significance in standard nor deviant stimuli (Repetition effects on deviant stimuli, $F(2,28) = 0.244$; $P = 0.785$; Repetition effects on standard stimuli, $F(2,28) = 1.963$; $P = 0.159$). Additionally, the typically fronto-central scalp potential distribution of the MMN (Alho, 1995; Näätänen & Alho, 1995) can be seen in Fig.3C as a function of stimulus probability and timing predictability.

DISCUSSION

The present study constitutes the first demonstration that timing predictability enhances the experience-dependent modulation of neural activity associated to stimulus probability encoding. Specifically, we have shown that isochronous stimulus repetition enhances the early part of the repetition positivity (about <200ms), an AEP indexing auditory sensory-memory trace formation. This suggests that predictable timing aids the propagation of repetition effects upstream the auditory pathway, as judged by the timing of AEP latencies. Furthermore, violating probability-based stimulus expectancies involving regular time relations elicited a greater error signal, as reflected by larger MMN amplitudes in the predictable compared to the unpredictable timing condition.

Using roving standard stimulation, enabling the observation of repetition-related effects, Baldeweg and colleagues showed in several studies that tone repetition modulates the AEP components in a conjoined and reliable way: an increase of the P50, decrease of the N1 and increase of the P2 AEPs, which they called the Repetition Positivity (RP; Baldeweg et al., 1999; Baldeweg et al., 2006; Haenschel et al., 2005). Our data argue for the view of the RP as a non-unitary phenomenon, as the modulation of the underlying AEPs, supported by their stable scalp topographies across the different experimental conditions, might reflect different processing stages of regularity encoding in the auditory pathway.

Particularly, we showed that P2 amplitude increased with repetition regardless of the timing predictability of the sound sequence. P2 amplitude increases with stimulus repetition in time-scales of minutes (Baldeweg et al., 1999) and days (Atienza et al., 2002), and correlates with stimulus expectancy driven by local and global stimulus probabilities (Costa-Faidella et al., 2011; for a review of the P2 AEP, see Crowley & Colrain, 2004). This suggests that P2, with neural generators localized to planum temporale (PT) as well as in area 22 (auditory association cortex; Godey et al., 2001), might reflect the encoding of the "*what*" aspect of auditory stimulation, in line with the idea that the PT is a crucial structure in the generation of auditory objects (Griffiths & Warren, 2002).

However, the N1 behaved differently, increasing to tone changes irrespective of timing predictability, but on the other hand showing decrements with an increased number of stimulus repetitions only in isochronous sequences. Thus, the N1 evoked by a repeated tone is affected by the *"when"* aspect of auditory stimulation. Our data seem at odds with a study by Budd and colleagues (1998) in which trains of isochronous tones, including tone repetitions at the first five positions of each train, were delivered to healthy participants. The authors found that after the second repeated tone N1 amplitude does not reveal a further decrease with repetition. Yet, differences might arise from the use of a higher number of repeated stimuli in our paradigm, leading to a stronger memory-trace effect. The reason why this further N1 amplitude decrement only took place in our predictable timing condition needs more consideration. For example, N1 amplitude decreases with temporal and pitch expectations (Lange, 2009), with previous knowledge of the sequence of stimulation (Clementz et al., 2002), and to self-generated tones (Baess et al., 2011). The common aspect in these different studies is that they support the involvement of predictive mechanisms in N1 amplitude attenuation. Following this reasoning, our results show that increasing the predictability of the auditory stimulation both in stimulus probability and stimulus timing leads to a pronounced N1 attenuation (Harada et al., 2005; Rothman et al., 1970; but Nelson et al., 1969, 1977).

As with the N1, repetition effects of the P50 were only observed in isochronous sequences. The increase of P50 amplitude

extends findings from previous studies using roving standard paradigms (Baldeweg et al., 2006; Haenschel et al., 2005) or embedding stimulus repetitions in changing acoustic backgrounds (Dyson et al., 2005). Here we showed that temporal regularity is a necessary requirement to elicit P50 repetition-related amplitude increments, strongly suggesting the existence of an inference generation mechanism involving the encoding of precise temporal contingencies (Bendixen et al., 2009; Clementz et al., 2002).

The fact that the P50 amplitude evoked to a deviant tone was not different from that evoked to its preceding standard supports the view that early AEPs reflect the attempt of the auditory system to predict the sound input in the immediate future (Bendixen et al., 2009), and that deviations from the predicted input are detected at later stages of stimulus processing, possibly reflected by the N1 (~110 ms) and the MMN (~150 ms; Näätänen & Winkler, 1999). Although the correlates of auditory deviance detection found in our study appear at these relatively long latencies (at ~110 ms after deviance onset and onwards), recent studies have shown mismatch responses at the middle-latency AEPs (~40 ms; Grimm et al., 2011; Slabu et al., 2010), supportive of a multi-stage deviance detection system in the auditory modality (Grimm & Escera, 2011). The disagreement with our results might arise from using shorter inter-stimulus intervals (< 300 ms compared to 708 ms used here), leading to stronger memory-trace effects on deviance detection.

The onset of RP in the latency of P50 (~70 ms; isochronous condition) implicates the primary auditory cortex in its generation, based on a latency comparison with intracranial generators of human AEP (Liegeois-Chauvel et al., 1991). This, with all caution in comparing different neural scales, makes the RP a possible human electrophysiological counterpart of SSA, with which it shares many properties: both occur without overt attention to sounds, are stimulus-specific and develop rapidly over multiple time-scales (Baldeweg, 2007; Nelken & Ulanovsky, 2007; Costa-Faidella et al., 2011). Although SSA literature is overwhelming (Anderson et al., 2009; Antunes et al., 2010; Farley et al., 2010; Malmierca et al., 2009; Perez-Gonzalez et al., 2005; Reches & Gutfreund, 2008; Ulanovsky et al., 2003; Ulanovsky et al., 2004; Zhao et al., 2011), no study up to date has attempted to explore SSA-timing interactions. To confirm that an irregular timing dampens the repetition effects at a neuronal scale, further research in animal models tapping the influence of timing predictability in the generation of SSA should prove instructive.

Summarizing, our study shows that the more regular, and thus predictable, the pattern of incoming sounds is, the shorter the latency of the AEP components exhibiting repetition suppression. Because human AEPs show a systematic hierarchy with latencies up to 70 ms generated along Heschl's gyrus, and later peaks generated in belt and parabelt (planum temporale) areas (Godey et al., 2001), our data suggests that the degree of predictability aids the propagation of repetition suppression upstream the auditory pathway. This idea is not new: Baldeweg (2006) raised it under the term *back-propagation hypothesis*, stating that with increasing number of repetitions a stimulus-specific memory trace could be detected at earlier auditory processing stages in a top-down fashion – in line with a predictive coding account (Friston, 2005). We extend this notion by including timing as an important variable in the formation of stimulus-specific memory traces at the level of the primary auditory cortex and perhaps further upstream.

It is important to note that sensory-memory trace formation is dependent on short-term synaptic plasticity, mainly mediated via NMDA receptor function, which is also essential in the generation of MMN/RP (Javitt et al., 1996; Umbricht et al., 2000; Näätänen et al., 2011). The lack of RP associated with timing uncertainty in our study might thus suggest the existence of a beat-based mechanism promoting a fine temporal adjustment of active top-down predictive signals (Nobre et al., 2007). A plausible candidate for such a mechanism is the entrainment of brain oscillations to stimulus presentation rate (Lakatos et al., 2008). Rhythmical deflections in the membrane potential could shift the excitability (i.e., depolarization) in local neuronal ensembles (Lakatos et al., 2005), aiding stimulus processing and memory trace formation via NMDA receptor activation. Future research using time-frequency decompositions of the electroencephalographic data may shed light on the interplay between entrained neural oscillations to rhythmic stimulation and repetition suppression.

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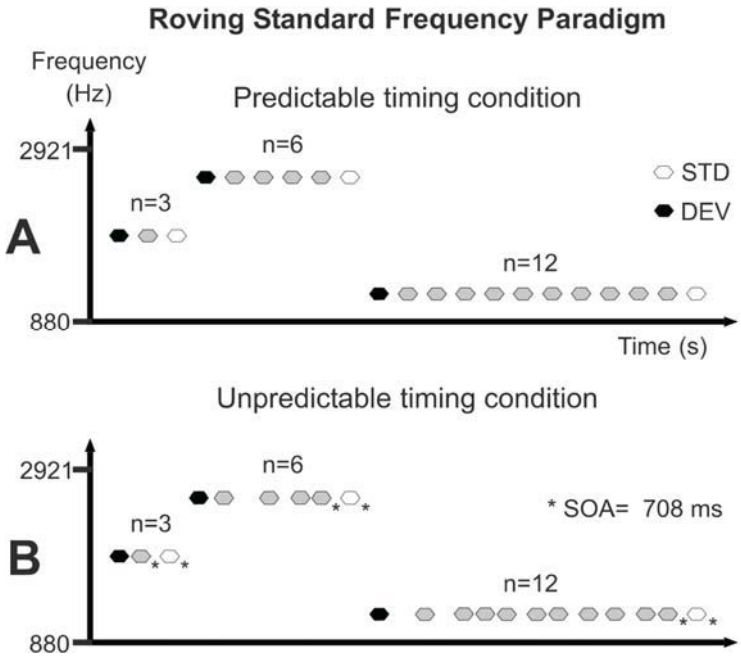


Figure 1. Schematic diagram of the roving standard frequency paradigm used in this study. Trains of 3, 6 and 12 equal tones were randomly delivered without inter-train pauses, with tone frequency varying from 880 to 2921 Hz across trains. In this arrangement, the first tone of a train acts as a low-probability stimulus compared to the previous train (deviant stimulus; DEV; *black hexagons*), whereas the last tone of a train acts as a high-probability stimulus inside that train (standard stimulus; STD; *white hexagons*). ***A.*** Predictable timing condition. The stimulus onset asynchrony (SOA) and the inter-train interval (ITI) were set constant to 708 ms. ***B.*** Unpredictable timing condition. The SOA varied pseudo-randomly between 364 and 1062 ms in 7 steps of 118 ms, with the constraint that the SOA previous to the last stimulus in a train as well as the ITI were always 708 ms (pointed by asterisks).

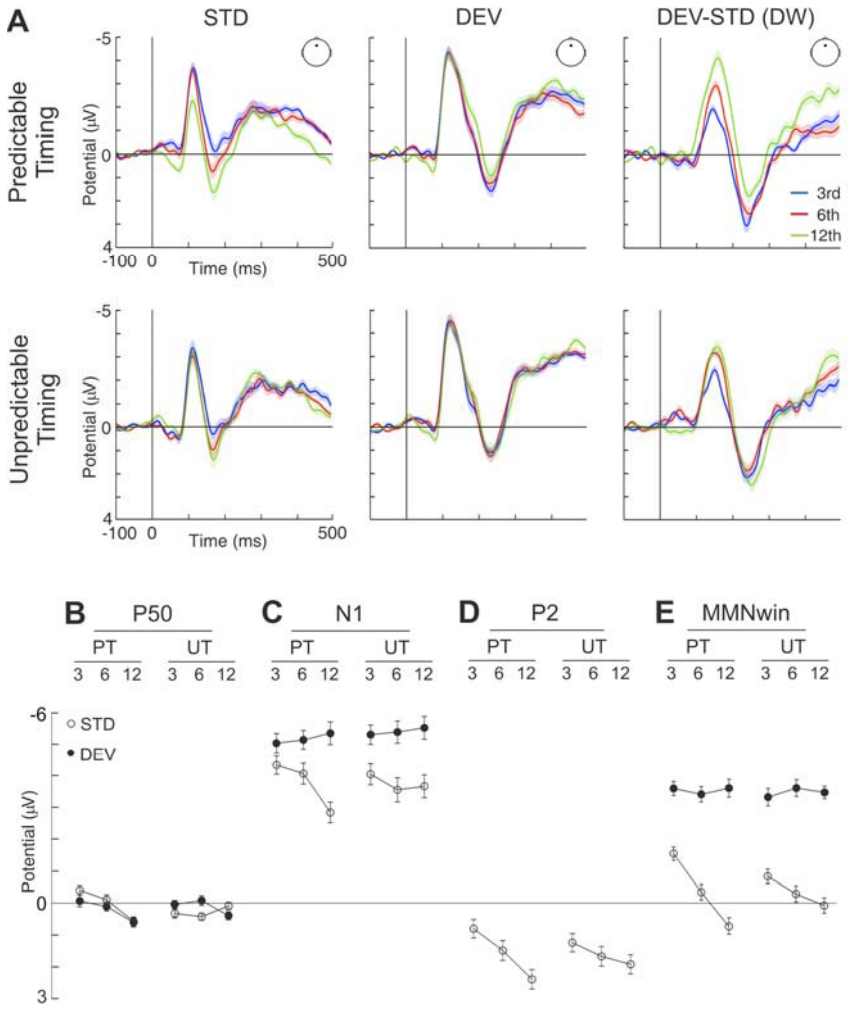


Figure 2. ***A.*** Grand-average waveforms for standard (STD), deviant (DEV) and deviant minus standard differences (DEV-STD DW) in predictable (*upper row*) and unpredictable (*bottom row*) timing conditions, separately for trains of 3 (*blue trace*), 6 (*red trace*) and 12 (*green trace*) tone presentations, as recorded from Fz electrode. Standard error of the mean is illustrated as a shadowed area around the curves. ***B.*** P50 amplitudes in predictable (PT) and unpredictable (UT) timing conditions elicited to STD (*white circles*) and DEV (*black circles*) stimuli separately for trains of 3, 6 and 12 tones (amplitudes in μV; error bars denote the standard error of the mean). P50 amplitude increased with repetition only in the predictable timing condition regardless of stimulus type. ***C.*** Same as in Fig.2B, but for N1 amplitudes, which were overall larger for DEV than STD stimuli but decreased with further repetition only for STD stimuli in the predictable timing condition. ***D***. Same as in Fig.2B and C, but for P2 amplitudes elicited to the STD stimulus. P2 amplitudes increased with tone repetition regardless of timing predictability. ***E.*** Same as in Fig.2B, C and D, but for amplitudes retrieved in a time window around the MMN. DEV stimuli elicited more negative amplitudes in the MMN time window than STD stimuli but only the latter were affected by repetition, an effect manifested as an increase of positivity, larger in the predictable than the unpredictable timing condition.

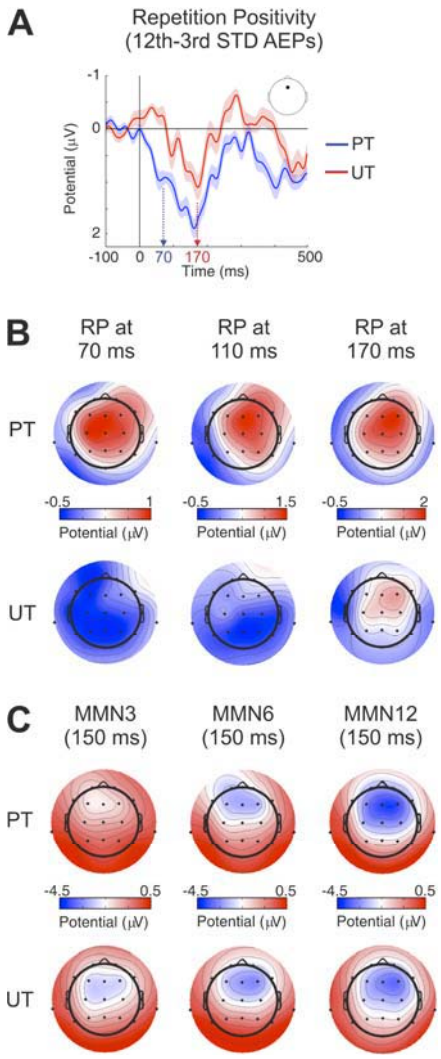
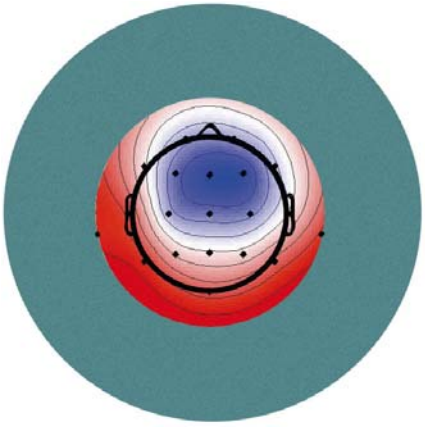


Figure 3. ***A.*** RP grand-average difference waveforms (AEP to the 12th minus the 3rd STD stimulus) for predictable (PT; *blue trace*) and unpredictable (UT; *red trace*) timing conditions at Fz electrode. Whereas the shape of the RP waveform is similar in both traces, the onset of the significant repetition-related positivity is ~100 ms earlier in the predictable vs. the unpredictable timing condition (marked by a blue arrow at the P50 TW, 70 ms; vs. a red arrow at the P2 TW, 170 ms, respectively). ***B.*** RP scalp potential distributions at 70, 110 and 170 ms for predictable (PT) and unpredictable (UT) timing conditions. Note how the development of the fronto-central repetition-related positivity takes place at an earlier latency when stimulation timing is predictable. ***C.*** MMN scalp potential distribution after 3, 6 and 12 tone presentations in predictable (PT) and unpredictable (PT) timing conditions. Note the repetition-related increase in amplitude and the typical fronto-central distribution of the MMN (using linked mastoids reference).

Summary of results and discussion



SUMMARY OF RESULTS AND DISCUSSION

In general terms, this PhD thesis aimed to explore the neuronal underpinnings of acoustic regularity encoding in the auditory system of healthy humans, by means of AEP analyses. Specifically, the first study aimed to investigate the dynamics of adaptation of a direct marker of regularity encoding, the RP, and of a marker of regularity violation, the MMN, to a complex sequence embedding local and global stimulus probabilities. Our results show that AEP amplitude modulations index the encoding of acoustic regularities in multiple time-scales simultaneously, and that these amplitude modulations can be fit to a simple linear model of stimulus expectancy, paralleling the behavior of non-human animal single-neurons in the primary auditory cortex. The second study aimed to explore the influence of timing in neuronal adaptation to stimulus probability. Our results show that predictable stimulation timing is crucial in the development of the sensory-memory trace to acoustic regularity at early stages of auditory processing, and that predictable timing boosts the effects of regularity violation in the AEP.

In both studies, stimulus repetition induced similar changes in the AEP to repeated stimuli in the form of a development of the RP: an increase of the P50, a decrease of the N1 and an increase of the P2 AEP, riding on a slow wave (Baldeweg et al., 1999; Baldeweg et al., 2006; Haenschel et al., 2005). Our data in both studies argued for the view of the RP as a non-unitary phenomenon, as the modulation of the underlying AEPs might reflect different processing stages of regularity encoding in the auditory pathway.

Particularly, both studies showed that the P2 (~145ms post stimulus onset in Study I and ~170ms in Study II) is the most sensitive AEP to acoustic stimulus probability. In Study I, we showed that the P2 increases in amplitude to both local and global probabilities in the sequence of stimulation simultaneously, supporting results from earlier reports showing P2 amplitude increments with stimulus repetition in time-scales of minutes (Baldeweg et al., 1999) and even days (Atienza et al., 2002). We also showed that the P2 AEP amplitude exhibits *one-trial* effects lasting about 300ms in this experiment (i.e., a partial reset of the sensory-memory trace due to the presentation of a stimulus violating the established regularity in the previous trial; Sams, et al., 1984). Furthermore, we showed that the P2 AEP undergoes a fast adaptation driven by the local event history preceding the current stimulus (five precedent trials) with a calculated time constant of ~1.5s (see the model of expectancy in Study I). Concurrently, P2 showed a slower adaptation time constant (~10s) to global aspects of stimulus probability, as seen by the decrease of the neural response to repeated stimuli forming a longer history of stimulation (see the exponential fit to AEP responses in Study I). This adaptation lasted ~10s (time to recover the responses), as seen by the decrease of the neural response to a deviant stimulus that has been preceded by several repetitions of the same acoustic stimulus. Interestingly, the adaptation to the local sequence of stimulation developed in a similar time range to that reported in primary auditory cortex neurons of the cat (Ulanovsky et al., 2004). Finally, and this involves as well processes involving the MMN AEP that will be reviewed below, we showed that AEP amplitudes in the time range of the P2 AEP can be fit to a simple linear model of expectancy, in which expectancy is defined as a combination of local

and global stimulus probabilities. The same type of model was used to fit single-neuron responses in the primary auditory cortex of the cat (Ulanovsky et al., 2004): This model comes from earlier research linking the P300 AEP to stimulus predictability (Squires et al., 1976), thus suggesting that inference based on updating probabilities is a basic property of the auditory system. In Study II, the P2 AEP was influenced by the local sequence of stimulation as well, increasing with stimulus repetition regardless of stimulation timing predictability. Hence, our results from both studies suggest that the P2 AEP, with neural generators localized to planum temporale as well as in area 22 (auditory association cortex; Godey et al., 2001), might reflect the encoding of the "*what*" aspect of auditory stimulation, in line with the idea that the planum temporale is a crucial structure in the generation of auditory objects (Griffiths & Warren, 2002).

In Study II, the amplitude of the P50 AEP (~70ms) increased with stimulus repetition for both repeated and deviant stimuli, but only when timing stimulation was predictable. Although not directly analyzed in Study I (see, however Appendix I), the fact that the analyzed RP ranges from 50 to 250ms post-stimulus onset, suggests that P50 amplitude to standard stimuli also increased with the number of stimulus repetitions. This increase of P50 amplitude with stimulus repetition extends findings from previous studies using roving standard paradigms (Baldeweg et al., 2006; Haenschel et al., 2005). The observation that the P50 amplitude evoked by a deviant tone was not different from that evoked by its preceding standard supports the view that early AEPs reflect the attempt of the auditory system to predict the sound input in the immediate future

(Bendixen et al., 2009), and that deviations from the predicted input are detected at later stages of stimulus processing, possibly reflected by the N1 (~110 ms) and the MMN (~150 ms; Näätänen & Winkler, 1999). This interpretation seems contrary to the findings in the MLR range, which suggest that deviance detection can take place at very early latencies (Grimm et al., 2011a; 2011b; Slabu et al., 2010), to the repetition effects described in sensory-gating studies (see the introduction section) and to the P50 deviance effect seen in Haenschel and colleagues (2005). There are, however, several issues that could explain these differences. First, the use of different paradigms (oddball, roving-standard, paired-click paradigm) could lead to different results: in oddball paradigms the local sequence of repeated stimuli is rarely longer than the one used in roving-standard paradigms, and paired-click paradigms only use two presentations of the stimulus, separated by long intervals between-pairs. Second, the length of the local sequence of stimulation in a roving standard paradigm (36 stimuli as maximum in Haenschel (2005) compared to 12 used here) could be critical in the strength of the encoded sensory-memory trace, allowing the detection of regularity violations at earlier and earlier stages of the auditory pathway (Baldeweg, 2006). Finally, different filter settings applied to the EEG data might bias the contribution of slow and fast neuronal oscillations in the computed AEP (see below for further discussion; see also Appendix I of Studuy I).

The latency of the P50 AEP implicates the primary auditory cortex in its generation, based on a latency comparison with intracranial generators of human AEP (Liegeois-Chauvel et al., 1991). This, with all caution in comparing

different neural scales, makes the RP (starting at the P50 latency range) a possible human electrophysiological counterpart of SSA, with which it shares many properties: both occur without overt attention to sounds, are stimulus-specific and develop rapidly (Baldeweg, 2007; Nelken & Ulanovsky, 2007). The fact that temporal regularity is a necessary requirement to elicit P50 repetition-related amplitude increments (Study II), strongly suggests the existence of an inference generation mechanism involving the encoding of precise temporal contingencies (Bendixen et al., 2009; Clementz et al., 2002). A plausible candidate for such a mechanism is the entrainment of brain oscillations to stimulus presentation rate (Lakatos et al., 2008). Rhythmical deflections in the membrane potential could shift the excitability (i.e., depolarization) in local neuronal ensembles (Lakatos et al., 2005), aiding stimulus processing and memory trace formation via NMDA receptor activation. This would be supported as well by results in Appendix I of Study I: when removing the contribution of slow brain oscillations (from 0.1 to 10 Hz), the P50 AEP to repeated tones was reduced in comparison to that elicited to deviant stimuli, and was not modulated by local or global stimulus probability, in agreement with previous research showing that P50 adaptation fully develops within one stimulus repetition (Rosburg et al., 2004).

With regard to the evidence for the encoding of acoustic regularity by means of regularity violation, both studies shed new light on the modulation of the MMN by stimulus probability and timing. Using a paradigm that controls for refractoriness effects (i.e., neuronal fatigue; Schröger & Wolff, 1996) in Study I, we found that the *true* MMN amplitude was enhanced with the local sequence

of stimulation. This agrees with other studies reporting MMN amplitude increments with the local sequence of stimulation (Giese-Davis et al., 1993; Sams et al., 1983) or lower deviant probabilities (Imada et al., 1993; Javitt et al., 1998), although none of them studied *true* deviance detection, thus including refractoriness effects to the standard stimuli in their MMN computation. Another new finding from Study I was the fact that *true* MMN was reduced to deviant stimuli formed by a sound with a long history of stimulation. Simple adaptation cannot account for this reduction because it was reverted by local sequence effects and reinstated with only one presentation of the stimulus (Ritter et al., 2002). Furthermore, in Study II we found that MMN amplitude, yet not *true* MMN in this case as no control condition was applied, increased with the local sequence of stimulation in both predictable and unpredictable timing conditions. However, this enhancement was larger when timing was predictable, although biased by stimulus probability and timing effects on standard stimuli AEP. Together with findings from Study I, both support the notion that MMN signals the violation of a regularity encoded as an integrated object representation (Näätänen & Winkler, 1999).

Altogether, the results from both studies support the idea that the auditory system generates predictive models based on encoded acoustic regularities by adapting its neuronal response to probabilistic stimuli. In Study I, AEP amplitude was shown to correlate with the expectancy of a stimulus derived by a computation of its local and global probabilities: when the confidence in the prediction increases because local and global stimulus probabilities induce strong expectations, the amplitude of the AEP increases in positivity towards an

enhanced P2, which as discussed above might index stimulus probability encoding *per se*; on the other hand, when the confidence in the prediction is decreased by a stimulus mismatching the established regularity, the amplitude of the AEP increases in negativity towards an enhanced MMN type of response, shown to index the violation of encoded regularities. In study II, we interpret the finding that repetition effects at early latencies of the AEP only take place when stimulation timing is predictable as supporting a theoretical hypothesis based on the generation of predictive models in the auditory system: the *back-propagation* hypothesis (Baldeweg, 2006). This hypothesis states that with increasing number of repetitions a stimulus-specific memory trace can be detected at earlier auditory processing stages in a top-down fashion. We extend this notion by including timing as an important variable in the formation of stimulus-specific memory traces at the level of the primary auditory cortex and perhaps further upstream. In addition, the lack of P50 repetition effects in unpredictable timing contexts (Study II), and the involvement of slow oscillatory activity in the P50 repetition effects to repeated tones (Appendix I of Study I), suggest the existence of an inference generation mechanism based on the entrainment of slow neuronal oscillations to rhythmic stimulation (Lakatos et al., 2008). Such a mechanism would provide accurate time-windows to optimize the processing of incoming stimulation at expected moments in time.

The two studies included in this PhD thesis leave open several questions and pose future challenges to be explored. First, a deeper characterization of the time-scales of adaptation in the AEP depending on stimulation parameters such as probability, timing (both in absolute values and in predictability) or complexity

of the acoustic regularity, as well as the brain areas involved, would prove useful in establishing tighter links with the SSA literature. Second, the fact that P50 amplitude increments with stimulus repetition depend on the contribution of slow oscillatory activity, and that unpredictable timing abolishes the repetition effects, claims for future experiments performing time-frequency analyses of the EEG data. This experiments could show whether slow neuronal oscillations get entrained to stimulation timing when timing is isochronous but not when it is irregular (Lakatos et al., 2008), and could show as well whether neuronal adaptation to repetition, as seen for instant as a decrease in power of high-frequency bands, depends on the instantaneous phase of entrained slow oscillations (Lakatos et al., 2005). Finally, the enhancement of the repetition effect by timing predictability claims for future single-neuron recording studies exploring the relation between SSA and timing. In addition, SSA experiments could test further the idea that timing predictability aids the propagation of repetition effects upstream the auditory pathway.

Conclusions

CONCLUSIONS

The conclusions of the present PhD thesis can be formulated as follows:

The human auditory system is able to encode the complex auditory stimulation by adapting its neural response in multiple time-scales simultaneously, as seen by stimulus probability-dependent modulations of the AEP (MMN and RP), paralleling the behavior of single-neurons in non-human animal primary auditory cortex. This property may underlie the formation of auditory objects, which typically have their features distributed over time.

The adaptation of neural activity in the human auditory system correlates with the degree of stimulus expectancy, with stimulus expectancy being defined as a linear combination of local and global stimulus probabilities. The amplitude of the AEP increased in positivity (towards a RP type of response) the more expected a stimulus was. Conversely, the amplitude of the AEP increased in negativity (towards an MMN type of response) the more unexpected a stimulus was. This might index the degree of confidence of a predictive model of the incoming acoustic input based on the encoding of the complex history of stimulation.

Timing predictability enhances the experience-dependent modulation of neural activity associated to stimulus probability encoding. Particularly, timing predictability appears to be crucial in the formation of sensory-memory traces to acoustic regularity at early stages of the auditory processing hierarchy, as

revealed by the abolishment of the early part of the RP. Thus, timing appears to be a crucial dimension of acoustic regularity in the generation of predictive models of the incoming acoustic input.

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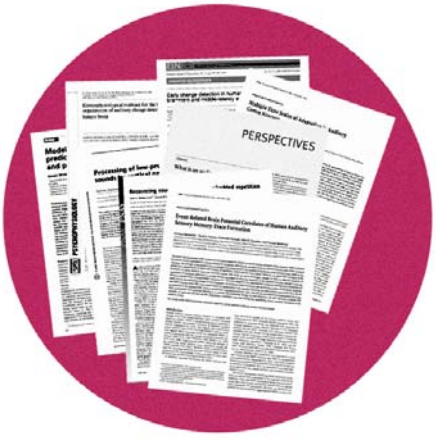

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Annex I
Summary (catalan version)

INTRODUCCIÓ

Els entorns naturals acústics són molt complexes i dinàmics. Múltiples fonts de so emeten sons al mateix temps, de manera que el sistema auditiu ha d'individuar la informació acústica, que arriba a les orelles en forma d'una barreja d'ones de pressió sonora, en objectes auditius als quals es pot orientar el comportament (Bregman 1990; Cherry, 1953; Griffiths & Warren, 2004). Com que els sons de la mateixa font contenen regularitats acústiques, el sistema auditiu les pot rastrejar i generar petjades a la memòria sensorial que es poden utilitzar com a models de predicció per individuar aquelles fonts en objectes auditius (Winkler *i cols*., 2009). La codificació de regularitats acústiques ha estat tradicionalment estudiada mitjançant el potencial evocat auditiu (PEA) de disparitat (PEAD; Näätänen, 2007; Näätänen *i cols.*, 1978), tot i que aquesta no és sinó una mesura indirecta, ja que és generada per la violació d'una regularitat establerta. Evidència directa que aporti suport a la codificació de regularitats acústiques s'ha trobat en enregistraments de la resposta de neurones individuals a la via auditiva d'animals no humans, en la forma d'adaptació específica a l'estímul (AEE; Ulanovsky *i cols*., 2003; 2004). En humans també es pot trobar un correlat directe de la formació d'una petja a la memòria sensorial. S'observa com a un patró de canvis que es donen en els PEA a la repetició d'un estímul, anomenat positivitat per repetició (PR; Haenschel *i cols*., 2005). Mentre que s'ha demostrat que la AEE opera en múltiples escales temporals, el que permetria la codificació de la complexa història d'estimulació auditiva, i que correlaciona amb l'expectativa d'un so, entenent expectativa com a una combinació lineal de probabilitats locals i

globals d'estimulació (Ulanovsky *i cols*., 2004), no s'ha trobat cap propietat semblant al sistema auditiu humà. Aquesta mancança a la literatura constitueix la motivació del primer estudi d'aquesta tesi doctoral. A més a més, els estudis que han explorat la formació de petjades a la memòria sensorial mitjançant l'estudi dels canvis d'activitat neuronal a la repetició d'estímuls, reflexada per l'AEE en neurones individuals d'animals no humans, o per la PR dels PEA humans, han utilitzat normalment estimulació isòcrona. Així doncs, el segon estudi d'aquesta tesi doctoral pretén explorar la influència que exerceix la regularitat temporal de l'estimulació (ritme) en la formació de la petja, per adaptació neuronal, a la memòria sensorial.

OBJECTIUS

Els objectius específics dels presents estudis es poden formular de la següent manera:

Estudi I

El primer objectiu és el d'examinar, mitjançant l'enregistrament dels PEA en participants humans sans, les dinàmiques d'adaptació del PEAD i de la PR a sons que formen una seqüència que conté aspectes locals i globals de l'historia d'estimulació. La hipòtesi principal planteja que el PEAD i la PR revelaran la codificació de les probabilitats de l'estímul en diverses escales temporals simultàniament, mostrant constants temporals d'adaptació més curtes pels aspectes locals de la història d'estimulació que pels globals. De ésser

demostrat, aquest fet establiria un paral·lelisme amb el comportament de les neurones individuals que mostren AEE a l'escorça auditiva primària en animals no humans.

El segon objectiu és el d'ajustar un model lineal simple de l'expectativa de l'estímul a les respostes electrofisiològiques enregistrades. La hipòtesi principal planteja que l'amplitud dels PEA correlacionarà amb l'expectativa de l'estímul, essent més negativa pels estímuls no esperats (cap a un tipus de resposta PEAD) i més positiva pels estímuls esperats (cap a un tipus de resposta PR).

Estudi II

El principal objectiu d'aquest estudi és el d'explorar la influència de la predictibilitat temporal en els canvis neuronals associats a l'estimulació repetida, mitjançant l'enregistrament dels PEA de participants humans sans. La hipòtesi principal planteja que, si l'amplitud de la PR indica la força d'una traça de memòria sensorial a la regularitat acústica, l'estimulació repetida amb predictibilitat temporal hauria de provocar amplituds majors de la PR que l'estimulació repetida sense predictibilitat temporal.

ESTUDI I

Resum (traducció de l'Abstract de l'article original)

Les neurones individuals de l'escorça auditiva primària del gat mostren constants temporals d'adaptació més ràpides per a històries d'estimulació curtes que no pas llargues. Aquesta habilitat de codificar la complexa estimulació auditiva passada en múltiples escales temporals habilitaria al sistema auditiu per a generar expectatives sobre l'estimulació que rep en curs. En aquest estudi vàrem provar si grans poblacions neuronals també exhibeixen aquesta habilitat, registrant potencials evocats auditius (PEA) humans a tons purs que apareixien en una seqüència que contenia aspectes curts i llargs de l'historia d'estimulació. Com a resultat principal, vàrem obtenir modulacions dinàmiques de l'amplitud del PEA P2 a l'estimulació repetitiva, simultàniament en un rang de milisegons a desenes de segons, així com modulacions de l'amplitud del PEA de disparitat (PEAD) a violacions de les regularitats establertes. Un model lineal simple d'expectativa, que té en compte l'historia d'estimulació a curt i a llarg termini, va descriure els nostres resultats, establint un paral·lelisme amb el comportament de neurones individuals a l'escorça auditiva primària.

ESTUDI II

Resum (traducció de l'Abstract de l'article original)

L'activitat neuronal al sistema auditiu disminueix amb l'estimulació repetida, coincidint amb la probabilitat d'estimulació en múltiples escales temporals. Aquest fenomen, conegut com a adaptació específica a l'estímul (AEE), és interpretat com a un mecanisme neuronal de codificació de regularitats que permetria la formació d'objectes auditius. De tota manera, tot i l'extensa literatura que cobreix enregistraments des de cèl·lules individuals a potencials evocats auditius (PEA) a nivell del cuir cabellut, les relacions temporals en l'estimulació han rebut molt poc interès. En aquest estudi vàrem investigar si la predictibilitat de les relacions temporals incrementa la modulació dependent de l'experiència de l'activitat neuronal associada a la codificació de les probabilitats d'estimulació. Vàrem utilitzar enregistraments electrofisiològics en participants sans exposats a l'escolta passiva de seqüències de sons. Tons purs de diferents freqüències van ser administrats en trens successius de nombre variable de repeticions, habilitant l'estudi d'efectes de repetició seqüencials als PEA. En la condició de relacions temporals predictibles, els tons van ser administrats amb intervals inter-estímul isòcrons, mentre que a la condició de relacions temporals impredictibles els intervals inter-estímul variaven aleatòriament. Els nostres resultats mostren que les relacions temporals impredictibles aboleixen la part primerenca de la positivitat per repetició (PR), un PEA que indica la formació de traces de memòria sensorial auditiva, mentre que no afecten a la part tardana (aproximadament >200ms).

Aquests resultats suggereixen que la predictibilitat dels intervals temporals ajuda a la propagació dels efectes de repetició en la via auditiva, probablement des de l'escorça d'associació auditiva (inclòs el "planum temporale") cap a l'escorça auditiva primària (gir de Heschl), jutjant pel temps de les latències dels PEA. Aquest fet comporta una crida d'atenció sobre les relacions temporals d'estimulació per a futurs experiments que versin sobre la formació de traces de memòria en enregistraments de PEA i codificació de les probabilitats d'estimulació en models animals.

RESULTATS I DISCUSSIÓ

En termes generals, l'objectiu d'aquesta tesi doctoral és el d'explorar els mecanismes neuronals de la codificació de regularitats al sistema auditiu d'individus sans, mitjançant l'anàlisi dels PEA. Específicament, el primer estudi va investigar les dinàmiques d'adaptació d'un índex directe de la codificació de regularitats acústiques, la PR, i d'un índex de violació de regularitats, el PEAD, en seqüències complexes de sons que contenien aspectes locals i globals de la probabilitat dels estímuls. Els nostres resultats mostren que les modulacions de l'amplitud dels PEA (PR i PEAD) indiquen que les regularitats acústiques es codifiquen en múltiples escales temporals, essent les constants temporals d'adaptació més ràpides (~1.5s) per a estímuls repetits en una seqüència local curta, i més lentes (~10s) per a la història d'estimulació en termes globals (Ulanovsky *i cols*., 2004). Aquesta troballa, a més d'establir un paral·lelisme clar entre el comportament de les respostes neuronals del sistema auditiu humà enregistrades mitjançant els PEA, i les respostes de neurones individuals

del sistema auditiu d'animals no-humans, suggereix que el sistema auditiu podria fer un ús simultani de múltiples constants temporals d'adaptació. Això li permetria la codificació en memòria sensorial d'objectes auditius, que típicament mostren els seus atributs distribuïts en el temps (Nelken *i cols*., 2003; Nelken & Bar-Yosef, 2008). A més a més, utilitzant un model lineal simple d'expectativa de l'estímul, definida com a una combinació lineal de probabilitats locals i globals d'estimulació (Ulanovsky *i cols*., 2004), hem pogut observar com l'amplitud del PEA correlaciona amb l'expectativa de l'estímul. Concretament, l'amplitud del PEA es torna gradualment més negativa com més inesperat és l'estímul, generant una resposta de tipus PEAD (Näätänen, 2007), llargament associada a la detecció de violacions de regularitats establertes. D'altra banda, l'amplitud del PEA es torna gradualment més positiva com més esperat és l'estímul, generant una resposta de tipus PR (Haenschel *i cols*., 2005), associada a la formació de petjades a la memòria sensorial. És particularment interessant el fet que la finestra temporal en la que es dona aquest fenomen als PEA coincideix amb la del PEA P2 (~145ms després del inici de l'estímul, en aquest estudi). Els increments en l'amplitud del PEA P2 han estat associats amb l'estimulació repetida en escales temporals de minuts (Baldeweg *i cols*., 1999) i fins i tot dies (Atienza *i cols*., 2002). A més a més, en el segon estudi d'aquesta tesi doctoral, l'objectiu del qual era el d'explorar la influència de la predictibilitat temporal en l'adaptació neuronal a l'estimulació repetida, els nostres resultats van mostrar que els increments del PEA P2 amb la repetició eren independents de la predictibilitat temporal: sigui l'estimulació rítmica o arrítmica, el increment de P2 correlaciona amb el nombre de repeticions d'un estímul. Conjuntament, tots dos estudis suggereixen una

interpretació del PEA P2 com a un índex pur de l'expectativa que es genera sobre la presentació d'un estímul en funció de quantes vegades ha aparegut aquest estímul amb anterioritat. Així doncs, donat que els generadors cerebrals del PEA P2 es localitzen al *planum temporale* i a l'àrea de Broadmann 22 (escorça auditiva d'associació; Godey *i cols.*, 2001), els nostres resultats concorden amb la idea de que el *planum temporale* és una estructura crucial en la generació d'objectes auditius (Griffiths & Warren, 2002).

D'altra banda, els resultats obtinguts al segon estudi d'aquesta tesi, que fan referència a la PR, mostren que la primera finestra temporal de la PR es veu altament afectada per la predictibilitat temporal de l'estimulació repetida. Quan la repetició d'un estímul és arrítmica, no s'observen efectes de repetició. Aquesta finestra temporal primerenca de la PR coincideix amb la latència del PEA P50 (~70ms), els generadors cerebrals del qual es localitzen a l'escorça auditiva primària (Liegeois-Chauvel *i cols.*, 1991). Aquest fet suggereix que la regularitat temporal de l'estimulació repetida juga un paper fonamental en la modulació de la resposta neuronal a la repetició en estadis primaris de la jerarquia de processament auditiu, augmentant la predictibilitat de l'estímul (Baldeweg, 2007). Un altre fet rellevant sobre el PEA P50, provinent dels resultats obtinguts a l'estudi I, és la forta implicació de les oscil·lacions neuronals lentes en la modulació de la resposta neuronal a la repetició. Ambdós fets suggereixen l'existència d'un mecanisme de generació d'inferències basat en la sincronització de les oscil·lacions neuronals lentes al ritme de l'estimulació (Lakatos *i cols.*, 2008). Tal mecanisme podria proveir finestres temporals precises per a optimitzar el processament de l'estimulació en curs als instants esperats en el temps.

CONCLUSIONS

Les conclusions de la present tesi doctoral es poden formular de la següent manera:

La primera conclusió estableix que el sistema auditiu humà és capaç de codificar la complexa estimulació auditiva mitjançant l'adaptació de la seva resposta neuronal en múltiples escales temporals simultàniament, com hem observat en forma de modulació dels PEA (PEAD i PR) dependent de la probabilitat de l'estímul, establint un paral·lelisme amb el comportament de les neurones individuals de l'escorça auditiva primària en animals no humans. Aquesta propietat podria ser la base de la formació d'objectes auditius, que presenten típicament els seus atributs distribuïts en el temps.

La segona conclusió estableix que l'adaptació de l'activitat neuronal del sistema auditiu humà correlaciona amb el grau d'expectativa de l'estímul, essent l'expectativa de l'estímul definida com a una combinació lineal de probabilitats locals i globals. L'amplitud dels PEA va incrementar en positivitat (cap a un tipus de resposta PR) com més esperat era un estímul. D'altra banda, l'amplitud dels PEA va incrementar en negativitat (cap a un tipus de resposta PEAD) com més inesperat era un estímul. Aquest fet podria indicar el grau de confiança d'un model predictiu de l'estimulació auditiva en curs basat en la codificació de la història complexa d'estimulació.

La tercera i última conclusió d'aquesta tesi doctoral estableix que la predictibilitat temporal incrementa la modulació dependent de l'experiència de l'activitat neuronal associada a la codificació de la probabilitat d'un estímul. Concretament, la predictibilitat temporal sembla ser crucial en la formació de les traces de memòria a la regularitat acústica en nivells primerencs de la jerarquia de processament auditiu, tal i com mostra l'abolició de la part primerenca de la PR. Així doncs, la predictibilitat temporal sembla ser una dimensió crucial de la regularitat acústica en la generació de models predictius de l'estimulació acústica en curs.

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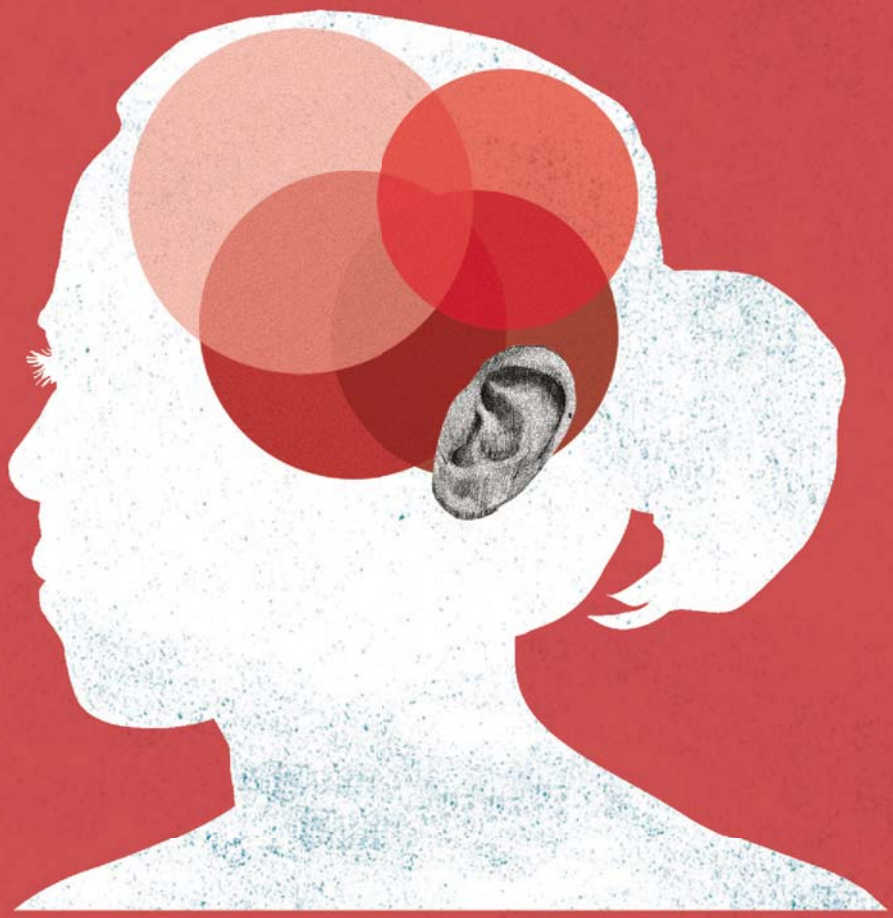

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