FUNDAÇÃO BIAL

BURSARIES FOR SCIENTIFIC RESEARCH

Final Report [February 2013]

Project title:

Psychophysiological mechanisms of hierarchical novelty detection in the human auditory brain

Bursary 37/10

Project Leader: Carles Escera

2011/2012

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FINAL REPORT FEBRUARY 2013

Summary of Project objectives and goal

The goal of the present project was to demonstrate that novelty detection is a basic principle of the functional organization of the auditory system, expanding from lower levels along the auditory pathway in the brainstem up to higher-order areas of the cerebral cortex. As novelty detection requires the modelling of regularity in the acoustic environment, we go beyond by proposing that increasing levels of complexity in acoustic regularity will be encoded in higher levels of the auditory system's hierarchy. Traditionally, auditory novelty detection has been studied by means of the mismatch negativity (MMN) event-related brain potential, generated in the auditory cortex with a latency of about 100-150 ms (Näätänen et al., 2007; Escera, 2007). To test these hypotheses, we planned now, however, to first record novelty responses to "deviant" auditory stimuli differing in a physical dimension from the repeating background in an oddball sequence and responses to stimuli that are controlled for refractoriness in the latency range of the Auditory Brainstem Response (ABR; up to 10 ms), the Middle Latency Response (MLR; up to 50 ms), and the Long-Latency Response, including the MMN (i.e., circa 150 ms). On a second phase of the project, we aim at recording novelty responses in these latency ranges to violations in a more complex type of regularities, such as the one requiring the combination several previous auditory events (i.e., stimuli) to define a complex regularity. Whereas we expect to find early indices of novelty detection of physical violation even at the level of the ABR, violation of complex rules would be present only in the higher levels of the auditory hierarchy (i.e., by the latency range of MMN).

Specific project objectives

The specific objectives of the project, as defined in the original application, were:

1. To test whether deviance detection occurs in the human brain in latency ranges similar to those described for novelty neurons in animals, and therefore much shorter than those of the typical novelty detection signature previously described in humans (i.e., the MMN).

This will be achieved by recording the Middle Latency Response (MLR) and the Auditory Brainstem Response (ABR) in healthy volunteers using a typical oddball paradigm of MMN previous studies. According to our hypothesis, we predict that such novelty responses will show up in the latency range of the Na, Pa, Nb, and Pb components of the MLR, and eventually in the latest waves of the ABR (i.e., wave A, and eventually wave V).

2. To demonstrate that increasing levels of complexity in acoustic regularity are encoded in higher levels of the auditory system.

This will be achieved by recording Long Latency Auditory EPs (namely, the MMN) together with MLRs elicited to deviant events violating complex regularities, such those defined by a particular combination of simple sound features (i.e., a particular frequency and a particular location). According to our hypothesis, we predict that such novelty responses to complex regularities will be seen only in later latency ranges (i.e., MMN) but not in earlier ones (i.e., MLR), contrasting with novelty responses for simple regularities which will be observed already at the MLR latency range.

Work conducted during the project (2011-2012)

During this first year of the project, we conducted, according to the research plan defined in the application, the full activities aimed at achieving objective #1, and we started also the activities related to objective #2 (see Progress Report 2011; also summarized here). During the second year of the project, we accomplished objective #2, and further we wrote up and published a review paper on the outcome of the project and related research (Grimm & Escera, 2012).

In general, the projects was implemented through an efficient project coordination, supervision and management (Activity 1). Also the experimental work related to achieve objectives #1 and #2 (Activities 2-6) and to the dissemination of their results (Activity 7) was successfully carried out.

Indeed, the project was coordinated and supervised towards its execution as planned (Activity 1), and we assess its implementation as very successful, as we were not only able to finalize the planned experiments but also to present their results in several congresses and to publish three scientific articles in peer-review journals (see section Dissemination for details). A fourth article is currently being written up.

As for the experimental work, we managed to conduct a literature review to set more accurately the state-of-the-art of the project (Activity 2), and a pilot phase (Activity 3) for adapting and testing recording protocols to ensure the quality of the recordings in the short latencies (ABR, MLR), and the design of the specific stimulus paradigms, materials and sequences for stimulation during acquisition. With this regard, we managed to record successfully the ABR and MLR using the same stimulus sequence and EEG acquisition parameters (Activity 4) and to analyze (Activity 6) and to report/disseminate (Activity 7) the corresponding results.

Experiment 1 (intensity changes).

In the first experiment, healthy participants, in a number of N=28 took part in this research, recruited among University of Barcelona students with an age range between 18 and 30 years, women or men, and right handed. Before the experimental session, all details of the research (except the hypotheses) were explained to the subjects, who were also informed about the characteristics of the methods (ERPs) and that they can abandon the experiment at their wish. After being informed, a written informed consent was obtained from each participant.

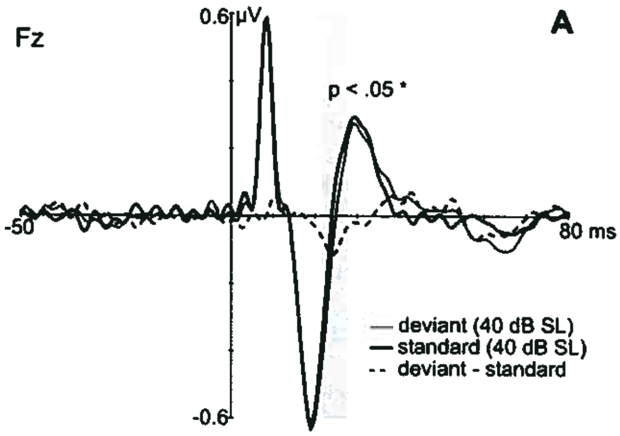
Methodology details. *Procedure.* The ERP experiments were conducted in a single laboratory session. Each session ~~will~~ lasted for approximately 3-4 hours, including subject preparation and recording. The ERP experiments was carried out in our laboratory at the University of Barcelona, equipped with a brand-new Neuroscan SynAmp RT recording system of 64 channels.

Experimental design. An oddball paradigm including the implementation of the so-called control condition was used. The control condition was implemented for the control of refractoriness: it is achieved by presenting the same physical stimulus acting as deviant in the oddball block with the same probability, but embedded in a context of other rare stimuli (i.e., different physical stimuli with same probability as the deviant in the oddball block) instead of in a context of repeating sounds.

EEG recordings were carried out with our NeuroScan system measuring data from a seven head positions (Cz, FCz, Fz, FC3, FC4, PO7, PO8) with the reference position being the link earlobes and the sampling rate of 20000 Hz and filtering bandwidth 0.1-1500 Hz allowing for ABR recording. Deviant responses were always compared to standard responses (highly frequent sounds) and to (rare, but non-deviant) sounds that control for refractoriness. This procedure allowed for disentangling of effects that are due to simple adaptation processes causing a suppressed response for frequently repeated stimuli (standard vs. deviant comparison) and effects that can only be explained by a true regularity extraction (deviant vs. control comparison).

Stimulus sequence. Although we planned a location deviant experiment in our original application, it turned out, after the literature review (Activity 2), that using an intensity deviant rather than a location deviant will be more scientifically relevant. Therefore we settled for an "intensity" experiment. Yet, subsequent piloting revealed that a "location" condition was possible for the MLR, although not for the ABR; we therefore conducted a second Experiment 1 on location changes (see below). As for the "intensity" experiment, sequences of 100 µs click tones of 1000 Hz were presented binaurally through headphones at varying intensities according to the experimental conditions. In the oddball condition a standard click of 50 dB SL and a deviant click of 40 dB SL were chosen with probabilities of p=6/7 and p=1/7. In the reversed oddball condition, these click sounds exchanged their roles. In the control condition, clicks of seven intensities were presented (10, 20, 30, 40, 50, 60, and 70 dB SL), each with a p=1/7.

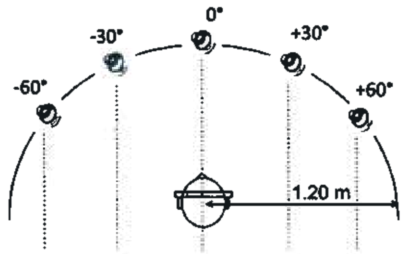
Results and discussion. ABR and MLR were obtained by averaging of the EEG epoch obtained to each stimulus type in each condition. The wave V for ABR and the waves Na and Pa were identified for standard, deviant and control responses, and their amplitudes analyzed by means of ANOVA for repeated mesures. The results show that whereas no trace of deviance detection could be identify in the latency range of the ABR, a clear deviance-related effect was evident in the time range covering the transition between Na and Pa components of the MLR (see Figure 1, from Althen et al., 2011). These results have two important implications: 1) they show for the firt time that regularity on intensity information of sound can be encoded already at the level of the generators of the MLR, and that detection of intensity changes takes places at very short latencies, circa 23 ms from sound onset. This is the first study showing that changes in sound intensity can be dectected at these very short latencies, as all former studies reported much longer latencies (i.e., in the latency range of the MMN). 2) They preclude the involvement of the lemniscal afferent auditory pathway in encoding the regularity of acoustic intensity, as no effects were observed on the ABR, a brain response generated from the cochlear nucleus up to the inferior colliculus and the auditory thalamus.



Subsequent Experiment 1 (location changes)

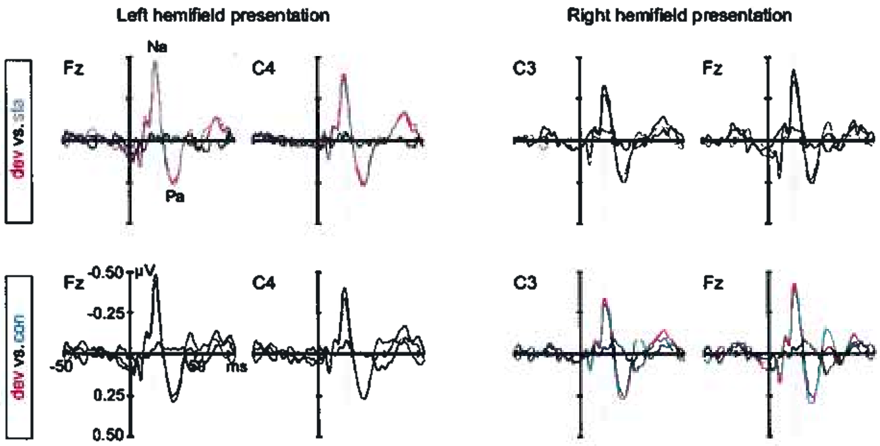
In this further experiment, the participants were 20 healthy volunteers (mean age 19.4 yr.). Laboratory protocols and ethic requirements were conducted as for experiment 1.

Methodology details. Procedure and experimental design were as for experiment 1, as well. The only differences were related to: EEG acquisition (from 31 scalp electrodes instead of 7), analyses settings (i.e., filters from 15-250 Hz) and stimulus sequence. In this experiment, stimuli were delivered from five loudspeakers placed at a distance radius of 1.2 m from the participant at the height of the head at azimuth angles of −60, −30, 0, +30, and +60° (see Figure 2, from Grimm et al., 2012). Three infrared LEDs mounted in a plastic headband on the subject's head and an infrared-sensitive camera placed above the subject's head allowed to measure torsional head position. Rotation of the head along the longitudinal axis was captured within the empty interval before each single stimulus presentation with reference to the head position as calibrated at the beginning of the block where subjects were instructed to direct the head to the central loudspeaker. Trials in which head rotations exceeded 1° relative to the preceding trial or 7.5° relative to the reference angle were excluded from further analysis. This was on average for 1.1% of the trials the case. The experimental protocol consisted of blocks of auditory sequences of five different conditions: (a) an oddball block presented in the left and right hemifield, respectively, (b) a reversed oddball block presented in the left and right hemifield, respectively, (c) a control block presenting tones from all five locations randomly (see Figure 2, from Grimm et al., 2012). Sequences consisted of click sounds (100 µs click length, 60 dB peak-equivalent SPL) separated by a variable stimulus onset asynchrony (SOA) ranging from 195 to 285 ms in ten steps that were equiprobably distributed over trials.



Location / Type of block	-60°	-30°	0°	+30°	+60°
Oddball right				80%	20% (RD)
Reversed Oddball right				20%	80% (RS)
Oddball left	20% (LD)	80%			
Reversed Oddball left	80% (LS)	20%			
Oddball right	20% (LC)	20%	20%	20%	20% (RC)

Results and discussion. In short, ocassional location changes elicited a contralateral enlargment of the Na component of the MLR, both in comparison to the same physical stimulus presented as standard and as control sounds (see Figure 3, from Grimm et al., 2012). In



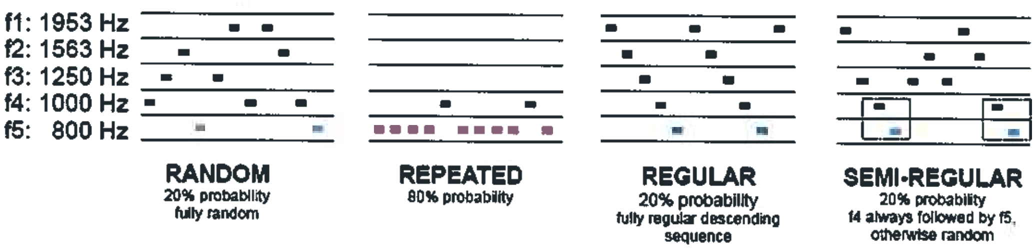
addition, these very same changes elicited also the MMN component of the long latency auditory evoked potentials. These results are the first to show that location regularities are encoded in the early stages of the auditory hierarchy, and that unexpected changes in these regularities are detected as short as 19-21 ms from change onset.

Experiment 2.

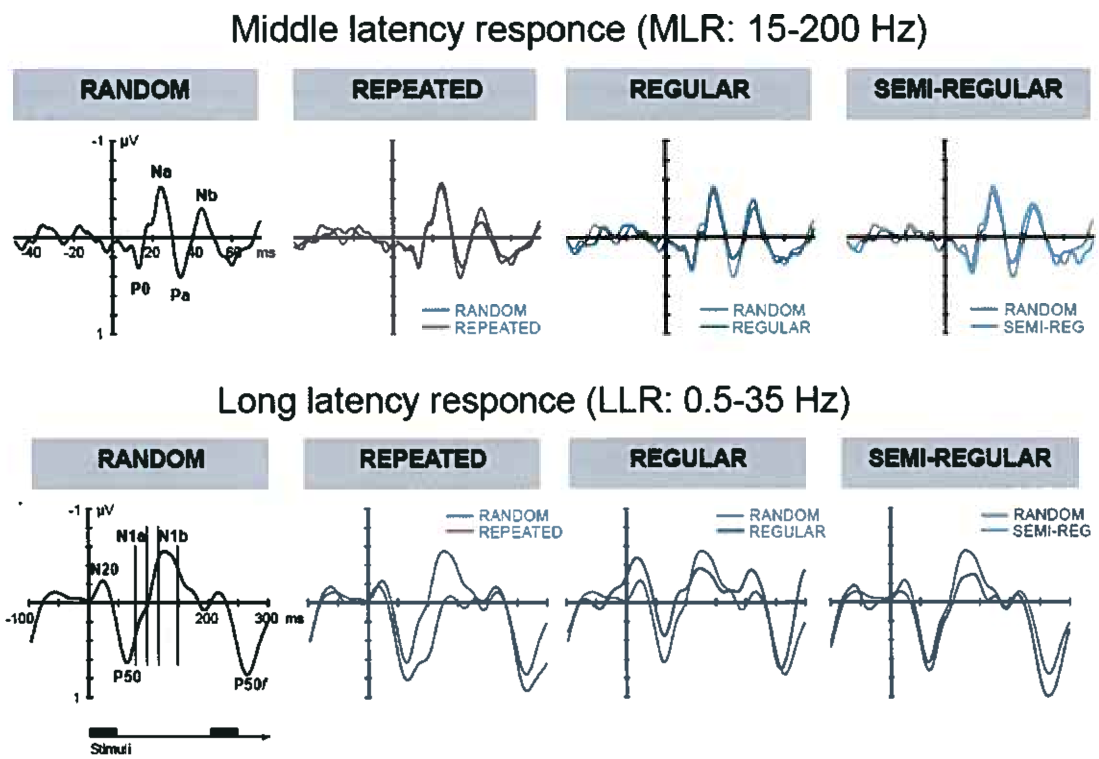
In order to address whether more complex forms of regularity can be encoded already at the level of the MLR, we have designed a second experiment based on the foundations of predictive coding. Essentially, the results obtained in experiments such as those described above can be interpreted as for the brain expecting the occurrence of the standard tone, and this has shown to reduced the amplitude of the N1 component of the long latency auditory evoked potentials (LLR), a phenomenon known as Repetition Suppression. Hence, we here aimed at determining whether context effects modulated by probability-related frequency adaptation or by more complex forms of predictability indeed would affect similar processing stages or even earlier ones.

Methodology details. MLRs and LLRs (including the MMN) were recorded in 14 healthy volunteers, using a paradigm that manipulated stimulus probability and stimulus predictability in different conditions. In particular, the same tone of frequency 1 (f1: 800Hz) was presented in five stimulation contexts (see Figure 4, from Grimm & Escera, 2013):

1) in fully RANDOM order (serving as a control condition).
2) taking the role of a frequent, REPEATED tone (f1: p=0.8, f2: p=0.2),
3) of a rare tone (f1: p=0.2, f2: p=0.8) in a random oddball paradigm; or being presented in blocks of five equi-probable tones (p=0.2) of different frequencies, which occurred equiprobably (not shown),
4) in a REGULAR descending pattern (f5-f4-f3-f2-f1-f5-f4...), and
5) in a SEMI-REGULAR pattern in which f2 was always followed by f1whereas otherwise the tones occurred randomly.



Results and discussion. The main findings were that sound repetition resulted in an attenuation of the Nb of the MLR and of the early portion of the N1 of the LLR (see Figure 5, from Grimm & Escera, 2013).. In addition, full regularity yielded an attenuation of the Pa of the MLR and the N1 of the LLR, and a partial regularity resulted in N1 of the LLR attenuation. These finding suggest that a repeated input is filtered by a probability-dependent adaptation mechanism at multiple stages: at latencies circa 45 ms and at 90 ms. Also, auditory stimulus predictability modulated distinct components of the auditory evoked potentials, with regular tones undergoing a differential processing early in the case of full regularity (circa 20-35 ms) and showing suppression at 135 ms (i.e., the N1 for both fully and partially regular tones. Critically, the neural processes showing probability-related adaptation can be dissociated from those sensitive to sequential predictability.



Theoretical model of auditory change detection (theoretical review).

Following the experimental work carried out within this project, and also on related experiments conducted in our laboratory, we have written up and published (Grimm & Escera, 2012) a theoretical review on what we believe is a new conception of the organization of the auditory system for change detection.

Indeed, models at use of change detection in audition have suggested that such is a rather higher and complex capability of the auditory system, that requires higher levels of the auditory pathway, i.e., the auditory cortex, to encode the acoustic regularity in sensory memory traces. Further, such a system would require a "comparison" process of each incoming stimulus against these traces, the MMN being elicited every time such an input does not match the trace.

According to our results, showing correlates of deviance (change) detection in very early stages of the auditory processing chain (i.e., < 20 ms), the traditional assumptions are not anymore supported by the evidence. Rather, these results suggest that the auditory system is organized towards encoding the acoustic regularity and detecting unexpected changes on it from the lower levels in the auditory brainstem to the higher levels of the auditory cortex. Furthermore, we suggest in our review that whereas simple levels of regularity would be encoded in lower levels of the hierarchy, i.e., eliciting change-detection correlated by the MLR components, more complex levels of regularity will require the "cortical" MMN system to be encoded and for the detection of the corresponding regularities.

All in all, we are convinced that our empirical results and our theoretical formulation within the framework of the fellowship awarded by the Bial Foundation has contributed to our understanding of the psychophysiological mechanisms that make human auditory perception possible.

Dissemination

Publications resulting from the project

Althen, H., Grimm, S., & Escera, C. (2011). Fast detection of unexpected sound intensity decrements as revealed by human evoked potentials. ***PLoS ONE***, 6(12): e28522. doi:10.1371/journal.pone.0028522.

Grimm, S., Recasens, M., Althen, H., & Escera, C.CA (2012). Ultrafast tracking of sound location changes as revealed by human auditory evoked potentials. ***Biological Psychology***, 89(1):232-239.

Grimm, S. & Escera, C. (2012). Auditory deviance detection revisited: Evidence for a hierarchical novelty system. ***International Journal of Psychophysiology***, 85, 88-92.

Grimm, S. & Escera, C. (2013). Differential effects of frequency adaptation and sequential predictability on auditory evoked potentials. *Manuscript in preparation.*

Contributions to scientific conferences

Althen, H., Grimm, S., Slabu, L., Escera, C. Evidence for early automatic detection of intensity deviants in the human middle-latency response. ***VI Reunión de la Red Temática de Neurociencia Cognitiva - V Workshop sobre Avances en el Estudio de la Actividad Cerebral***. Murcia (Spain), July 2010. Poster.

Althen, H., Grimm, S., Slabu, L., Escera, C. Evidence for early automatic detection of intensity deviants in the human middle-latency response. ***VII Congreso de la Sociedad Española de Psicofisiología y Neurociencia Cognitiva y Afectiva (SEPNECA)***. Valencia (Spain), September 2010. Poster.

Althen, H., Grimm, S., Slabu, L., Escera, C. Evidence for early automatic detection of intensity deviants in the human middle-latency response. ***Donders discussions 2010***. Nijmegen (The Netherlands) October 2010. Poster.

Althen, H., Grimm, S., Slabu, L., Escera, C. Evidence for early automatic detection of intensity deviants in the human middle-latency response. ***"III Brainglot Workshop" from Programme Consolider - Ingenio 2010***. Castellón (Spain), November 2010. Poster.

Althen, H., Grimm, S., Slabu, L., Escera, C. Early automatic detection of intensity deviants reflected in the middle-latency range of the human electrical brain response. ***19th Annual Meeting of the Annual Meeting of the Cognitive Neuroscience Society (CNS)***. San Francisco (USA), April 2012. Poster.

Althen, H., Grimm, S., & Escera, C. (2011). Fast detection of unexpected sound intensity decrements as revealed by human evoked potentials. ***Bial Foundation's 9th Symposium***. Porto (Portugal), 28-31 March 2012. Web post.

Grimm, S. & Escera, C. (2012). Differential effects of frequency adaptation and sequential predictability on auditory evoked potentials. ***19th Annual Meeting of the Cognitive Neuroscience Society (CNS)***. San Francisco (USA), April 2012. Poster.

In addition, contributions to the following conferences are expected in June, September and October 2013, respectively:

- Organization of Human Brain Mapping (HBM), Seatle (USA) - presenter: Marc Recasens.
- Sociedad Española de Neurociencia (SENC), Oviedo (Spain) - presenter: Carles Escera.
- Society for Psychophysiological Research (SPR), Firenze (Italy) - presenter: Carles Escera.