NAIMA – ANR 2015 Major Societal Challenge "Life, Health and Well-being"

NEURO-AFFECTIVE INVARIANTS of AUDITORY PERCEPTION in MICE AND MEN

1. Strategic relevance

Understanding human auditory perception is an important challenge both for the development of computer applications that can perform intelligent hearing, and to design strategies to best rehabilitate the declining hearing capacities of the **aging populations of our Western societies.** While human psychoacoustics is providing increasingly precise description of how human recognize, interpret and emotionally evaluate sounds, many of the biological bases and of the computational underpinnings of complex auditory scene analysis are still lacking. Yet, this knowledge is a key to progress towards intelligent sensing and high-performance auditory rehabilitation.

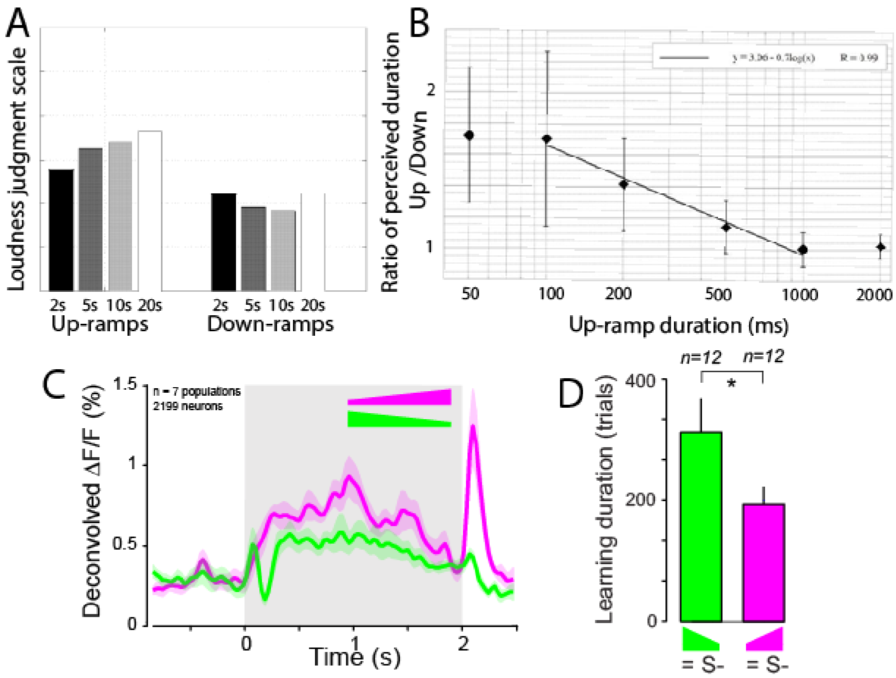
Project NAIMA proposes to bridge human psychoacoustics and cutting-edge mouse physiology methods in order to tackle the neural and affective mechanisms underlying **two of the most vexing mysteries of our perception of everyday sounds**. First, that auditory perception crucially depends on the temporal dynamics of sounds (Neuhoff J., 1998). Second, that some sounds are more pleasing than others (Zentner et al. , 1996).

Multiple studies have shown that the loudness of a sound - the sensation in terms of which a human listener judges it on a scale extending from quiet to loud - is affected by its temporal intensity profile (Neuhoff, J., 1998). This is particularly evident in experiments showing that perceived loudness is systematically greater for sounds with rising intensity profiles than for sounds with decreasing profiles. We have recently observed that these effects exist also in mice (Fig. 1), opening avenues to tackle the mechanisms of temporal feature processing in the mouse model using modern neurophysiological techniques, from which we expect rapid feedback on the understanding of the related human psychophysics.

In the same effort, we plan to take advantage of our unique consortium of mouse physiologists (Bathellier team, UNIC) and human psychophysicists (Perception and Sound Design team, IRCAM) to develop cortical measurements and behavioral tasks to assess the valence of different sounds in mice, in particular sounds with properties related to consonant and dissonant percepts in human. Given the wealth of methods now existing to address the function of precise brain circuits in mice, and in particular of the centers implicated in unpleasant (Amygdala) and pleasant (Ventral Tegmental Area) judgments/emotion, these new developments will give interesting perspectives for the identification of the link between sounds and emotional/esthetic judgments.

Altogether, by uncovering the biological bases of the preference biases for sounds, NAIMA will provide decisive data to step into more precise models of complex sound perception. Applications include algorithms to better process time-fluctuating sounds and to predict the emotional content of sounds, paving the way towards **richer and more fulfilling**

experiences for populations with hearing loss, such as speech recognition with competing speakers ("cocktail party") or music listening.



A. Human loudness judgment for up- and down-ramps (Sucini et al. 2007). **B**. Relative perceived ramp duration in human (up- divided by down- ramp) (Meunier et al. 2014). **C**. Mean population response for 2199 neurons imaged in the mouse cortex for up- (*magenta*) and down-ramps (*green*). **D**. Learning duration for associating the down- or up-ramp associated with negatively rewarded behavior in mice.

2. Scientific objectives

Task1. Neuronal invariants of the perception of time-varying sounds in mice and men

Multiple studies have shown that the temporal intensity profile of a sound can affect several aspects of its perception. This important fact however is still lacking neuronal explanations. The seminal experimental demonstration of such effects involves simple sounds (pure tones, harmonic sounds, white noise) with rising intensity (up-ramps) or decreasing intensity (down-ramps). Modern psychophysics has shown that up-ramps are perceived louder than their associated down-ramps despite having the same physical intensity (Susini et al, 2007). In addition, short up-ramps (< 500ms) are also perceived as having a longer duration than down-ramps (Schlauch et al, 2001), an effect that is not seen in longer ramps (> 500ms) (Meunier et al, 2014, Fig. 1B).

To understand the mechanisms of these perceptual asymmetries, data on human brain activity is scarce and mechanistic neuronal models are inexistent. Human fMRI data shows that up-ramps produce stronger auditory cortex activation than down-ramps (Seifritz et al. 2002). Recent electrophysiological results in awake cats also showed a persistence of excitation in the primary auditory cortex, which was found to be longer for up-ramps than for down-ramps for durations from 2.5 to 80 ms (Wang et al, 2014). While this data indicates that the psychophysical effects indeed have cortical correlates, these do not cover the whole range of ramp duration, and are too restricted in their spatio-temporal precision to inform on underlying mechanisms.

It was initially proposed that the perceptual emphasis on up-ramps reflects a bias in favour of approaching sound sources (Neuhoff, 1998), however despite its biological appeal this interpretation does not explain the underlying neural mechanisms. Meanwhile, molecular psychophysics measurements have shown that loudness judgements for long ramps depended strongly on the time period in which a sound's intensity reaches its peak value (Ponsot et al, 2013). Therefore fading memory effects could be the source of the perceptual asymmetry as the peak is closer to the time of judgment for up-ramps (Susini et al., 2010).

Despite sophisticated paradigms, human psychoacoustics is grinding to a halt on the problem, because of the difficulty to do direct neuronal population recordings on human listeners (Seifritz et al. 2002). **The disruptive originality of our approach to this 15-year-old question is to harness the experimental power of the mouse animal model.** First, contrary to men, the mouse model is uniquely suitable to neuronal population recordings in brain tissues in vivo. The Bathellier team is expert in GCAMP6 awake two-photon imaging recordings and will apply this technique to the project. Previous results with this technique have shown that neuronal activations reflect the animals' choices, thus linking neuronal representations to behavior (Bathellier et al., 2012). In addition, sound learning experiments interpreted with **computational models** based on the reinforcement-learning framework showed that sounds that are more salient cortically are also learnt faster by mice (Bathellier et al., unpublished, e.g. Fig. 1D). In other words, it is now possible to do loudness psychophysics with mice, and to extend it down to its neuronal bases.

In a pilot study, we used GCAMP6-based two-photon calcium imaging to record more than 2000 neurons in the auditory cortex of awake mice while playing up-ramps and down-ramps. We observed that population firing rate is overall larger for increasing than for decreasing ramps (Fig. 1C). We also showed that mice learn faster to associate actions with up-ramps than with down-ramps, suggesting that for mice as for men up-ramps are more salient stimuli than down-ramps.

Project NAIMA will build on this promising observation to:

(1) measure response dynamics in population of thousands of awake mouse neurons (pooled across populations of ~300 neurons recorded simultaneously) during up- and down-ramps of different durations as well as stationary sounds of various durations.

(2) analyze the dynamics of population activity to identify the groups of neurons that structure the global population response, for example signaling different aspects of the sound time course (onset, offset, steady components).

(3) build models inspired by population activity recordings and based on non-linearly interacting subpopulations to reproduce the main observed characteristics of cortical population activity in mice

(4) make subsequent predictions of loudness judgments by mice, which we will validate in the mouse lab, and by human listeners, which we will validate back in the psychophysics lab.

Task2. Affective invariants of sound preference in mice and men.

The human auditory system perceives certain combinations of musical tones as esthetically pleasing (*consonant*, e.g. a perfect fifth C-G) or unpleasing (*dissonant*, e.g. a minor second C-C#), a property which is key to the organization of much of western tonal music (Helmholtz, 1870). Consonance was long held to result from the peripheral interaction of frequency components within single auditory filters of the cochlea, a phenomenon also called roughness/beatings (Plomp & Levelt, 1965). However, recent dichotic listening paradigms (Bidelman and Krishnan, 2009) in which dissonance was induced without beating, as well as discrimination studies with amusic patients (Cousineau et al, 2012), whose perceptive abilities are normal for roughness but impaired for dissonance, suggest that consonance is more probably processed centrally..

Moreover, while the percept for consonance is linked to clear behavioral responses in humans, e.g. emotional arousal (Zentner et al., 1996), animal studies on the matter have been inconclusive: while domestic chicks appear to exhibit spontaneous preference for images presented with consonant tone intervals (Chiandetti and Vallortigara, 2011), neither preference nor learning of consonant relations could be elicited in rats (Panksepp and Bernatzky, 2002) and primates (McDermott and Hauser, 2004; but see Sugimoto et al., 2010). Consonance seems to have an hedonic effect on animals, but this effect may be too small to detect in standard behavioral situations which require strong reinforcing drives to produce measurable effects. As for loudness above, the unavailability of animal models of the aesthetic response to consonance strongly limits our understanding of its biological bases.

Strong with the same tools that - we argue - make loudness psychophysics possible in mice (calcium imaging, automated behavioral setups, computational models), project NAIMA proposes to develop a mouse model of the preference bias for consonant combinations of sounds. The project will:

(1) design consonant and dissonant stimuli adapted to the (higher-frequency) mouse hearing range

(2) monitor cortical responses for these sounds using calcium imaging to identify potential correlates of sound preferences

(3) design a novel behavioral paradigm in which mice are allowed to freely explore a box, the “Mouse Music Arena”, in which their displacements are coupled with consonant or dissonant stimuli (similar to a place preference test). We expect that, in the low stress context of the automated behavior setup, the small positive and negative reinforcements produced by tone intervals will drive trained mice to favor displacements producing consonant intervals. Hence we will be able to assess preference for certain tone intervals based on statistical measures on trajectories in the “Mouse Music Arena”. The establishment of this protocol will pave the way for a causal investigation of the brain structures implicated in sound preferences in future studies.

3.Proposal's coherence

The project is a tight collaboration between two teams (at UNIC and IRCAM) with complementary strengths. The **requested funds (350 k€ over 3 years)** will be split almost equally between IRCAM and UNIC and will cover animal costs, small equipments, consumable as well as salaries for a PhD student and a postdoctoral researcher jointly supervised by the consortium to perform mouse and psychophysical experiments

B. Bathellier team, UNIC, CNRS UPR 3293, Gif-sur-Yvette (project PI)

Key expertise:

- specialized in two-photon calcium imaging in awake behaving mice, with all the necessary equipment for the project's GCAMP6 imaging experiments.
- expert in mouse behavior - recently received a 35k Fyssen Foundation Grant (Project MOUSECOG, 2014) to acquire material for automated behavior, which will be used in task2 to establish sound preference behavior.
- expert in quantitative analysis and neural network modeling. We will use this expertise to develop simple non-linear models explaining cortical data

Achievements:

B. Bathellier is trained in physics and neurophysiology. In 2012, he was recipient of the ATIP Avenir program, of a Retour PostDoc ANR grant, Marie Curie CIG grant and DIM Ile de France grant (for the UNIC laboratory). Recent publications related to the project: Bathellier et al. Neuron 2012, Bathellier et al. PNAS 2013.

Perception and Sound Design team, IRCAM, CNRS UMR9912, Paris

Key expertise:

- P. Susini is an expert in loudness psychoacoustics. Funded by 2011 ANR LOUDNAT, his team develops the molecular psychoacoustics paradigms used in task1.
- JJ. Aucouturier is an expert on music affective neuroscience. His team develops the behavioral and electrophysiological paradigms used in task2.

Achievements

Team leader P. Susini (PhD, 1999; HDR, 2011) is trained in psychoacoustics and experimental psychology. He was coordinator for the FP6 project CLOSED (2006-2009), treasurer for Société Française d'Acoustique (2000-2006) and General Chair of the 2008 International Conference on Auditory Display. CNRS researcher J.J. Aucouturier (PhD, 2006) is trained in signal processing (UPMC) and cognitive neuroscience (University of Tokyo, Japan). He is the PI of the 2013 ERC Starting Grant project CREAM (Cracking the Emotional Code of Music).

! Breaking ! Oct. 16th: IRCAM's Perception team is the 2014 recipient of the *Decibel d'Or* distinction from the Ministry of Ecology, Sustainable Development and Energy

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