Sounds4Coma:

Towards a data-driven neurophysiology of auditory consciousness in health and coma

"Sometimes, I remember the epileptic seizures I had as a kid. Waking up from them was like ascending from depths. I was blind. I couldn't move - I could only hear. People whispering, my mother, father, brother. The little cracks and noises in the house. There were stages: sounds came first. Seeing was what came last. And then, the feeling of the body, of being able to move. But ***it was sounds which reconnected me; sounds, which brought me back****. Sometimes I think I'd like my music to reflect some of this. I don't know what to say… I've never told anyone before."*

French composer Pascal Dusapin. *Entretiens sur la musique,* 2012.

I. Pre-proposal's context, positioning and objective(s)

Project's objectives and research hypotheses

The detection of consciousness in non-responsive patients is not only one of the most vexing theoretical questions facing modern science but also a major clinical issue (Owen, 2019). The possibility that a patient lying down with eyes closed may in fact, through the channel of sound, be covertlt comprehending some or all of what is going on around them has far-reaching legal and ethical implications, as evidenced by the recent case of Vincent Lambert in France (Veshi, 2017). The use of sound stimulation in the intensive care unit (ICU) holds tremendous promise to reach to these patients but, despite much research, remains plagued with critical theoretical and methodological issues.

Project Sounds4Coma brings together an interdisciplinary consortium of academic and medical experts in acoustics, system science, neurophysiology and critical care, in order to propose **a radically novel approach to using sound for the detection of covert signs of consciousness in coma patients**.

First, Sounds4Coma proposes to build on our recent advances in data-driven methods for auditory cognition (Ponsot et al., PNAS 2018; Goupil et al., Nature Communications 2020) to create **new computational methods able to engineer sound stimuli that are optimized and personalized** for coma patients, thus improving the *sensitivity* of consciousness diagnosis**.**

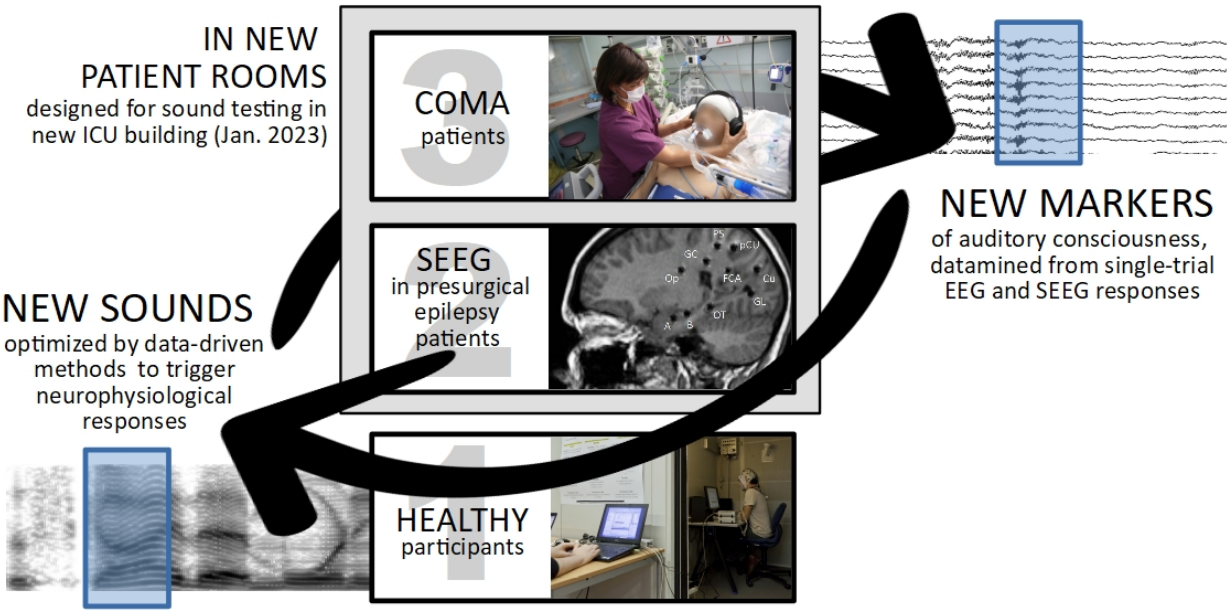
Second, Sounds4Coma proposes to use the consortium's unique expertise in scalp and intracranial electroencephalograpy (EEG) signal processing (Pizzo et al., Nature Communications 2019) to **discover novel neural markers of covert auditory consciousness in healthy participants and patients,** thus improving the *precision* of consciousness diagnosis.

Finally, even as these methodological and theoretical possibilities materialize, the state of today's typical ICU's acoustic environment, with its constant cardiac monitor and respirator alarms, would severely limit their deployment (Wenham & Pittard, 2009). Project Sounds4Coma builds on the opportunity of the construction of a new building in GHU Paris Psychiatrie et Neurosciences to **build a world-unique research plateform consisting of two pilot ICU rooms specifically designed for sound and coma research**. This plateform will not only host the project's clinical studies, but also serve as a basis to promote the wider clinical adoption of the technologies developped in the project.

If successful, Sounds4Coma will radically transform how sound is used in ICUs in France, Europe and beyond and provide thousands of critical patients with new tools and procedures enabling better informed diagnoses and more ethically-acceptable life-support decisions.

Position of the project in relation to the state of the art

The typical approach to using sound stimulation in coma has been largely unconcerned with the precise acoustical properties of the stimuli and with the cognitive characteristics of the patients' reactions. First, sounds are selected relatively arbitrarily, on the basis of their supposed saliency: pure tones, 40-Hz click trains, but also e.g. recordings of a patient's family member, or their own name (Fischer, Dailler & Morlet, 2008). These procedures have **no way to guarantee that these sounds are optimal to trigger responses**.



For instance, in the sound alarm literature, it is well-known that sounds as interchangeable as a pure-tone or square-wave in fact widely differ in their capacity to wake people up (Bruck et al., 2009). When the sensitivity of auditory testing for consciousness can be as low as 32% (Andre-Obadia et al. 2018), there is therefore a troubling possibility that diagnoses are missed because of suboptimal sounds.

Second, patients' responses to these sounds are measured with relatively rudimentary ERP paradigms (MMN, P3a) which index large, integrative responses that are difficult to link to specific behavior or cognitive capacities (Andre-Obadia et al. 2018). As a result, if an 'own-name' stimulus triggers a P3a response in a given patient, doctors have **no way to know what exact residual cognitive capacity this indicates :** maybe the patient is fully conscious (e.g., locked-in) ; maybe they are minimally conscious but able to evaluate the stimulus as personally relevant, to recognize it as speech or to process its emotional tone (Pruvost-Robieux et al, 2020) ; more simply, maybe they are only able to register basic acoustic changes with respect to the baseline (Chennu & Bekinschtein, 2012). Recent improvements of these procedure have employed more complexe sequences of tones (Faugeras et al. 2012), or more powerful EEG machine learning (Claassens et al, 2019), but still lack sensitivity to most covert forms of consciousness.

Innovative nature of the project, ambitiousness and originality

Sounds4Coma departs from this state of art by introducing a novel paradigm for coma neurophysiology based on new **data-driven methods in audio and EEG signal processing**. Recently developped in cognitive neuroscience, but inspired by system-identification techniques in system science, data-driven methods aim to discover task-relevant signal features *a posteriori*, by analyzing participant responses to large sets of systematically-varied stimuli, such as pictures of faces (Adolphs et al. 2016) or speech samples (Goupil et al., 2020). Combined with neurophysiology, these methods can not only optimize stimuli to trigger certain brain responses (e.g. the N170 visual potential, Jaworska et al., 2018) but also, conversely, reveal what single-trial brain features respond to these stimuli (Zhan et al., 2019).

This approach, which has **never been applied to clinical neurophysiology**, holds tremendous promise for the study of consciousness in health and coma. First, by applying such data-driven methods to auditory stimuli, Sounds4Coma will depart from the traditional approach of positing sound features a priori (e.g., a patient's own-name) in hope that they hit (or, often, miss) certain pre-specified electrophysiological markers of consciousness and, instead, engineer acoustic stimuli that directly optimize the probability to observe these responses. Second, by combining data-driven methods with advances in scalp and intracranial EEG signal processing, Sounds4Coma will improve on traditional 'maximally-conscious' indices of coma recovery and identify more specific, finer-grained markers of auditory consciousness in the EEG/SEEG signal measured in response to these sounds.

<u>Methodology to reach the scientific objectives</u>

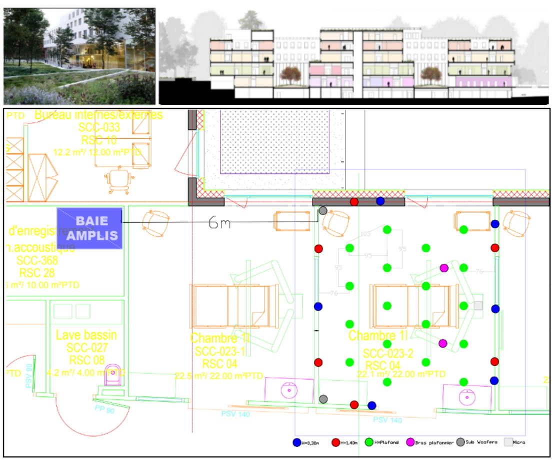
In a recent proof of concept, the Sounds4Coma consortium has shown that it is possible to use data-driven methods to optimize the pronunciation of a recording of a patient's own name and improve the latency of the corresponding P300 response by an average of 80ms (Pruvost-Robieux et al., 2020). Building on this recent work, Sounds4Coma proposes bring the power of data-driven techniques to the domain of auditory processing under loss of consciousness. We will apply these techniques with surface EEG/EMG in healthy participants (WP1), with stereoelectroencephalography (SEEG) in presurgical epilepsy patients (WP2) and finally with scalp EEG in comatose patients (WP3).

WP1. Healthy participants: The methodology for sound and EEG reverse-correlation will be developped on healthy participants by partner 1 (FEMTO-ST). Extending the visual methodology of Jaworska et al. (2018), typical experiments will involve passive or active ERP paradigms, in which participants are presented with a large number of randomly manipulated sound stimuli (e.g. own-name recordings of various prosody) and will optimize, on an individual basis, the sounds' acoustic properties against the properties of the single-trial EEG/SEEG measured in response to the sounds (ex. amplitude and latency of P3 own-name response).

WP2. SEEG : Cortical responses to the auditory paradigms developped in WP1 will be studied by partner 2 (IPNP) on (conscious) patients with depth-electrodes (SEEG) implanted for the presurgical assessment of focal drug-resistant epilepsies (electrodes will be analysed only if located outside of the epileptogenic zones identified by epileptologists). Typical experiments will record from electrode sites in auditory (Heschl, STG/STS) and emotional areas (Amygdala/Hippocampus), and look for neural markers dissociating conscious and unconscious responses to sounds (e.g. smiling in response to smiling sounds, while not consciously detecting that they are smiling – Arias, Belin & Aucouturier, 2018).

In both WP1 and WP2, the acoustic properties of the sounds will be manipulated e.g. using phase vocoder algorithms in pitch x time space (Ponsot et al. 2018) and single-trial relationships between stimulus features and EEG/SEEG source activity will be measured e.g. with mutual-information methods (Zhan et al. 2019).

WP3. Coma patients : Finally, we conduct pre-clinical studies to test whether these optimized sounds and neural signatures built in WP1 and WP2 correlate with positive diagnoses in coma patients. Typical studies, led by partner 3 (GHU), will include patients admitted to the ICU for ischemic/hemorrhagic stroke or cardiac/respiratory failure and who haven't recovered complete wakefulness or awareness (Glasgow Coma Scale GCS < 8, or GCS > 8 and no command following). Patients will be tested as part of standard neurophysiological evaluation during their stay at the ICU, and the new procedures will be compared to existing clinical standards on their predictive value for patients' functional outcome (Glasgow Outcome Scale GOS), assessed 3 months after onset of coma.



<u>Sound4Coma Plateform :</u> The patient studies of WP2&3 will be conducted in two pilot patient rooms, constructed as part of a new neurology and critical-care building in GHU Paris Psychiatrie et Neurosciences (http://neuro-sainte-anne2022.fr, cost: 82,773M€), to open during the project's first year (Jan. 2023). GHU, in partnership with Institut de Recherche et Coordination en Acoustique/Musique (IRCAM) in Paris, has already committed for a structural investment of 300k€ to build the two rooms with very high acoustic performance (average level inside the room < 23 dBA, room reverberation equiv. to that of an auditorium ; see floor plan on the left). In project Sounds4Coma, co-funding is sought from DGOS to equip the rooms for sound research (3D multi-loudspeaker system embedded in walls and ceiling, separated 15sqm control room) and staff the plateform with a full-time audio engineer/technician to support its operation during the project. Beyond the project, the plateform will also host external patients referred to GHU for research or audio/coma evaluation, as well as sound artists residencies.

Ability of the project to address the research issues covered by theme 8.7

Sounds4Coma strongly fits with Theme 8.7 «Technologies pour la santé» because it is an *interdisciplinary* endeavour bringing together one *engineering* and one neuroscience laboratory, applying emerging techniques borrowed from *system science* in order to *improve the clinical tools and methodology* used for the *monitoring, functional evaluation and prognosis* of comatose patients, which will contribute to better predictions and decisions concerning these patients' *autonomy* after they recover.

II. Partnership (consortium or team)

The Sounds4Coma consortium brings together two academic partners specialized in health tech and cognitive neuroscience, and one clinical partner specialized in coma science.

Coordinator: Trained in artificial intelligence (PhD University of Paris, 2006), **Jean-Julien Aucouturier** (Directeur de recherche CNRS, FEMTO-ST Institute; previously at IRCAM, Paris) received postdoctoral training in cognitive neuroscience (Riken BSI, Japan) and clinical neurophysiology (University of Lille, France). His project management experience includes being PI of two successful ERC projects (StG CREAM, 2014-2019; PoC ACTIVATE, 2020-2021) and co-PI of ANR projects REFLETS (2017-2021) and SEPIA (2020-2023). His work has been published in top-tier journals such as PNAS (2016, 2018, 2019), Current Biology (2018) and Nature Communications (2020), and has received the 2018 Early Career Prize of the French Hearing Foundation.

Partner 1 (FEMTO-ST Institute) in Besançon (UMR6174, Université de Franche-Comté, CNRS, ENSMM, UTBM) is one of the country's largest technological research unit, with 700 researchers spanning all fields of engineering and system science, and an internationally-recognized hub for health technology, incl. robotic medical devices, biomechanics, neuroscience. Project coordinator **JJA** will supervise FEMTO-ST's involvement in the project, bringing expertise in data-driven audio methods and healthy participants EEG.

Partner 2 (Institut de Psychiatrie et Neurosciences de Paris - IPNP) in Paris (UMR1266, INSERM, Université de Paris) is a multi-disciplinary institute spanning all fields of molecular, cellular, cognitive and system neurosciences, with a translational focus on psychiatry and neurology problems. Prof. **Martine Gavaret,** M.D., PhD. (Professor of Clinical Neurophysiology, epileptologist, Université de Paris) will coordinate IPNP's involvement in the project, bringing expertise in neurophysiological assessment and SEEG signal processing.

Partner 3 (GHU Paris Psychiatrie et Neurosciences), formerly Hôpital Sainte-Anne, is Paris' first hospital for mental health and neurology, employing over 600 medical doctors. Prof. **Tarek Sharshar**, M.D., PhD. (Prof. of Neuro-Critical Care, Univ. de Paris; Head of Neuro-Critical Care Dept., GHU) will coordinate GHU's involvement in the project, bringing expertise in coma assessment and clinical trial management.

III. References related to the project

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