AAPG2021	SOUND4COMA		PRC + DGOS
Coordinated by:	Jean-Julien AUCOUTURIER (FEMTO-ST)	48months	957,833.62€
8.7. Technologies pour la santé			

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.

Partner	Name	First name	Current position	Role in project	Involvement
FEMTO-ST	**AUCOUTURIER**	**Jean-Julien**	**Permanent (Directeur de recherche CNRS)**	**Project coordinator Coordinator WP 1**	**20p.month**
FEMTO-ST	To be recruited		PhD student	*Research in WP1: Methodological developments for extending audio reverse-correlation to EEG/EMG in healthy participants*	36 p.month
FEMTO-ST	To be recruited		Postdoctoral Fellow	*Research in WP1-2-3: Peripersonal maps of audio awareness, in health, SEEG and coma*	36 p.month
IPNP	**GAVARET**	**Martine**	**Permanent (Professeure des Universités – Praticienne Hospitalière PU-PH)**	**Partner Scientific leader + Coordinator WP2**	**10p.month**
IPNP	To be recruited		PhD student	*Research in WP2-3: Scalp and intracranial EEG markers of unconscious voice processing in epilepsy and coma*	36 p.month
GHU	**SHARSHAR**	**Tarek**	**Permanent (Professeur des Universités – Praticien Hospitalier PU-PH)**	**Partner Scientific leader + Coordinator WP3**	**10p.month**
GHU	DELANOE-VIEUX	Carine	Design Researcher. Director of the Laboratory for Cultural Innovation by Design (LABAH)	*Societal / artistic dissemination of project's results (section III.b)*	6p.month
GHU	To be recruited		Clinical neurophysiology technician (infirmier/ manipulateur radio EEG)	*Data collection in WP2-3: EEG/SEEG investigations in epilepsy and coma patients*	24p.month
GHU	To be recruited		Clinical coordinator (Attaché de recherche clinique)	*Patient data management in WP2-3*	24p.month

Changes made compared to the pre-proposal: No major change made in the project's consortium or budget. Following round 1 evaluations, we have given a detailed description of our clinical methodology, including our rationale for patient etiology, cohort size and details of the ethical approvals already obtained for the work.

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I. Proposal's context, positioning and objective(s)

a. Objectives and research hypothesis

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 covertly 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.

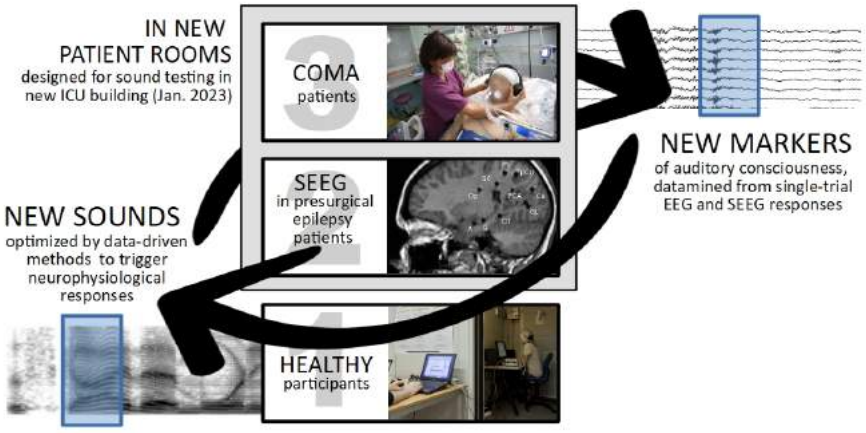

Fig. 1: Project Sounds4Coma proposes a novel approach to use sound for the detection of covert signs of consciousness in coma patients. *We will apply data-driven methods to auditory stimuli, combine them with EEG/SEEG and search for markers of auditory consciousness in a continuum spanning healthy participants, presurgical epilepsy patients and coma patients, all in a new specialized platform designed for the project by its clinical partner.*

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 (Figure 1):

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-electroencephalography (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 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 develop a world-unique research platform consisting of two pilot rooms (one in epileptology ward, the other in ICU), specifically designed for sound and consciousness research. This platform will not only host the project's clinical studies, but also serve as a basis to promote the wider clinical adoption of the technologies developed in the project.

b. Position of the project as it relates to the state of the art

State of art: Sounds for coma evaluation

The typical approach for using sound stimulation in the clinical assessment of consciousness in coma and disorders of consciousness (Chennu & Bekinshtein, 2012, for a review) has been largely unconcerned with the precise acoustical properties of the stimuli and with the cognitive correlates of the patients' reactions.

First, sounds are selected relatively arbitrarily, on the basis of their supposed saliency: pure tones (in our own work: Andre-Obadia et al. 2018), 40-Hz click trains (Gorska & Binder, 2019), but also e.g. voice from a patient's own mother (Machado et al. 2007), or recordings of 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 from deep sleep (a 3:1 ratio in young adults – 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 real possibility that patients who are denied a good prognosis would show preserved electrophysiological responses if they were tested with sounds that are more adapted to their neurological state.

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 indexes: maybe the patient is fully conscious (e.g., locked-in); maybe they are minimally conscious but able to respond to personally relevant stimulus, to recognize it as speech or to process its emotional tone (in our own work: Pruvost-Robieux et al, in prep; Rachman, Dubal & Aucouturier, 2019); more simply, maybe they are only able to register basic acoustic changes from the baseline (Chennu & Bekinschtein, 2012). Recent improvements of these procedures have employed more complex 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.

Originality: Data-driven methods for sound design

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 developed in cognitive neuroscience, but inspired by system-identification techniques in system science, data-driven methods (based on techniques such as reverse-correlation, classification images or bubbles; see Murray 2011 for a review) aim to identify the signal features that are relevant to the participant's behavior by analyzing participant responses to large sets of systematically-varied stimuli (Jack & Schyns, 2017; Adolphs et al. 2016). In the visual modality, these techniques are combined with face synthesis algorithms to study cognitive processes such as the recognition of faces (Mangini & Biederman, 2004) or emotional expressions (Jack et al., 2012). Combined with EEG or MEG neurophysiology, these methods can not only optimize stimuli to trigger some brain responses (e.g. the N170 visual potential, Jaworska et al., 2018) but also, conversely, can reveal what single-trial brain features respond to these stimuli (Zhan et al., 2019).

In our recent work (Ponsot et al., PNAS 2018; Goupil et al. Nature Communications, 2021), we have shown that it is possible to use a similar approach to study voice perception. To do so, we developed a voice-processing algorithm able to manipulate the temporal pitch dynamics of arbitrary recorded voices in a way that is both fully parametric and realistic (Burred et al. 2019). We then used this technique to generate thousands of new, natural-sounding variants of the same word utterance, for instance a recording of the word "really", each with a randomly manipulated pitch contour. We then asked human listeners to evaluate hundreds of pairs of such random pronunciations, deciding in each pair which sounds e.g. most interrogative. By superposing the random prosodic profiles of the utterances that were chosen in each pair, we were able to reconstruct the participants' mental representation of what constitutes an interrogative prosody for this word: a final rise of the pitch on the second syllable of the word (Figure 2). Extending this technique, we were able to determine what is the optimal way to pronounce a word so that it is perceived as dominant or trustworthy (Ponsot et al, PNAS 2018), smiling (Ponsot, Arias & Aucouturier, JASA 2018) or confident and honest (Goupil et al, Nature Communications, 2021). The software toolbox built to support this methodology (CLEESE; Burred et al. 2019) is open-source and has been downloaded more than 2000 times since March 2018.

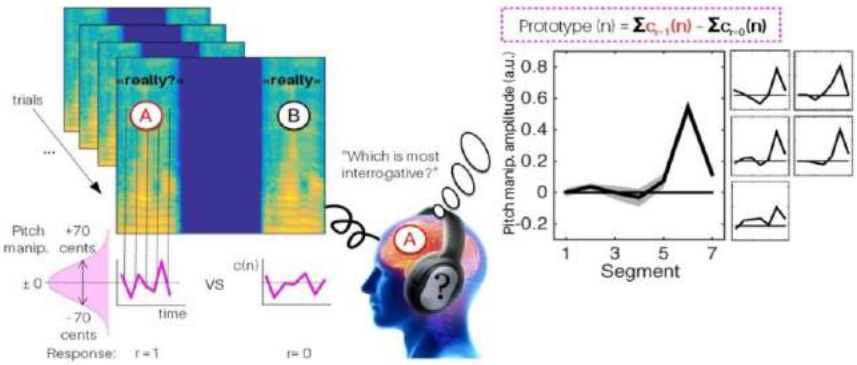

Figure 2. Contributions of project's partners to the state-of-art of data-driven methods. *(**Left**) Participants were asked to judge utterances of the word "vraiment" ("really") which were digitally manipulated to have random pitch contours. (**Right**) Prosodic mental representations associated with interrogative judgments showed a clear pitch increase at the end of the word. Figure adapted from Ponsot et al. PNAS, 2018.*

Preliminary results

This approach, which has never been applied to clinical neurophysiology, holds tremendous promise for the study of consciousness in health and coma. 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., in prep). We retrospectively analyzed a cohort of 191 patients from Lyon and Paris Hospitals who underwent consciousness evaluation with the "own-name" protocol (Fischer, Dailler & Morlet, 2008), along with an acoustical analysis of the pronunciation of the recordings used for this evaluation. By reverse-correlating the latency of the observed P300 response on the characteristics of the sounds, we found that patient names pronounced with a rising intonation (i.e., like a question) were more likely to generate earlier electrophysiological responses than other types of pronunciations (Figure 3). These results suggest, first, that one can use data-driven methods to engineer personalized acoustic stimuli that directly optimize the probability to observe markers of consciousness and, second, that one can combine these methods with advanced EEG signal processing to identify more specific, finer-grained markers of auditory consciousness in the EEG/SEEG signal measured in response to these sounds.

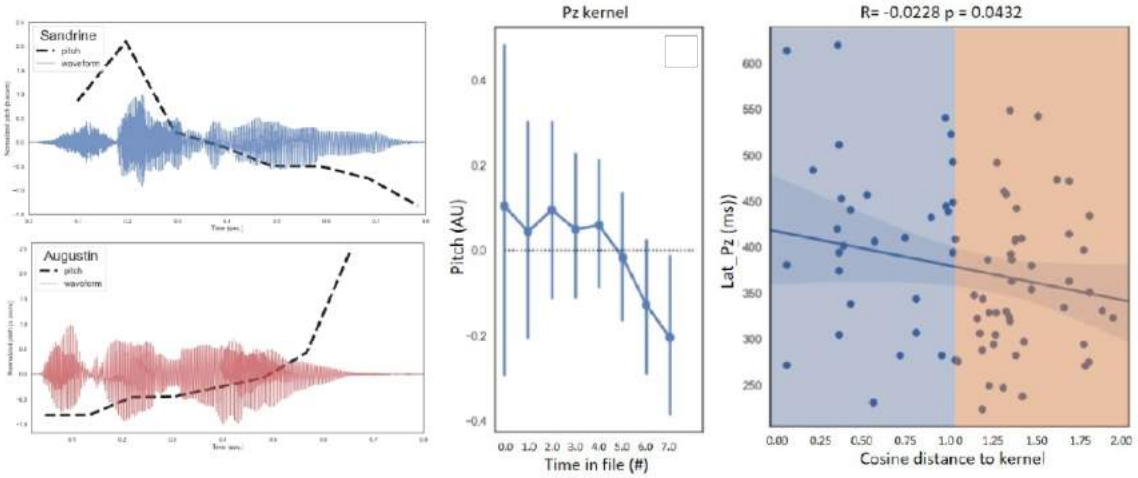

Figure 3. Preliminary results: Names pronounced with rising intonation generate earlier *P3 responses. **Left**: Two examples of patient name recording used for coma evaluation, arbitrarily pronounced with falling (patient 'Sandrine') and rising intonation (patient 'Augustin'). **Middle**: Reverse-correlation kernel of a linear observer model attempting to classify name intonations into a low or high P300 latency outcome, showing significant negative weights at the end of the word. **Right**: P300 latency in response to a name significantly decreases with increasing distance of that name's intonation to the kernel (Pruvost-Robieux et al., in prep).*

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c. Methodology and risk management

Building on this recent work, Sounds4Coma proposes bring the power of data-driven techniques to the domain of auditory processing under loss of consciousness. The methodology for sound and EEG reverse-correlation will be developed on healthy participants (WP1) and then applied in patients with increasing disease severity, first with stereoelectroencephalography (SEEG) in presurgical epilepsy patients (WP2) and finally with scalp EEG in comatose patients (WP3). In each of these modalities (Figure 4), we will examine a continuum of tasks indexing increasing meaningful markers of consciousness, ranging from sensory/attentional (Task A: own-name) and sensorimotor/social (Task B: smile mimicry) to exhibiting a sense of self (Task C: peripersonal sounds).

Task A: Intonation in own-name recognition

Rationale: EEG paradigms in which frequent tone stimuli are intermixed with rare audio recordings of a participant's own name were shown to elicit a P300 wave which correlates, in some patient studies, with a good prognosis for awakening from coma (Fischer et al. 2008; Cavinato et al., 2009). Yet, important discrepancies persist according to the etiologies and duration of coma (André-Obadia et al. 2018). Our preliminary results with retrospective data show that the own-name P3 is highly sensitive to how the patient's name is pronounced (Pruvost-Robieux et al., in prep.), which suggests that name intonation can be optimized or personalized to increase the clinical (i.e. assessment of consciousness) and prognosis (i.e. prediction of neurological outcome) values of the test.

Objectives: The three objectives of work in Task A are methodological**:** to develop a data-driven methodology able to automatically discover what type of name intonation is most likely to trigger P300 responses; fundamental (basic science): to reveal what single-trial brain features respond to the intonation of own-name stimuli; and clinical**:** to test the clinical and prognosis values of own-name stimuli with optimized or personalized intonation built using this methodology.

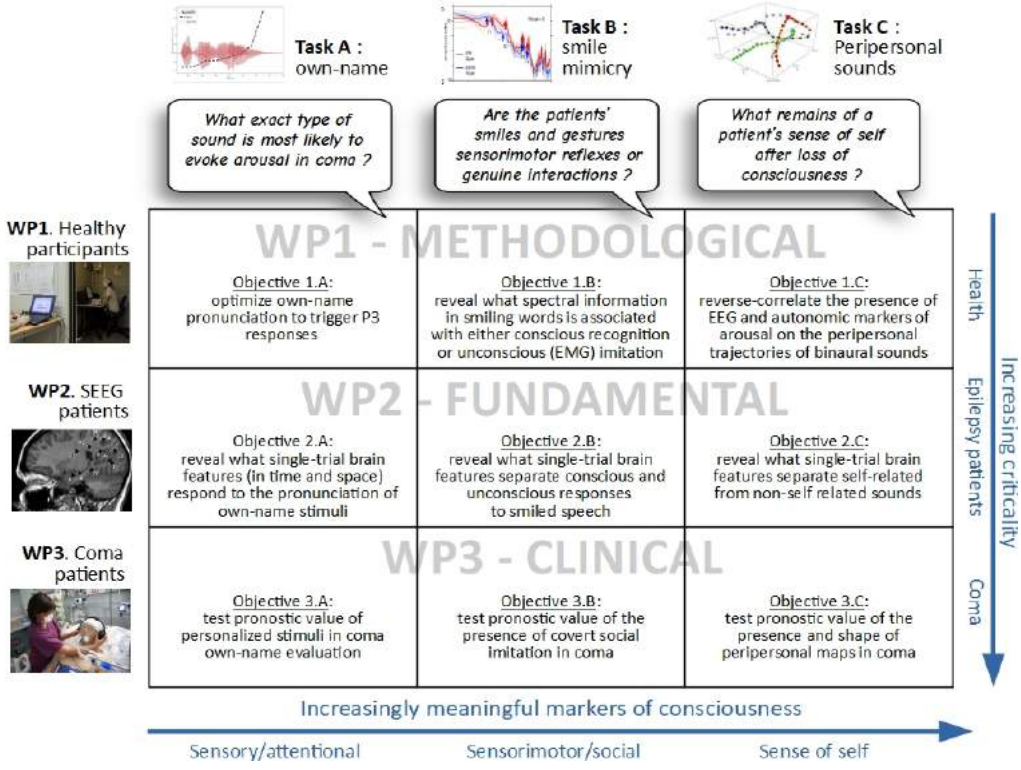

Figure 4 – Project methodology:
Sounds4Coma will develop sound and EEG data-driven methods for the evaluation of consciousness, in a continuum of increasingly critical patients (vertically, from healthy participants, WP1; to presurgical epilepsy patients, WP2; and coma patients, WP3) and for a continuum of tasks indexing increasingly meaningful markers of consciousness (horizontally, from sensory – attentional, task A; to sensorimotor – social, task B; and sense of self; task C)

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Work programme: The methodology for sound and EEG reverse-correlation will first be developed on healthy participants (WP1.A, M1-M24, 24 m.). The protocol will then be replicated in presurgical epilepsy patients, and the analysis pipeline of WP1.A will be extended for stereoelectroencephalography (SEEG) signals (WP2.A, M9-M27, 18m.). Finally, optimal sounds constructed in WP1A and WP2A will be tested in comatose patients to assess their correlation with other neurological and neurophysiological marker of consciousness and to assess their association with outcome, notably awakening and recovery of consciousness at 3 and 6 months (WP3.A, M12-M36, 24m.). See Figure 6 (Gantt chart).

Deliverables:

[DA1] A complete open-source stimulus generation and analysis pipeline for reverse-correlation EEG experiments, to be developed in WP1.A and reused in WP2.A and WP3.A (Python toolbox + methods journal article, ex. PLOS Computational Biology);

[DA2] A report on the neural generators of P3 sensitivity to own-name prosody, measured by SEEG (experimental journal article, ex. Cortex);

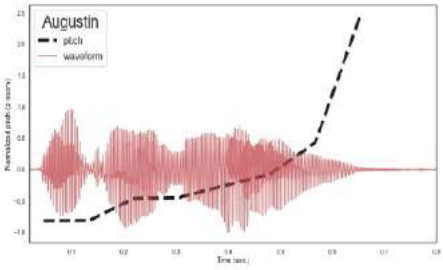
[DA3] A report comparing the positive predictive value (PPV) for awakening of own-name stimuli with optimal intonation with standard, arbitrary-intonation stimuli (medical journal article, ex. Clinical Neurophysiology);

[DA4] A web-service providing an easy way to generate own-name stimuli with optimal intonation (e.g. using text-to-speech synthesis), which will be made available to the community if DA3 demonstrates their improved predictive value.

Partner's contributions: Partner 1 (FEMTO-ST), an expert in voice signal processing, healthy participant EEG and data-driven methods, will conduct the methodological work of WP1.A and be responsible for deliverables DA1 and DA4. **Partner 2 (IPNP)**, an expert in clinical neurophysiology, epileptology and SEEG signal processing, will conduct the experimental work of WP2.A, using the analysis pipeline DA1, and be responsible for deliverable DA2. **Partner 3 (GHU)**, an expert in neurocritical care and coma patient management, will conduct the clinical work of WP3.A, using the web-service DA4, and be responsible for deliverable DA3.

Methods and technical decisions:

Signal processing: In all Task-A experiments, we will present participants and patients with a large quantity of own-name recordings with systematically-varied intonation. Intonation will be manipulated by cutting recordings in small successive time segments (e.g. every successive 100 milliseconds) and applying a random transformation of each segment's pitch, duration or amplitude, using the consortium's CLEESE toolbox (Burred et al. 2019).



Physiological measures: Names will be presented in S/EEG oddball paradigms, in which participants and patients are tasked to either detect/count rare occurrences of their names with respect to a more frequent standard (active task, P3b), or to attend to a sequence of continuously varied intonations (passive tasks, P3a). In **WP1A**, EEG will be recorded from 63 scalp locations (actiCHamp, Brain Products GmbH, Germany), in order to allow source localization (e.g., Rachman, Dubal & Aucouturier, 2019). In **WP2A**, SEEG will be recorded from electrode sites in auditory (Heschl, STG/STS) and emotional areas (Amygdala/Hippocampus/orbito-frontal cortices). For all SEEG experiments in the project (WP2A-B-C), the anatomical location of depth-electrodes depends on the estimated location of each patient's epileptogenic zone, which is in routine determined on the basis of clinical, video-EEG recordings and MRI. SEEG signals will be analyzed for the project only if located outside of the epileptogenic zone as identified post-recording by epileptologists (see e.g. in our own previous work, Bartolomei et al., 2016). Finally, in

WP3A, EEG will be recorded from four electrodes placed on Fz, Cz, Pz and linked mastoids. Although high-density EEG measurements are possible for certain coma patients (e.g., Bourdillon et al. 2020), the limited number of electrodes is standard clinical practice to control infection risk for patients with cranial flap or intracranial pressure monitoring (Andre-Obadia et al., 2018).

Analysis: In **WP1A**, we will use the methodology of Ponsot et al. (2018) to reverse-correlate the amplitude and latency of P3-like responses in single-trial ERP data on the intonation properties of the sounds. In **WP1.B**, we will use the methodology of Jaworska et al. (2018) to identify what single-trial brain features (evoked SEEG activity measured at each sensor and time point) respond to the intonation of own-name stimuli. In addition to evoked activity, we also intend to study synchrony between intra-cerebral signals recorded from the neural networks known to be involved in emotional processing, during emotional vs neutral subject own name and thus to document the stronger impact of emotional vs neutral stimuli (see e.g. Liégois-Chauvel et al., 2014; Bartolomei et al. 2016, and in our own previous work, Bartolomeri et al. 2005). Interdependencies between SEEG signals will be estimated with the Anywave software (Colombet et al., 2015) which computes a nonlinear regression analysis based on the h coefficient. In more details, a piecewise linear regression is performed between each pair of signals, testing all the shifts of one signal relative to the other within a maximum lag. Coefficient h^2, the goodness of fit of the nonlinear regression, is bounded between 0 (no correlation) and 1 (maximal correlation) (Wendling and Bartolomei, 2001). In **WP1.C**, severe stroke and subarachnoid hemorrhage (SAH) patients remaining comatose five days after sedation discontinuation will be included (see details on recruitment below) and will undergo routine neurological (i.e. GCS, CRS-R and Four scores), neurophysiological (SSEP, AEP, ERP, 24h video EEG) and neuroradiological (ie. 3T MRI) tests. The new acoustic paradigms will be then compared to these conventional tests for characterizing depth DOC at time of neuro-ICU assessment and for predicting the neurological recovery at 3 and 6 months.

Task B: Smile mimicry

Rationale: Even when patients appear to react to sounds, distinguishing volitional from reflex behavior remains a major clinical conundrum in DoCs (Fischer & Truog, 2015). Evaluating covert consciousness requires diagnostic procedures that are able to separate pre-attentive, non-conscious patterns of activity from that of conscious patients who have rich information-processing capacities but, because of cognitive/ motor dissociations, are unable to translate them into a complete communicative response (Naccache, 2017). Our recent research has shown that healthy participants react to smiling-voice stimuli by imitating smiles on their own face, and that these motor reactions occur partly independently from conscious awareness (Arial, Belin & Aucouturier, 2018). Demonstrating such covert capacity for social interaction in coma would have profound implications (Fiacconi & Owen, 2016).

Objectives: The three objectives of work in Task B are methodological**:** to develop a data-driven methodology in the context of smile imitation measured with facial electromyography (EMG), to reverse-correlate what acoustic information processing separates overt recognition from covert imitation; fundamental: to reveal the neural bases of conscious and unconscious dissociations in smiling-voice mimicry; and clinical**:** to test the prognosis value of smiling-voice imitation in coma patients

Work programme: As for task A, the methodology for sound and EEG/EMG reverse-correlation will first be developed on healthy participants (WP1.B, M9-M33, 24m.). The protocol will then be replicated in presurgical epilepsy patients (WP2.B, M12-M30, 18m.), and finally be tested in comatose patients to evaluate their predictive value for awakening (WP3.B, M18-M42, 24m.). See Figure 6 (Gantt chart).

Deliverables:

[DB1] Extension of the DA1 deliverable to include stimulus generation and analysis pipeline for data-driven EMG experiments, to be developed in WP1.B and reused in WP2.B and WP3.B (Python toolbox + methods journal article, ex. PLOS Computational Biology);

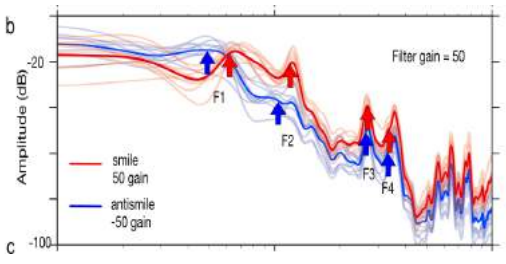
[DB2] A report on the neural generators of conscious and unconscious facial mimicry to smiled speech, measured by SEEG (experimental journal article, ex. Cortex);

[DB3] A report evaluating the positive predictive value (PPV) for awakening of smile mimicry in coma patients (medical journal article, ex. Clinical Neurophysiology)

Partner's contributions: As for task A, Partner 1 (FEMTO-ST) will conduct the methodological work of WP1.B and be responsible for deliverables DB1. Partner 2 (IPNP) will conduct the EMG+SEEG experimental work of WP2.B, using the analysis pipeline DB1, and be responsible for deliverable DB2. Partner 3 (GHU) will conduct the clinical work of WP3.B and be responsible for deliverable DA3.

Methods and technical decisions:

Signal processing: In all Task-B experiments, participants and patients will be presented voice stimuli (e.g., isolated vowels /a/) with systematically-varied spectral content evoking various oro-facial gestures such as smiling (Ponsot et al. 2018). Spectral content will be manipulated using a random frequency equalizer composed of 25 log-separated frequency points spaced between 100 and 10 000 Hz, with gain values (in dB) drawn from Gaussian distributions.



Physiological measures: Smiling/non-smiling sounds will be presented in S/EEG oddball paradigms, in which participants and patients are tasked to detect/count rare occurrences of smiling sounds (active task, P3b), while their facial reactions to the sounds are recorded with facial EMG. EEG and SEEG will be recorded in similar locations and with similar material as in Task A. Facial EMG will be recorded with bipolar electrodes from corrugator supercili and zygomaticus major muscles (Arias, Belin & Aucouturier, 2018). **Analysis**: In **WP1B** (healthy participants), we will use the methodology of Ponsot et al. (2018) reverse-correlate independently (1) sound features that influence overt detection without imitation, (2) sound features that influence EMG responses without overt detection and (3) sound features that influence both physiology and behaviour (i.e. diagnostic features – Figure 5). In **WP2B** (epilepsy patients), as before, we will use the methodology of Jaworska et al. (2018) to reveal what single-trial brain features (evoked SEEG activity measured at each depth electrode lead and time point) code for that diagnostic information, and look for its effect on intra-cerebral signal synchrony. In **WP1.C**, stroke and SAH patients remaining comatose five days after discontinuation of sedation will be tested for EMG reactions in response to sound sequences designed with the signal features of WP1B, and the presence of facial reactions will be compared to existing standard tests on their clinical and predictive values for assessment of depth of DOC and neurological recovery at 3 and 6 months respectively.

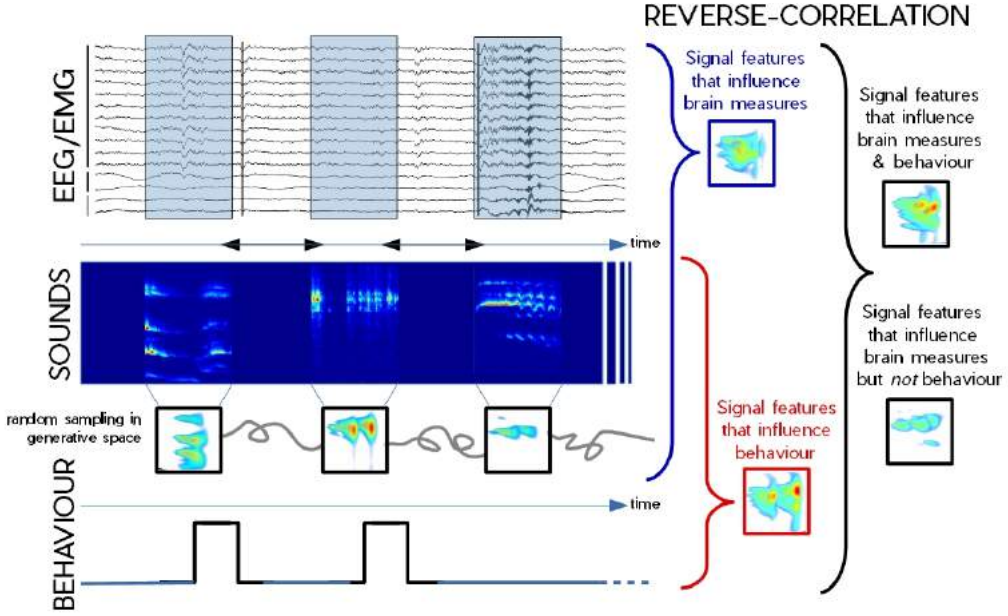


***Figure 5. Reverse-correlating behavior, physiology, and both**: combining behavioral reverse-correlation with simultaneous physiological recording (EEG, EMG) allows the project to separate overt responses (e.g. button clicks when detecting smiling sound deviants, Task B) and covert responses (e.g. facial imitation of smiling sounds), and to identify new neural markers of covert auditory consciousness.*

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Task C: Peripersonal sounds

Rationale: Recent research has suggested that multimodal integration in a person's peripersonal environment is a marker of having a sense of self (Noel et al. 2019). In Task C, we will present to participants sounds with randomly varied motion in their 3D auditory field (e.g. looming or receding sources) and we will reverse-correlate the presence of evoked EEG or autonomic markers of arousals on the trajectories of the sounds, to establish peripersonal/environmental maps of arousal and see how these are affected in coma.

Objectives: The three objectives of work in Task C are methodological**:** to develop a data-driven methodology in the context of binaural or 3D sound presentation, to reverse-correlate what spatial trajectory of sounds around the participant triggers arousal; fundamental: to reveal how loss of consciousness alters peripersonal maps; and clinical**:** to test the prognosis value of peripersonal maps of sound awareness in coma patients

Work programme: As for task A and B, the methodology for 3D sound and EEG/EMG reverse-correlation will first be developed on healthy participants using binaural sounds (WP1.C**,** M12-M24, 12m.). The protocol will then be replicated in presurgical epilepsy patients, using 3D sound in the hospital acoustic rooms (WP2.B, M18-M36, 18m.), and finally be tested in comatose patients to evaluate their predictive value for awakening (WP3.B, M24-M47, 24m.). See Figure 6 (Gantt chart).

Deliverables:

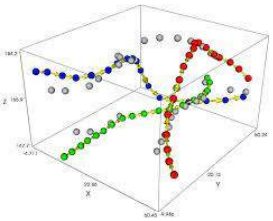
[DC1] Extension of the DA1-DB1 deliverable to include the randomization of binaural and 3D sound trajectories, and analysis pipeline for data-driven EEG/EMG experiments, to be developed in WP1.C and reused in WP2.C and WP3.C (Python toolbox + methods journal article, ex. PLOS Computational Biology);

[DC2] A report on the neural generators of 3D sound awareness, measured by SEEG (experimental journal article, ex. Cortex);

[DC3] A report evaluating the positive predictive value (PPV) for awakening of peripersonal/environmental sound awareness in coma patients (medical journal article, ex. Clinical Neurophysiology)

Partner's contributions: As for task A-B, Partner 1 (FEMTO-ST) will conduct the methodological work of WP1.C and be responsible for deliverables DC1. Partner 2 (IPNP) will conduct the EMG+SEEG experimental work of WP2.C, using the analysis pipeline DC1, and be responsible for deliverable DC2. Partner 3 (GHU) will conduct the clinical work of WP3.C and be responsible for deliverable DC3.

Methods and technical decisions:



Signal processing: Participants will be presented with abstract sounds (e.g. synthetic voices as in Woods & McDermott, 2015) with systematically varied trajectories around the participant's body (i.e. looming or receding from the participant at various distances and angles). In WP1.C, the sounds will be presented binaurally via headphones, while in WP2.C and WP3.C, sounds will be presented using the 3D sound system of the hospital acoustic rooms. Binaural and 3D spatialization of sounds will be generated with sound spatialization toolboxes such as IRCAM's Spat (Carpentier, Noisternig & Warusfel, 2015) or 3DTI (Cuevas-Rodríguez et al. 2019). Binaural sound processing will use prerecorded head-related transfer functions (HRTFs) such as the LISTEN dataset (Warusfel, 2003).

Physiological measures: In WP1.C and WP3.C, moving sounds will be presented while recording the participants' continuous EEG, facial EMG and cardiovascular measures using finger photoplethysmography (PPG). EEG markers of arousal will be defined as abrupt shifts in EEG frequency following sound presentation (Catchside et al. 2002). EMG markers of arousals will be defined as blink

reflexes measured from the orbicularis oculi muscles (Calabrò et al. 2020). Cardiovascular markers will be defined as shifts of fingertip skin blood flow and finger PPG wave amplitudes (Catchside et al. 2002). In WP2C, SEEG will be recorded in similar locations and with similar material as in Task A-B.

Analysis: In **WP1C** (healthy participants), we will take inspiration from the methodology of Balachandar & Carlile (2019) to reverse-correlating sound motion on EEG/autonomic markers of arousal. Instead of spectral cues, the procedure will generate peripersonal/environmental gradient fields indicating the topographic properties of the participant's body representations (for inspiration, see e.g. emotional body maps in Nummenmaa et al., 2018). In **WP2C** (epilepsy patients), we will use the methodology of Jaworska et al. (2018) to reveal what single-trial brain features (evoked SEEG activity measured at each depth electrode lead and time point) code for peripersonal space processing (Bernasconi et al., 2018) and, as before, study how it covaries with intracerebral synchrony. In **WP1.C**, we will test the procedure as a biomarker of residual consciousness (computing e.g. distance from maps derived from controls), test its coincidence with depth of disorders of consciousness but also its predictive value for neurological outcome, especially of awakening, vegetative states and minimally conscious states. In particular, we will address whether the unconscious peripersonal space shrinks because of decreased capacity to act on the world, or extends because of increased vulnerability (Bufacchi & Iannetti, 2018).

Risks and fall-back solutions

While all parts of tasks A, B and C cooperate across partners towards its objectives, each part (healthy participants, SEEG patients and coma patients) is also independently valuable as a research item, can be published in its own sake, and has fall-back solutions in case other parts are delayed. See Table 1 for details.

Participant/patient characteristics:

Healthy participants: Experiments in WP1 will recruit young (18-30) participants from the University of Bourgogne Franche-Comté Experimental platform. Inclusion criteria: normal hearing, right-handed, no antecedent of psychiatric disorder.

SEEG patients: Experiments in WP2 will include conscious patients with depth-electrodes (SEEG) implanted for the presurgical assessment of focal drug-resistant epilepsies. Intracerebral signals will be analyzed only if located outside of the epileptogenic zone identified by epileptologists, using the epileptogenicity index (see e.g. in our own previous work, Bartolomei et al., 2011)

Comatose patients: In order to get a homogenous population of comatose patients, clinical studies in WP3 will include only patients with a persisting coma five days after discontinuation of deep sedation required for controlling the intracranial hypertension after either a severe stroke (i.e. ischemic or haemorrhagic) or a subarachnoid haemorrhage (SAH). The rationale is that it is specifically for this cohort of severe brain injured patients that prognostication of neurological outcome should be improved. The assessment of consciousness in these patients will rely on a standardised multimodal approach that includes neurological scores (Glasgow coma scale and Coma recovery scale-revised for assessing depth of DOC and FOUR score for assessing brainstem reflexes) and neurophysiological tests (24h video EEG, somatosensory, auditory and event-related evoked potentials) and 3T MRI. The patients will be followed-up to 6 months after ICU-admission. We will use standardized scales to assess at 3 and 6 months the patients' recovery (Glasgow Outcome Scale Extended, GOS-E), consciousness (Coma Recovery Scale Revised, CRS-R), cognitive (Montreal Cognitive Assessment, MOCA) and functional status (Barthel Index for Activities of Daily Living , ADL). The GOS-E is the most frequently used primary endpoint in studies of neuroprognostication of comatose patients, with GOS-E of 4 or 5 indicating good outcome (observed in a third of these patients, Luauté et al 2005). We will be able to assess whether each patient has awakened, reached vegetative state (VS) or minimally conscious state (MCS). We will minimize self-fulfilling prophecy by avoiding physician to take into account acoustic tests in their decision for continuing, limiting or withdrawing care. The clinical feasibility for this procedure is excellent, as all the tests mentioned here are routinely performed in partner 3's ICU and all patients are currently followed-up after discharge as is needed here.

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Workpackage	Risks and fall-back	Fall-back for other tasks
WP1 (healthy)	**1. Task A-B-C: Difficulty with participant recruitment** (e.g., because of covid restrictions) → methodological development can be done on very small samples (eg. N=5, Zhan et al. 2019) **2. Task A-B:** Mutual information between stimulus acoustics and P300 so weak that **reverse-correlation requires too many deviant trials** → reverse-correlate N100 responses on every trial 3. **Task C:** Measures of EEG/autonomic arousals **too slow to present a sufficient number of trials** → test healthy participants during sleep (Catchside et al. 2002) and/or convert to an auditory-tactile interaction paradigm (Bernasconi et al., 2018)	**WP1 delayed or impractical →** Methodological development of WP1.A-B-C can be done directly on SEEG patients, as part of WP2.A-B-C
WP2 (SEEG)	**1. Task A-B-C: Difficulty with patient recruitment** is unlikely, contrary to healthy participants, because presurgical assessment of focal drug-resistant epilepsies is considered priority care (higher risk of SUDEP - sudden deaths in epilepsy - in focal pharmacoresistant epilepsy patients; Tomson et al. 2005). 2. **Task A-B-C: SEEG signal analysis unreliable for reverse-correlation →** fall-back on localizing SEEG sources on grand-average ERPs, without reverse-correlation, which is already novel (e.g. Tang, Hamilton & Chang, 2017) **3. Task C: Delayed availability of new building with acoustic patient rooms →** use binaural sounds with headphones, as in WP1.C	**WP1 and WP2 delayed or impractical →** Clinical testing in WP3.A-B-C can be done with optimized sounds learned from retrospective data analysis (Task A; Pruvost-Robieux et al., in prep) or from behavioral reverse-correlation (Tasks A-B-C; Ponsot et al. 2018).
WP3 (coma)	**1. Task A-B-C: Difficulty with patient recruitment** (unlikely, coma evaluations by partner 3 have continued at usual rate throughout the covid pandemic in 2020) → possibility to include patients in multicentric manner (Lyon hospitals, w/ collaborator N. André-Obadia) **2. Task A-B-C: Delayed availability of new building with acoustic patient rooms →** patient evaluations can be started in standard rooms with earphones, and using binaural sounds for Task C **3. Task A-B-C: No improvement of predictive value compared to standard paradigms** → the methodology can be adapted to other acoustic features. **Task A**: own-names with varying identity (e.g. familiar vs stranger) or gender (male vs female). **Task B**: other types of sounds triggering facial reactions, such as scraping or disgusting sounds (Cox, 2008). **Task C:** convert to a passive auditory-tactile interaction paradigm (Bernasconi et al., 2018)	**WP3 delayed or impractical →** WP1A-B-C and WP2A-B-C stand on their own as research results. Complementary funding can be sought from DGOS/PHRC to conduct further clinical studies on coma patients after the end of the project.

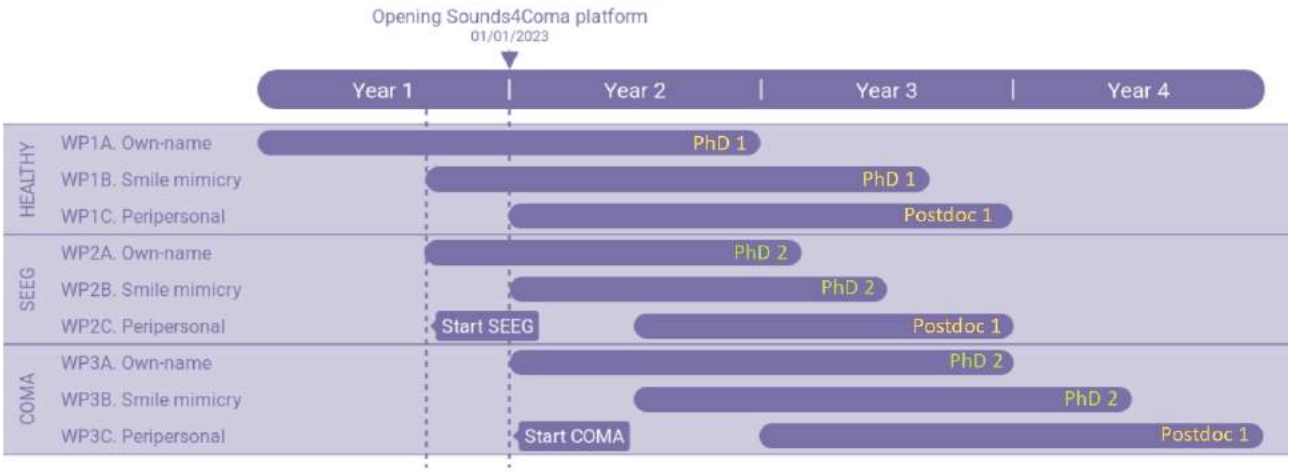

Figure 6. Project GANTT chart. *Methodology development and experiments on healthy participants are planned on 24m. for WP1.A-B (PhD 1, FEMTO-ST) and WP1.C (Postdoc1, FEMTO/IPNP). SEEG experiments include patients for 18m for WP2.A-B (PhD 2, IPNP) and WP2.C (Postdoc1, FEMTO/IPNP). Coma studies include patients for 24m. for WP3.A-B (PhD2, IPNP) and WP3.C (Postdoc1, FEMTO/IPNP), starting at the opening of the Sounds4Coma platform.*

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Sample / cohort sizes:

Reverse-correlation experiments (WP1-2): The data-driven experiments of WP1 and WP2 are designed to make inferences on large number of trials replicated in small number of participants (Smith & Little, 2018). For all tasks in WP1 and WP2, we will use sample sizes of N=10-15 healthy participants (WP1) and SEEG patients (WP2). These sample sizes are typical of such studies (see Zhan et al., 2018: N=6; Ponsot et al. 2018: N=10). About 25 epilepsy patients per year are included for SEEG exploration in the GHU epileptology unit, among whom 15 are estimated to include SEEG electrodes in the auditory/emotional sites of interest for the project, which means that we will be able to recruit the patients in less than three years.

Clinical studies (WP3): The clinical studies of WP3 aim to include 50 comatose patients for each Task (WP3A, WP3B, WP3C). Given that more than 75 stroke or SAH patients develop persisting coma every year in partner 3's ICU and that a patient can participate in more than one task, we will be able to recruit the patients in less than three years. Studies with ~50 patients are typical of exploratory clinical studies (e.g. Fischer, Dailler & Morlet, 2008: N=50; Faugeras et al, 2012: N=49), and will allow assessing whether our acoustic paradigms help to better characterize the depth of disorder of consciousness and better predict the neurological recovery (e.g. GOS-E) than conventional tests.

If successful, the design of a large-cohort validation study for confirming these preliminary results is beyond the scope of the project, but the project will serve as a basis for securing additional funding such as DGOS/PHRC or commercialization schemes such as EIC Pathfinder.

Ethics: In accordance with French regulations, all studies are subjected to prior approval by the regional clinical ethical committee (*Comité de protection des personnes*) and data-protection agency. Feasibility of the project is excellent, as the ethical approvals for the most critical parts of the project (own-name SEEG in WP2.A and coma in WP3.A) have already been obtained:

- WP2: EXPRE-SON-IN: Intracerebral Recordings of P3a Responses to Expressive Own-names, available on: https://clinicaltrials.gov/ct2/show/NCT04810832
- WP3: EXPRE-SON-REA: Expressive Own Names in Neurophysiologic Assessment of Comatose Patients, available on: https://clinicaltrials.gov/ct2/show/NCT04798508

Upon the start of the project, these two protocols will be extended to include the use of other sound stimuli (smile, and 3D sounds) for the studies of WP2.B-C and WP3.B-C. In addition, an ethical application for the (less ethically demanding) healthy participant studies of WP1.1-B-C is currently under evaluation, and is expected to be obtained in Summer 2021, ahead of project start.

Sound4Coma Platform: The patient studies of WP2&3 will be conducted in two pilot patient rooms, constructed for the purpose of the project as part of a new neurology and critical-care building in GHU Paris Psychiatrie et Neurosciences (http://neuro-sainte-anne2022.fr, cost: 82,773M€; Figure 7), 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 (one in the ICU and one in the neighbouring epilepsy unit) 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), as well as one neurophysiological/acoustic laboratory (in which sounds can be develop and broadcasted and neurophysiological responses analysed).

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), staff the platform with a full-time neurophysiology technician to support its operation during the project, and host two sound artist residency for added societal impact. The resulting platform (acoustic room + laboratory) will be unique in the world and will benefit from the administrative support and the high-value medical environment and scientific network of its co-operating institutions (INSERM, CNRS, IRCAM and Université de Paris).

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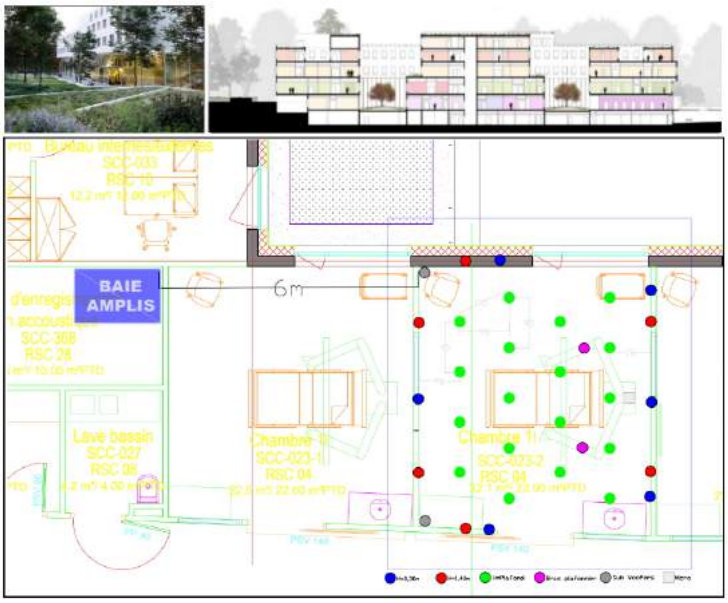

***Figure 7. The Sounds4Coma platform**: Project Sounds4Coma builds on the opportunity of the construction of a new building in GHU Paris Psychiatrie et Neurosciences to build a world-unique research platform consisting of one ICU room, one SEEG room, specifically designed for sound and coma research. This platform will not only host the project's clinical studies in WP2 and WP3, but also serve as a basis to promote the wider clinical adoption of the technologies developed in the project.*

II. Organisation and implementation of the project

a. Scientific coordinator and its consortium / its 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 Univ. of Paris, 2006), **Jean-Julien Aucouturier** (Directeur de recherche CNRS, FEMTO-ST Institute; previously at IRCAM, Paris) received subsequent postdoctoral training in cognitive neuroscience (Riken BSI, Japan, 2008-2011) and clinical neurophysiology (University of Lille, France, 2017-2018). 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).

JJA's work has been published in top-tier journals such as PNAS (2016, 2018, 2019), Current Biology (2018) and Nature Communications (2021), and has received the 2018 Early Career Prize of the French Hearing Foundation for his pioneering work in voice reverse-correlation. He is co-inventor of 4 patents on voice and music technology, incl. one leading to the creation of voice-technology startup Alta Voce (2020).

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 and neuroscience. Project coordinator **JJA** will supervise FEMTO-ST's involvement in the project, bringing expertise in data-driven audio methods and healthy participants EEG. After 8 years spent in IRCAM, Paris, investigating how speech and music emotions affects the brain in health and disease (http:\\cream.ircam.fr), JJA has joined the FEMTO-ST institute in Jan. 2021 with a research program in computational neurophysiology and reverse-correlation methods. The Sounds4Coma proposal aims to set the agenda for his new team, and foster a new stream of clinical innovations at the boundary of engineering and neurology.

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.

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Prof. **Martine Gavaret,** M.D., PhD. (Professor of Clinical Neurophysiology, epileptologist, Université de Paris & Head of the Neurophysiology and Epileptology department, GHU Paris Psychiatrie et Neurosciences, Sainte Anne) will coordinate IPNP's involvement in the project, bringing expertise in neurophysiological assessment and SEEG signal processing. She was trained in Neurophysiology and epileptology in Institut de Neurosciences des Systèmes, Marseille, and holds a PhD in Neuroscience (Université de la Méditerranée).

As a member of the French Neurophysiology Society, MG has contributed to the "Recommendations for the use of electroencephalography and evoked potentials in comatose patients" (Andre-Obadia et al. 2018). In epileptology, she is specialized in non-invasive presurgical investigations such as high resolution EEG, magnetoencephalography (MEG) source localization and has performed the first EEG, MEG and SEEG co-recordings in the Marseille MEG platform. MG brings to the project high clinical research expertise in neurophysiology and epileptology. Her work has been notably published in Brain Connectivity (2020), Brain Topography (2020, 2016, 2014), Nature Communication (2019), Stroke (2021), Epilepsy research (2016), Epilepsia (2014).

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. The hospital's neuro-ICU is integrated in a building that includes all the neurological specialities. The Neuro-ICU involves a multidisciplinary medical team constituted by neurologists, anaesthetists-intensivists and a rehabilitation physician. The Neuro-ICU is highly specialized in the management of severe brain injured patients but also in the multimodal assessment of disorders of consciousness (DOC). Among the 280 patients admitted every year, about 70 develop DOC, including delayed awakening. More than 50 comatose patients per year are referred for multimodal evaluation, including continuous EEG, cognitive-evoked potential and 3T MRI.

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. T.S. was trained in Neurology and intensive Care Medicine (Paris-Descartes University) and holds a PhD in Neuroscience from Imperial College, London, UK.

TS brings to the project high clinical research expertise in neurocritical care topics, including assessment of prognosis value of the neurological and neurological responses in deeply sedated critically ill patients, but also clinical trials on status epilepticus, sepsis associated encephalopathy and long-term post-ICU follow-up. A member of the international "curing coma" consortium, TS is involved as principal investigator or scientific supervisor in six clinical trials, sponsored by the Ministry of Health (Programme Hospitalier de Recherche Clinique) with a total of funding raise > 1.8 M euros. His original work or reviews have been published in Lancet (2003), Lancet Neurology (2006), Lancet Respiratory Medicine (2015) Nature Communication (2015), JAMA, British Journal of Anesthesiology (2018), Neurology (2021). As of April 2021, T.S. is the chief of the Neurological Pole of the GHU-Psychiatrie & Neurosciences.

Implication of project staff in other projects:

Name of researcher	p.m	Call, funding agency	Project's title	Scientific coordinator	Start - End
JJ AUCOUTURIER	4 p.m	ERC PoC	ACTIVATE (*Augmenting the Value of Conversations with Voice Technologies*)	JJA	Sept. 2020-March 2022
JJ AUCOUTURIER	15 p.m	ANR PRC	SEPIA (*Sensory-Emotional Processing in Autism*)	Marie Gomot (iBrain, Tours)	Mar 2020-Feb. 2024
JJ AUCOUTURIER	15 p.m	ANR PRCE	REFLETS (*Rétroaction Faciale et Linguistique et États de Stress Post-Traumatiques*)	Catherine Soladié (CentraleSupelec)	Sept. 2017-Aug. 2021

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Note: In addition to the above funding, partner's scientific leader M.G. is clinical investigator/co-investigator of the following ongoing clinical trials (FWA 00005831: "*Localisation de source des activités électromagnétiques intercritiques dans l'espace anatomique cérébral*"; EUDRACT 2016- A00160-51: "*tDCS à la phase aiguë des infarctus cérébraux chez l'homme*"; CHSA: "*Effet de la compensation du déficit en vitamine D dans le traitement de l'épilepsie pharmacorésistante*")

b. Implemented and requested resources to reach the objectives

Partner 1: FEMTO-ST (335k€)

Staff expenses. The project will support the hiring of **one PhD student** for 36m, working on the methodological developments of WP1A and WP1B (extending audio reverse-correlation to EEG/EMG paradigms in healthy participants); hired by CNRS (Doctoral contract, total: 119,000€); directed by JJA, co-supervised by MG; background: computational modeling, EEG signal processing; and **one postdoctoral researcher** for 36m, working on task C (data-driven methods for peripersonal maps of audio awareness) across healthy participants (WP1C), SEEG (WP2C) and coma patients (WP3C). The postdoc will be based in FEMTO-ST, with frequent visits to IPNP in the second and third year. Hired by CNRS (CDD Chercheur <3 year experience, total: 142,281.62€). Co-supervised by JJA and MG. Background: cognitive neurosciences.

Instruments and material costs: Equipment for the project includes one laptop workstation for the PhD student and the postdoctoral researcher (2x 2,000€) as well as research-grade audio headphones (ex. Beyerdynamics DT770; 3x 200€) and sound cards (RME Fireface, 2x 1,000€). Supplies for EEG/EMG experiments include spare electrodes and electrolyte gel (Bionics SA: 500€). Total: 7,000€

Building and ground costs: n/a. **Outsourcing / subcontracting:** n/a

General and administrative costs & other operating expenses: Travel for the project includes coordination meetings between Besançon and Paris, quarterly (250€ x 4 times yearly; year1: 2 pers; year 2: 3 pers; year 3: 3 pers; year 3: 2 pers.; total: 10,000€); and travel for 3 international conferences such as Association for Scientific Study of Consciousness (ASSC), Science of Consciousness (TSC), Society for Neurosciences (SfN), Neurosciences in Critical Care Symposium (NICIS), 1500€ x 2 people x 3 meetings; 9,000€. Total: 19,000€.

In addition, the project will support open access manuscript charges at e.g. Nature Human Behaviour, PNAS, Current Biology, and other suitable journals for the project's results. (Total cost: 4x 2,500€, 10,000€) and participant fees for the healthy participant studies of WP1 (10€/hr; 100 participants x1.5hr; total 1,500€).

Partner 2: IPNP (135k€)

Staff expenses. The project will support the hiring of **one PhD student** for 36m, working on the fundamental and clinical objectives of WP2A-B and WP3A-B (scalp and intracranial EEG markers of unconscious voice processing in epilepsy and coma); hired by INSERM (Doctoral contract, total: 100,500€); directed by MG, co-supervised by JJA; background: medical doctor (neurology)

Instruments and material costs: Equipment for the project includes one laptop workstation for the PhD student (2,000€), research-grade audio headphones (ex. Beyerdynamics DT770; 200€) and sound cards (RME Fireface, 1,000€), as well as one software license for the Brainvision Analyzer EEG software (7,500€). Material and supplies for SEEG and ICU EEG experiments are covered by partner GHU as part of routine clinical care. Total: 10,200€

Building and ground costs: n/a. **Outsourcing / subcontracting:** n/a

General and administrative costs & other operating expenses: Travel for 3 **international conferences** such as Association for Scientific Study of Consciousness (ASSC), Science of Consciousness (TSC), Society for Neurosciences (SfN), Neurosciences in Critical Care Symposium (NICIS), 1500€ x 2 people x 3 meetings; Total 9,000€.

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Partner N: GHU (490k€; Not included in ANR costs; co-financement sought from DGOS)

Staff expenses

Funding is sought from DGOS to support the hiring of **one clinical neurophysiology technician** for 24m (48m half-time), working on SEEG/EEG data acquisition for the experiments of WP2 and WP3; hired by GHU (4,242€ monthly; total: 101,832€); supervised by MG; background: nurse/clinical technician; and **one clinical project coordinator** ("technicien d'étude clinique") for 24m (48m half-time), working on ethical clearance, patient inclusion and patient data management in the experiments of WP2 and WP3; hired by GHU (4,122€ monthly; total: 98,928€); supervised by TS; background: clinical project management. The project will also support personnel costs for punctual tasks: trial monitoring (4,500€ x 3 m.; total: 13,500€), ethics clearance (4,971€ x 2m; total: 9,942€), biostatistics (5,000€ x 2m.; total: 10,000€) and data management (4,500€ x 2m.; total: 9,000€). Total non-permanent staff expenses: 243,202€.

Instruments and material costs: Partner GHU is committed to support on its own funds the equipment of the two patient rooms of the Sounds4Coma platform (Figure 6) with technical ICU material (scopes, ventilation, etc.). Additional funding is sought from DGOS to equip the two rooms in non-medical, audio material: in each room, 28x passive compact loudspeakers installed in walls and ceiling (e.g. Amadeus PMX 5 MKIII 2-ways, unitary cost: 800€) + 2 x loudspeakers installed in mobile supply-unit arm (unitary cost: 800€), 28x sets of loudspeakers fixation/protection (unitary cost: 150€), 2x compact subwoofers (e.g. Amadeus ML 12 MKII, unitary cost: 1,215€), 4x 8-channel amplifiers (e.g. Powersoft Ottocanali 4K4, unitary cost: 3,300€), 1x professional USB3.0 audio interface (e.g. RME Digiface Dante, unitary cost: 1,299 €), racks and cables for connection to control room (3,000€). In accordance with DGOS rules for financing investments, this material will be purchased by GHU and rented to the project as "surcoût médical". Total cost (two rooms): 90,000€; and equip the Sounds4Coma laboratory with EEG software compatible with the clinical equipment (Micromed software license x 2: 16,000€). Total: 106,000€.

Building and ground costs: n/a. Note that GHU has already committed for a structural investment of ca. 300k€ to build the Sounds4Coma platform, which will be made available to the project for no cost.

Outsourcing / subcontracting: Funding is sought from DGOS to support subcontracting for consulting in acoustic engineering (e.g. from Institut de Recherche et Coordination en Acoustique/Musique – IRCAM, Paris) to install and calibrate the platform's audio equipment (2 weeks, year 1), as well as configuration and support for SEEG and coma data collection in all three tasks (1 week x 3 tasks in WP2 and WP3). Total: 8 weeks; 20,000€; and organizing/hosting 2 one-year artistic residencies for sound designers and composers to work on sound design and art installations to disseminate the project's results (15,000€ each, Total: 30,000€). Total: 50,000€

General and administrative costs & other operating expenses: Funding is sought from DGOS to support travel cost for 2 international conferences, such as the NINDS/NCS Curing Coma Symposium (1,500€ x 2 ; total 3,000€); and promotion/insurance costs for the project's clinical studies (case-report forms e-CRF: 5,000€; consent form prints for N=150 patients: 600€; insurance: 1,000€). Total: 9,600€

III. Impact and benefits of the project

a. Fields of impact

Scientific: The scientific impact of our project will be both theoretical and methodological. First, the project will change what we know of auditory and emotional information processing during coma/disorders of consciousness. Second, it will introduce a novel data-driven methodological framework for doing so, and disseminate it with new open-source tools simplifying both stimulus production and data analysis (deliverables DA1, DB2, DB3), modelled after our successful CLEESE toolbox (https://forum.ircam.fr/projects/cleese/details, 2000 downloads since March 2018). Beyond coma, these results and methods will also impact research in other non-conscious states such as sleep (e.g. "what exact types of sounds wake people up from sleep?") and general anaesthesia (e.g. "what features of the surgical

audio environment are processed by patients under anaesthesia?"), but also in the science of dreams ("can auditory content get incorporated in dreams?"), speech/language ("how are words heard by the aphasic brain?") and psychiatry ("what are the neural bases of auditory hallucinations?").

Clinical: The incidence of coma in the general population is estimated at 8.5 per 100,000 for traumatic causes (59% of which involve car accidents) and an additional 6 per 100,000 for non-traumatic causes (e.g. infection), per year (Masson et al. 2003). This represents more than 110,000 patients per year in Europe alone, 40% of whom will evolve to vegetative and minimally-conscious states, or death (Luaute et al. 2005). For these patients and their family, our findings will provide new procedures for better informed diagnosis and more ethically-acceptable life-support decisions. Within the scope of the project, our clinical studies will allow assessing whether our acoustic paradigms better characterize the depth of disorder of consciousness and better predict neurological recovery than conventional tests. Beyond the project, additional funding will be sought (e.g. in the form of DGOS/PHRC or pre-commercialization schemes such as EIC Pathfinder) to conduct large-cohort validation studies confirming the most promising of these procedures. This project's scientific and clinical impact will be helped by the high involvement of project members in scientific animation, e.g. through the organization of conferences (e.g. CuringComa) and courses (T.S. is co-director of "DU Neuroréanimation", France's main venue of ICU training for MDs)

Economic: The sounds and clinical procedures developed in the project (e.g. a web service to generate optimized stimuli for testing, on demand – deliverable DA4) have potential to be improve the efficiency and effectiveness for health care services, and to be in high demand by patient families. They will be considered for IP protection and commercialization, possibly in the form of a sounds4coma start-up company to be created after the project and hosted e.g. in the GHU's E-health business incubator *Pensées (Pépinière d'Entreprises en Sciences et E-Santé du GHU Paris).* Beyond the project's immediate results, the sounds4coma patient rooms equipped and bootstrapped by the project will also be operated as a research platform, which can be utilized by external research groups and health-tech companies to test new sound and multimodal paradigms in patient care.

Societal: Beyond science, studying patients reactions to e.g. personalized emotional sounds will initiate a profound shift of paradigm from the present tendency to consider coma patients as 'computing machines' which work, or don't (can they count beeps? can they react to verbal command?), to that of considering the patient as an emotional individual. This change of paradigm will not only change caregivers' (see e.g. "*unconscious patients do not need to be treated for depression because they are unconscious*" - Fins, 2020), but also societal attitudes to unconsciousness, with potentially important ethical and legal implications (e.g. what is the status of a patient which can't pass the CRS-R, but nevertheless smiles when listening to music?)

Cultural: From Marcel Proust to Philip Glass, the scientific and philosophical question of consciousness has long been a source of inspiration for the arts (Epstein, 2004). In 2019 we issued a call for artistic residency, funded by the VERTIGO STARTS EU program, to host sound designers and composers in the context of the GHU ICU. The call generated more than 25 international applications and resulted in an interactive music piece composed by British artists Joe Acheson and Ali Tocher (Tocher et al., 2020). By exploring the relations between sound perception and consciousness, and providing a world-unique clinical platform allowing unprecedented 3D sound installations at the patient's bedside, the project therefore has a high potential to entertain rich relations with the artistic community, something we will explicitly address by funding new art residencies (see below)

b. Initiatives covering relations between science and society

Project members are already highly active in relations between science and society, with participants in general public science events (e.g. Pint of Science, UNESCO Semaine du son, etc.), science communication (https://lejournal.cnrs.fr/videos/dis-moi-bonjour-et-je-te-dirai-qui-tu-es), media relations (e.g. https://www.franceinter.fr/emissions/et-je-remets-le-son/et-je-remets-le-son-08-decembre-2019) and art/ science collaborations (Tocher et al., 2020). Beyond these actions which we will continue to deploy in relation to the project, Sounds4coma will fund two specific initiatives aiming to directly engage with

society. First, the project will fund a call for two successive art residencies (one in 2022-2023, another in 2024-2025), modelled on our successful 2019 call (Tocher et al. 2020) to host sound designers and composers in our clinical platform to explore sound and consciousness issues in healthcare. Residencies will be coordinated by the GHU's Laboratory for Cultural Innovation by Design LABAH (https://www.ghu-paris.fr/fr/le-lab-ah, Dir: Carine Delanoe-Vieux) using the format developed by the VERTIGO STARTS project (Henchoz et al. 2019), and their results will be publicized in collaboration with IRCAM/Centre Pompidou in Paris. Second, the project will also organize a public consultation on ethical issues resulting from the project's results, probing e.g. attitudes towards the status of patients who react to emotional sounds while failing traditional clinical tests for consciousness. The consultation will use the format of empirical ethics recently introduced to probe public's attitudes to e.g. autonomous vehicles (Bonnefon et al. 2016) or deep-fakes (Guerouaou, Vaiva & Aucouturier, 2021), in which online participants are asked to rate the acceptability of situations presented as text vignettes. The study will be conducted in collaboration with the GHU's Laboratory for Cultural Innovation by Design LABAH and will investigate the attitudes of both caregivers, patient families, coma survivors as well as the general public.

c. Strategy for disseminating and exploiting results

Scientific results from the projects will be disseminated with publications in general-science journals (e.g. from our previous work, PNAS, Nature Communications, Current Biology) and medical journals (e.g. from our previous work, JAMA, Lancet). Results will also be disseminated by making the project's new software tools available as open-source libraries (deliverable DA1-DB1-DC1) or web-services (deliverable DA4).

The commercialization potential of the project's results will be explored at the end of the project using the maturation services of our mother institutions CNRS (CNRS Innovation), INSERM (INSERM transfer) and GHU. We will notably investigate the possibility to create a start-up company, to be hosted by the GHU's E-health business incubator *Pensées.*

Finally, the media platform for disseminating project's result is broad and has been nurtured by previous projects of Sounds4Coma members. Project coordinator JJA was the 2014 laureate of Association des Journalistes Scientifiques de la Presse d'Information (AJSPI) and spent one month as resident scientist at the science dept. of the Agence France Presse (AFP) news agency, which lead to strong relations with the science media community which continue to this day. Dissemination about our research work is also strongly supported by Fondation pour l'Audition, which creates broad general public campaigns about all topics at the intersection of hearing and health (https://www.youtube.com/watch?v=toHbRQMHB-w).

V. References related to the project

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AAPG2021	SOUND4COMA		PRC + DGOS
Coordinated by:	Jean-Julien AUCOUTURIER (FEMTO-ST)	48months	957,833.62€
8.7. Technologies pour la santé			

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Requested means by item of expenditure and by partner:

		Partner 1: FEMTO-ST	Partner 2: IPNP	Partner: GHU
Staff expenses		261,281.62	100,500.00	0
Instruments and material costs (including the scientific consumables)		7,000	10,200.00	0
Building and ground costs		0	0	0
Outsourcing / subcontracting		0	0	0
General and administrative costs & other operating expenses	Travel costs	30,500	9,000.00	0
	Administrative management & structure costs	35,853.79	14,364.00	0
Sub-total		334,635.42	134,064.00	0 (*)
Requested funding		**468,699.42 (**)**		

(*) Budget of clinical partner GHU (489,134.20€) is sought from DGOS, and not to be funded by ANR.

(**) Total budget: 468,699.42 (ANR) + 489,134.20€ (DGOS) = 957,833.62€