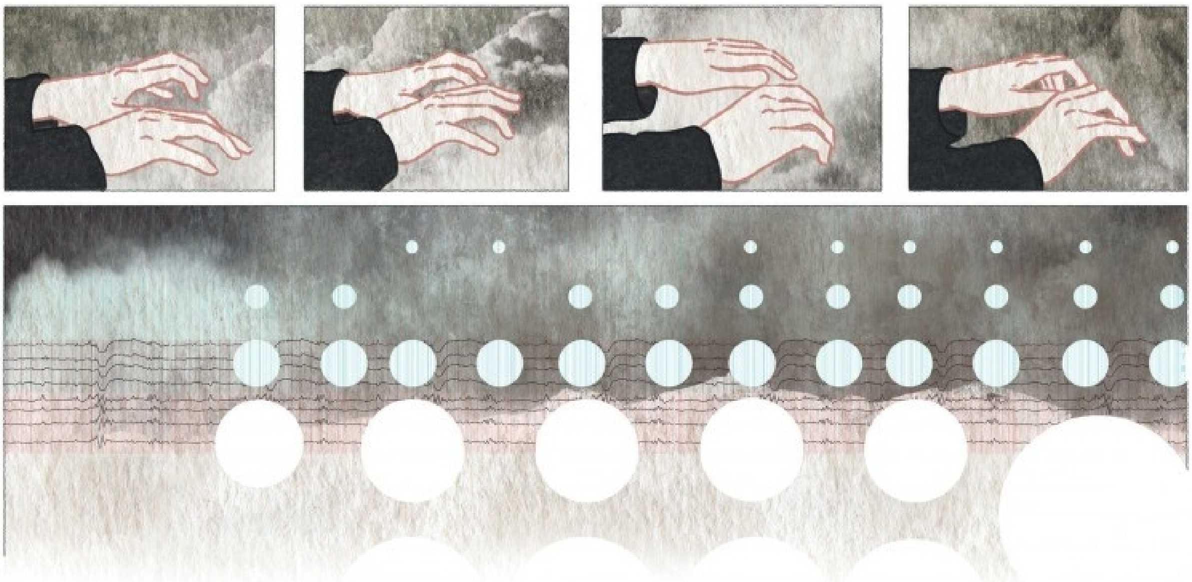
ERC Advanced Grant 2019
Part B2
SOUNDS4COMA
Reaching to the Unconscious with Sound Technologies



S.Revel. Glenn Gould in a coma. (*Glenn Gould, A Life Off Tempo*, 2016)

Section a. State-of-the-art and objectives

State-of-the-art

The identification of consciousness, i.e. the ability to formulate subjective reports about oneself or the world (Dennett, 1992), in non-responsive patients is not only one of the most vexing theoretical and empirical questions facing modern neurosciences (Miller, 2005), 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 comprehending some or all of what is said and going on around them has far-reaching legal and ethical implications, as evidenced by the cases of Terri Schiavo in the USA (Fins & Schiff, 2005) and, most recently, Vincent Lambert in France (Veshi, 2017). The use of sound stimulation in the intensive care unit (ICU), either through verbal commands (Owen et al., 2006; Claassen et al., 2019), standardized sound stimuli (Davis et al., 2007; Faugeras et al., 2011) or enriched sound environments (Lewinn & Dimancescu, 1978), holds tremendous promise to reach to these patients and provide them with better diagnosis and better care.

Yet, despite a growing body of academic research and clinical practice on the subject, the use of sound in the ICU remains plagued with critical theoretical and methodological issues.

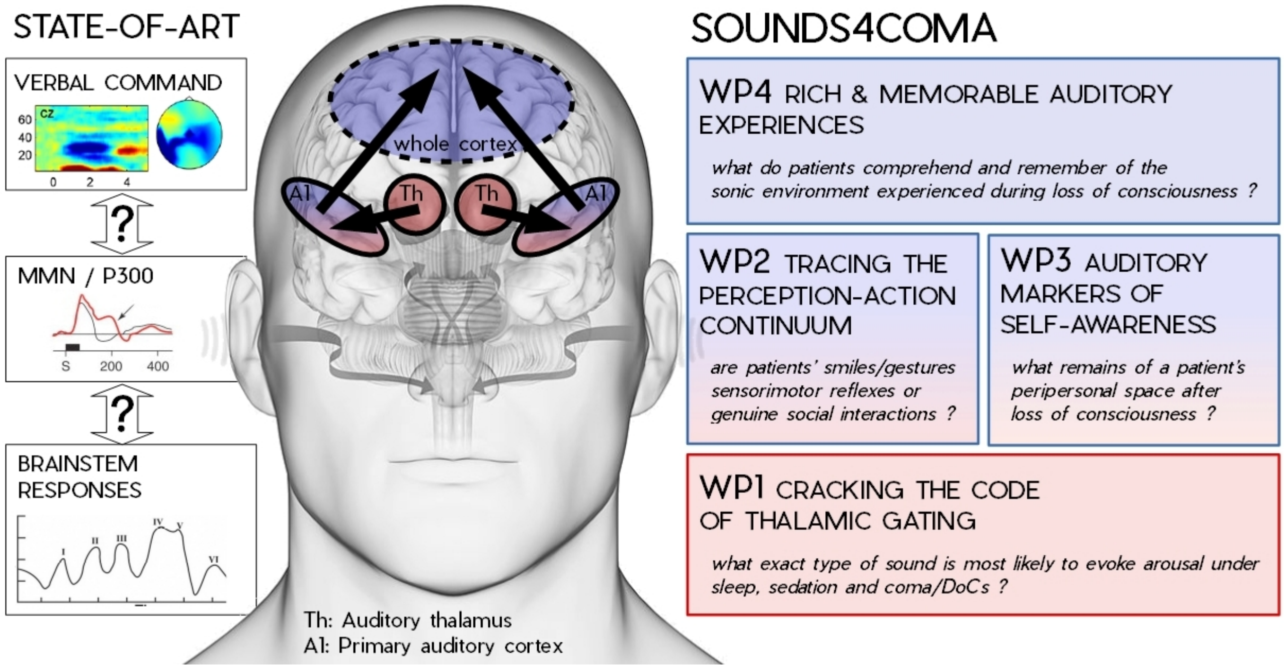
First, the recording of auditory event-related potentials (ERPs) in response to trains of e.g. pure tones or voice recordings is routinely used to evaluate cortical function in coma and disorders of consciousness (DoCs), because of their high positive predictive value for awakening (André-Obadia et al. 2018). Yet, almost nothing is known about what sounds - be them pure tones, speech, or other - are able to pass the thalamocortical relay, which is thought to be severely altered during these states (Alkire, Haier & Fallon, 2000). From the sound alarm literature, it is well-known that sounds that may seem 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 standard ERP testing in the ICU can be as low as 32% (Fischer et al. 1995), there is therefore a real possibility that patients who are denied a positive prognosis would show preserved electrophysiological responses if they were tested with sounds that are more adapted their neurological state.

Second, a critical factor in separating vegetative states (VS; patient awake but unaware of the self or environment; Laureys et al., 2010) from minimally-conscious states (MCS; patient awake and retains intermittent awareness of the self and environment; Giacino et al 2002) in patients awakening from coma is the identification of cortically-mediated behaviour (Naccache, 2017). In clinical practice, this criteria almost always translates to determining whether patients are able to respond to verbal command, either with behavioural assessment of the auditory items of the Coma Recovery Scale (CRS-R, Gerrard, Zafonte & Giacino, 2014) or with the identification of covert responses in brain imaging modalities such as fMRI (Owen et al., 2006) or EEG (Claassen et al., 2019). Yet, it is well-known from the cognitive neurosciences that there is a great continuum of auditory processing abilities intermediate between purely subcortically-mediated behaviour (VS) and full-fledged language comprehension. For instance, even outside of conscious awareness, healthy participants are able to discriminate their own voice from someone else's (Rachman, Dubal & Aucouturier, 2019), to parse concurrent streams of voice (Legendre et al., 2019), to react discriminantly to sound sources that loom toward their body (Noël et al., 2019), and even to comprehend prosodic intonation and react with appropriate facial expressions (Arias, Belin & Aucouturier, 2018). It is probable, therefore, that by focussing on using sound to detect overt responses to verbal commands, we routinely deny a MCS diagnosis (and thus weight dramatically on decisions to withdraw life support; Demertzi et al., 2011), to patients who, yet, would react to looming sound sources, revealing a sense of self, or even covertly smile back at the intonation of a family member, revealing a capacity for social interaction.

Third, because of the organization of healthcare in critical care departments, all of such auditory testing is typically done intermittently, e.g. once at the acute phase of coma, and possibly once again in the chronic DoC patients. Yet, daily fluctuations in residual consciousness are a well-documented hallmark of DoCs, with CRS-R auditory items typically scoring higher in the morning than afternoon for both VS/UWS and MCS (Cortese et al., 2015). Even in physiological states like sleep, recent evidence suggests that the same participant, a few hours or minutes away, may be able to detect salient auditory stimuli - or not - depending on the presence of slow oscillations in N2 or N3 sleep (Vallat et al., 2017; Blume et al., 2018), or to memorize newly presented stimuli – or not – depending on the presence of rapid eye movements (REMs; Andrillon et al., 2017). In a technological era where EEG monitoring can be automatized (Claassen et al., 2004) and synthesized sound environments can be updated and played continuously (Finney & Janer, 2010), does it still make sense to rely on scarse, isolated auditory testing and hope that the moment coincides with the patient's most elevated levels of attention?

Finally, in a context where auditory stimulation appears so uniquely critical to a patient's diagnosis and level of care, does it make sense that the modern ICU environment be so acoustically hostile, with average background noise levels reaching 60-70 dBA (a 40 dBA excess over World Health Organization's recommended levels; Wenham & Pittard, 2009)? With its constant alarms, cardiac monitors and respirators, today's ICU environment in effect relegates auditory testing to only the loudest of sounds and the least subtle of acoustic differences, and compells clinicians and researchers to exclude modern sound technologies such as 3D/binaural sound diffusion and audio virtual reality (Hong et al., 2017) from their array of diagnostic and rehabilitation options.

In summary, despite a mass of research and clinical practice using auditory testing to diagnose and rehabilitate patients with disorders of consciousness, we still do not have a cognitively-principled and technologically-appropriate way to use sounds in the ICU. **Sounds for coma are, so far, a wasted opportunity** for science and clinical medicine, and a troubling ethical issue for our society as a whole. In our view, this situation has two causes: First, research has paid almost no consideration to what type of acoustic signals is able to best reach to these patients, i.e. it has operated in complete dissociation with modern knowledge in acoustic signal processing. Second, it has paid no attention to what aspects of their auditory cognitive processing are indicative of a rich, memorable conscious experience, i.e. a complete dissociation with the modern auditory cognitive neurosciences.



Objectives

Our goal is to mobilize some of the most powerful techniques in the two fields of signal processing and cognitive neuroscience and establish a radically novel approach to sound in the ICU : instead 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, we will **engineer acoustic stimuli that directly optimize the probability to observe these responses**. Working like probes, our sounds will target neurological functions that approximate a caudal–rostral progression along the auditory pathway, ranging from a better characterization of the thalamo-cortical auditory relay to the primary auditory cortex (Objective 1), to the emergence of interactive behaviour (Objective 2) and self-awareness (Objective 3), up to the construction of rich, memorable auditory experiences (Objective 4). At each of these stages, the project will develop novel sound technologies to explore these functions in healthy and clinical participants, produce key new knowledge in how they are altered in sleep, anesthesia and coma/DoCs, and use this knowledge to develop high-impact clinical applications for sleeping health, surgical safety and critical care.

Objective 1: Cracking the auditory code of thalamic gating

A major theoretical model of loss of consciousness under sleep, anesthesia and disorders of consciousness is that the thalamo-cortical relay of information to the primary sensory cortices is disrupted (the thalamic gating hypothesis; Alkire, Haier & Fallon, 2000). Because thalamic neurons encode auditory information with specific spectrotemporal receptive fields (Miller et al., 2002) before projecting sensory afferents to the primary auditory cortex, thalamic gating is expected to affect the transmission of sounds differently depending on their auditory characteristics. All subsequent auditory testing with sources in the cortex, e.g. the mismatch negativity (MMN) or P300 prevalent in DoC diagnosis (André-Obadia et al. 2018), are affected by the sensory properties of this relay, yet almost nothing is known about what types of sound are favored for transmission to the cortex during loss of consciousness.

Our first objective is to reveal, on an individual basis, what exact type of sound is most likely to evoke arousal under loss of consciousness. To do so, we will use data-driven methods (Ponsot et al., 2018; Jaworska et al., 2018) to analyse the electrophysiological responses of unconscious participants to large sets of sounds with systematically-varied acoustic properties, and reveal which of these properties evoke maximum arousal (WP1, p.8).

By «cracking the code of thalamic gating», the project will be able to design better fire alarms (WP1.1; 37% of US fire fatality occur during sleep – Ahrens, 2008), less intrusive medical alarms during anesthesia or critical care (WP1.3; 60% of ICU patients report insomnia or sleep deprivation – Waye et al., 2013), and create optimized and personalized test sounds for MMN and P300 testing for DoC patients (WP1.3).

Objective 2: Tracing the perception-action continuum

Even when sensory information reaches the cortex, distinguishing volitional from reflex behaviour remains a major clinical conundrum in DoCs (Fischer & Truog, 2015). A considerable amount of pre-attentive bottom-up processing can be accomplished in the absence of conscious awareness (Chennu & Bekinschtein, 2012). Differentiating VS/UWS and MCS states requires diagnostic procedures that are able to separate such unconscious 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). In short, how do we know if patients process stimulus information in a task-relevant manner, in the absence of overt behavioural responses?

Our second objective is to establish a novel methodology to assess the depth of auditory information processing in the absence of behavioural metrics. To do so, we will adapt techniques recently developped in the visual neurosciences (Zhan et al., 2019) to auditory tasks such as recognizing and reacting facially to emotional spoken sentences, and reveal what elements of the single-trial EEG and EMG code for task-relevant information processing, before and after loss of consciousness (see WP2, p.10).

Findings from this paradigm will allow the project to design new speech-prosody-based tests of residual consciousness and provide family and caregivers with single-trial feedback about whether DoC patient behaviours (smiles, gestures) are sensorimotor reflexes or genuine social interactions (WP2.3).

Objective 3: Auditory markers of self-awareness

Even with eyes closed, the auditory modality gives us rich and behaviorally-relevant information about where sound sources are in the 3D space (Asutay & Västfjäll, 2015), and how these sources move around us (Seifritz et al., 2002). All these abilities presuppose a sense of body ownership and self-location, i.e. a minimal form of self-awareness (Blanke, 2012). Although it has been suggested that they would discriminate between locked-in patients with intact consciousness and patients with DoCs (Noel et al., 2019), almost nothing is known about how these capacities are altered after loss of consciousness.

Our third objective is to use 3D sound stimulations to characterize what remains of a patient's sense of self after loss of consciousness. To do so, we will, first, examine passive arousals evoked by binaural sounds with systematically-varied trajectories in the 3D space around the participant, and analyse these responses to compute maps of arousal around the listener (for inspiration, see e.g. Nummenmaa et al., 2018). Second, we will adapt auditory-tactile tasks able to measure the extent of a participant's peripersonal space (Canzerioni et al. 2012) in order to trace where and when this multisensory information is integrated in the EEG signal before and after loss of consciousness (see WP3, p.11).

Findings from this paradigm will allow the project to provide caregivers with individualized feedback on patients' thresholds for privacy or body safety during sedation and critical care (WP3.1), as well as biomarkers of residual self-awareness in sedation and DoCs (WP3.2).

Objective 4: Rich and memorable auditory experiences

Finally, at the top-most level of cognitive processing, little is known about what participants comprehend and remember of the sonic environment experienced during loss of consciousness. In sleep, participants were recently found able to learn new associations between tones and odors (Arzi et al., 2012), and about abstract patterns of noise (Andrillon et al., 2017), but there is disagreement about what EEG morpho-elements (slow waves, spindles, etc.) index the mechanisms that supporting such recognition and learning. In general anesthesia, the rare complication of « anesthetic awareness » (post-operative recollection of events occurring during surgery) also suggests that comprehension and encoding can be preserved (Sebel et al., 2004); in particular, sedation appears to largely preserve neural activity in speech perception networks, but it remains debated whether this translates to intact comprehension or memorization (Davis et al., 2007; Krom et al., 2018). In coma/DoCs, while similar anecdotal evidence exists (in Owen, 2017, one awakening patient is accounted to exclaim: *«If I ever hear that Celine Dion album again, I will kill you!»*), comprehension and recollection of auditory events after recovery has never been formally studied.

Our final objective is to establish EEG markers of auditory recognition/encoding and track how these evolve dynamically during loss of consciousness. To do so, we will present sleeping and sedated participants with continuously varied sequences of music or environmental soundscapes (conceptually, an auditory version of the tennis-vs-walk-around-the-house task of Owen et al., 2006), and test, upon awakening, for their recognition of the same material (sensory encoding) or different material of the same sound sources (semantic encoding). We will then link stimulus familiarity measured post-awakening to the EEG spectra measured during the unconscious exposure of the corresponding stimuli (see WP4, p.12)

Findings from this paradigm will allow the project to design biomarkers of anesthetic depth (WP4.2), to study the circadicity of auditory attention in DoC patients, and test whether standard behavioural (CRS-R) or MMN/ P300 procedures are improved when administered during peaks of such markers (WP4.3).

Impact

If successful, the project will therefore impact the sciences of consciousness to the point of changing both *what* we know of information processing during sleep, anesthesia and coma/DoCs, but also *how* we acquire this knowledge. The project will stop the current trend of selecting sounds for DoC diagnosis arbitrarily, with no consideration for their precise acoustical content and cognitive processing, and replace it with a completely new methodological framework in which sounds are engineered to optimize the probability to observe electrophysiological responses, and their information processing can be demonstrated in the single-trial, response of a participant's brain before and after loss of consciousness.

In the life sciences, this methodological framework will provide disruptive new tools for empirical research. For the first time, we will be able to address such elusive questions as *what exact types of sounds wake people up ?; does the social brain shut down while sleeping ?; does the peripersonal space shrinks or extends during sleep ?*. Beyond the scope of the project, our procedures will also find applications in the science of dreams (*can auditory content get incorporated in dreams?*), memory (*can novel auditory information intrude in the consolidation of memories?*), speech/langage (*how are words heard by the aphasic brain?)* and psychiatry (*what are the neural bases of auditory hallucinations?*).

In clinical practice, our findings will provide patients with new procedures for healthier sleep, more efficient -alarms, more safely-monitored anesthesia and, for the most critical among them, better informed diagnosis and more ethically-acceptable life-support decisions. Within the scope of the project, clinical trials will be conducted to formally evaluate the most promising of these procedures. Beyond the project, additional funding will be sought (e.g. in the form of ERC Proof of concept grants, patent applications and startup creation) in order to realize their full commercial or societal potential.

Section b. Methodology

Three key methodological insights

1) Powerful data-driven techniques from the cognitive neurosciences.

The typical approach to using sound stimulation in the study of sleep, anesthesia and DoCs (Chennu & Bekinschtein, 2012, for a review) has been so far largely unconcerned with the precise acoustical properties of the signals presented to participants. Sounds are selected relatively arbitrarily, in view of their supposed saliency or relevance: pure tones (e.g. in sleep, Cote, Etienne & Campbell, 2001), 40-Hz click trains (e.g. in anesthesia, Krom et al., 2018), but also e.g. voice from a participant's own mother (in sleep, Blume et al., 2018; in DoCs, Machado et al., 2007), from a mother's own child (in sleep, Formby, 1967) or someone calling the participant's own name (in sleep and DoCs, Perrin et al., 1999; 2006). When sounds are explicitly compared, it is with highly inefficient experimental paradigms, e.g. testing each separately on their ability to wake people up in the middle of the night, which only allows a limited number of comparisons (e.g., tones of three frequencies and a single male voice, over 1 night in Bruck & Thomas, 2008). This practice of positing signal features a priori severely limits the scientific and clinical interpretation of results (Burred et al., 2019).

To avoid these shortcomings, in recent years, a series of powerful data-driven paradigms (built on techniques such as reverse-correlation, classification images or bubbles; see Murray, 2011 for a review) were introduced in the field of psychophysics and cognitive neuroscience to discover task-relevant signal features empirically, by analyzing participant responses to large sets of systematically-varied stimuli (Adolphs et al. 2016; Jack & Schyns, 2017). In the visual modality, these techniques are combined with photorealistic face synthesis algorithms (Yu, Garrod & Schyns, 2012) to study cognitive processes such as the recognition of faces (Mangini & Biederman, 2004) or emotional expressions (Jack et al., 2012). In the auditory modality, data-driven techniques are still an emerging trend, and often require innovations in acoustic signal processing (Burred et al., 2019). For instance, they have been applied on raw signal spectrum to study vowel recognition (Brimijoin et al., 2013), on spectrograms derived from cochlear modeling to study speech intelligibility (Varnet et al., 2015), on spectrotemporal modulation spectrums derived from cortical models to study musical instrument recognition (Thoret, Depalle & McAdams, 2017) and, in our own recent work, on source-filter parameters derived from phase vocoder models to study the perception of emotional or social prosody (Ponsot et al, 2018). Critically for our purpose here, data-driven techniques can be combined with electrophysiology to reverse-correlate stimulus properties on single-trial ERP responses (e.g. the N170 visual potential, Jaworska et al., 2018) or reveal where and when task-relevant information is processed in the dynamical response of the brain (e.g. MEG activity in the visual fusiform gyri; Zhan et al., 2019), but these recent methods have never been applied to auditory stimuli to-date (Schyns & Ince, 2019).

The first methodological originality of our project is to bring the power of these data-driven techniques to the domain of auditory processing under loss of consciousness, **and use them to engineer acoustic stimuli that optimize the probability to observe target electrophysiological responses**.

We will apply these techniques to reverse-correlate EEG and cardiovascular markers of arousals on the properties of sounds played during unconsciousness (WP1); to reverse-correlate facial imitation behaviour on the acoustical properties of emotional speech during awareness, and then continue tracing these features in the single-trial EEG after loss of consciousness (WP2); to establish peripersonal maps of arousal from sounds with random 3D trajectories around a participant (WP3); and to reverse-correlate post-awakening recollection of sounds on the EEG activity measured during their prior unconscious presentation (WP4).

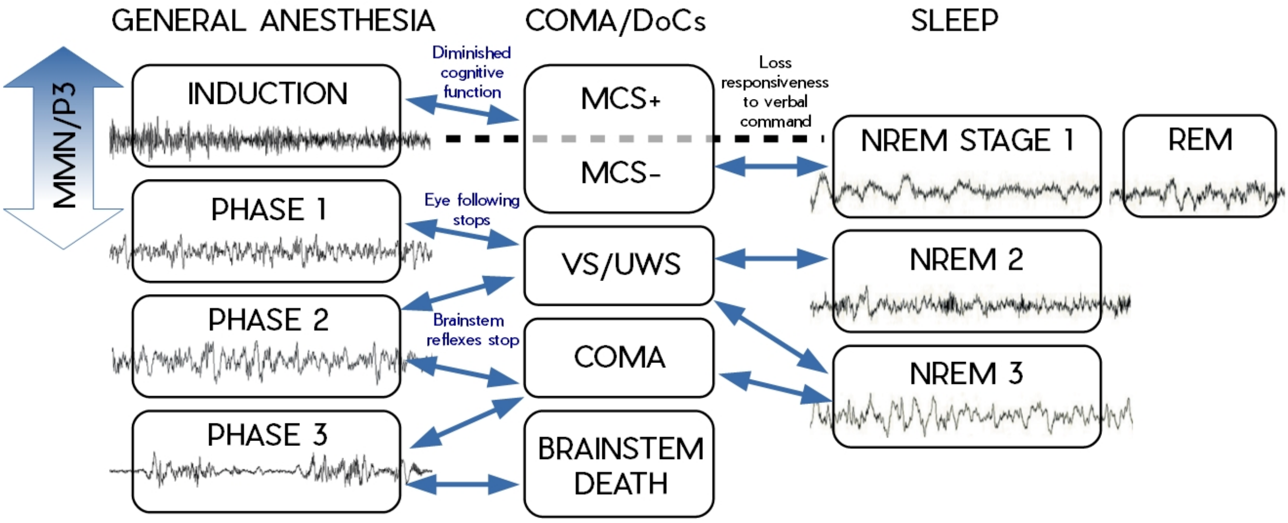
Data-driven approaches have several critical advantages for the project :

- Contrary to traditional group-level approaches which require large number of participants (Smith & Little, 2018), they make inferences on large number of trials, replicated in small number of participants, an approach ideally suited to a context where it is difficult to recruit large cohorts but where each sleeping/sedated/comatose participant can be stimulated numerous times (eg. 300 NREM2-sleep trials within a short nap in Kouider et al., 2014; 4000+ stimulus presentations during a night's sleep in Blume et al., 2018).
- They make it possible to estimate individual statistics, and thus make conclusions at the level of a single participant/patient (see e.g. Adolphs et al., 2005) – a critical advantage for diagnostic procedures.
- They allow the building of personalized sound stimuli and electrophysiological markers which can be replicated across participants if general inferences are sought for e.g. sleep and sedation, but can also be used individually for DoC patients, whose etiologies and paths of recovery may be too distinct for generic treatments.

2) A well-principled continuum of experimental models.

The second methodological originality of our project is to progress along a well-principled continuum of experimental models spanning sleep (physiological, endogenous, reversible loss of consciousness), general anesthesia (pharmacologically-induced, reversible) and coma/DoCs (pathological, irreversible).

While behavioural and electrophysiological similarities between various stages of sleep, general anesthesia with hypnotic agents like propofol and coma/DoCs have been often noted in the literature (Figure 3 ; Brown, Lydic & Schiff, 2010; Chennu & Bekinschtein, 2012), translational research programs that link these three states have been few and far between (see e.g. Perron et al., 1999, followed by Perrin et al., 2006). Yet, both sleep onset, light (NREM-1) sleep and the anesthesia induction stage show progressively diminished cortical function and loss of responsiveness to verbal command, and may serve as functional models of MCS states (Naccache, 2017). In these stages, ERPs such as MMN and P300 can be elicited, with amplitudes decreasing with the progressive loss of responsiveness at the onset of sleep (Ogilvie, 2001; note reappearance with REM sleep) or with increased levels of anesthesics infusion (Plourde & Picton, 1991). NREM-2 sleep and anesthesia maintenance phase 1, with progressive loss of eye following and brainstem reflexes, have similarity to VS/UWS. In NREM-2 sleep, there is no evidence of MMN/P300, which may be replaced by the N350 K-complex (Bastuji et al., 1995) and, correspondingly, absence of MMN is a poor marker of prognosis for recovery from VS (Wijnen et al., 2007). Finally, phases 2-3 of anesthesia maintenance (burst suppression) and, to some extent, N3 slow-wave sleep, may functionally approximate coma and brainstem death (depressed brainstem reflexes, decreased pain sensitivity; Brown, Lydic & Schiff, 2010).



Using sleep and anesthesia as models for DoCs and pooling the development of our experimental and computational procedures across these three states yield several critical advantages for the project:

- Sleep research allows the project to recruit large numbers of non-clinical participants in the sleep lab, with light ethical procedures, and therefore constitutes a model of choice for the development of experimental procedures (see WP1-1, WP2-1, WP3-1, WP4-1).
- Contrary to coma, both sleep and anesthesia make it possible to causally induce changes between levels of consciousness: participants can be tested with active auditory tasks before induction, and then electrophysiological markers of information processing can continue to be traced throughout loss of consciousness (WP2 & WP3). Similarly, participants can be presented with stimuli during unconsciousness, and then tested with active tasks upon awakening (WP4).
- Humans spend one third of their lives asleep and, each day, an estimated 60,000 patients receive general anesthesia for surgery in the US only (Brown, Lydic & Schiff, 2010). Besides providing a stepping stone to understand neurological dysfunction in coma, results in the two contexts of sleep and anesthesia will therefore stand on their own, and thus largely mitigate scientific risk and amplify the impact of the project.

In summary, by pooling its research efforts across the three models of sleep, general anesthesia and DoCs, SOUNDS4COMA will not only be methodologically equipped for a critical breakthrough in the study of disorders of consciousness, but also amplify its impact many-fold with important findings and applications in the domains of sleep and anesthesia.

3) The IRCAM/Sainte-Anne ICU: a unique technological plateform

While research in a sleep/EEG laboratory provides flexible conditions for the diffusion of sound stimuli, from earphones to multi-loudspeaker systems, the deployment of modern sound methodologies in the clinical context of an ICU remains an unprecedented technical challenge: average background noise is high (respirator, patient monitoring alarms, staff conversations, etc.; Tegnestedt et al., 2013), sound-absorbing materials and finishes are almost entirely lacking (Walsh-Sukys et al., 2001) and it is nearly impossible to incorporate sound diffusion devices and controls in such a highly-constrained environment (Thompson et al., 2012) when they were not originally planned. While ICU acoustics is universally recognized as a critical issue for patients and staff (Wenham & Pittard, 2009), the problem is generally ignored in the structural conception of new units.

The final key methodological asset of the project is to build on the unique opportunity of the construction of a new Neurology and Critical-care building in Hôpital Sainte-Anne, Paris (Neuro-Sainte-Anne, cost: 82,773M€), for which a partnership was made with the PI's own laboratory (IRCAM, specialized in sound/acoustics) to build two pilot ICU rooms with very high acoustic performance (average level inside the room < 23 dBA, room reverberation equivalent to that of an auditorium) and entirely fitted for sound diffusion (3D multi-loudspeaker system embedded in walls, ceiling and supply-unit arm, with a separated 15sqm control room).

To the best of our knowledge, this technical plateform, a structural investment estimated at 150k€ (3,250€/sqm), will be the only one of its kind in the world. With the building expected to be operational in Jan. 2023, the plateform will constitute a timely and ideal testing-bed for the novel methodologies developed in the project. Support from the ERC will provide the means to:

- equip the rooms with the sound technology needed for the diffusion of customized sound alarms (WP1), expressive speech synthesis and transformation (WP2), 3D moving sound sources (WP3) and full audio virtual reality (WP4) with unprecedented levels of patient comfort and realism,
- to staff the plateform with a full time audio engineer/technician supporting its operation during normal medical practice for the project's clinical studies, and
- to establish an appropriately-ambitious fundamental and translational research program for the plateform, which has the ambition to radically transform how sound is used in ICUs in France, Europe and beyond.

<u>Research plan:</u> (legend: S Sleep, A Anesthesia, C Coma/DoCs)

WP1. Cracking the auditory code of thalamic gating

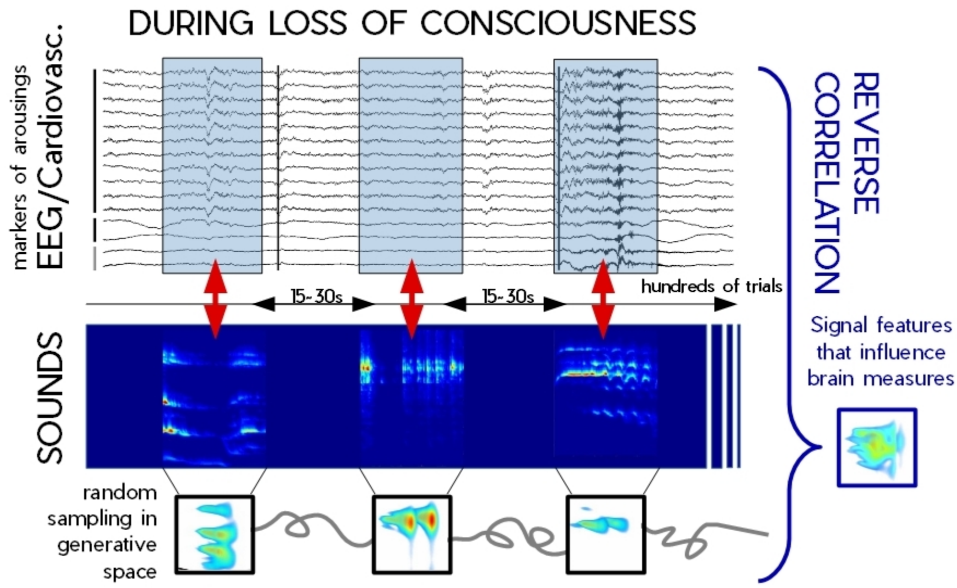
The objective of WP1 is to reveal, on an individual basis, what exact type of sound is most likely to evoke arousal under sleep, sedation and coma/DoCs.

WP1.1. What sounds wake people up from sleep? S

We will present N=10 healthy sleeping participants (in naps for stages NREM1-2, and/or full nights for stages NREM3-REM) with a large quantity of subthreshold sounds (inter-stimulus interval = 15-30s) computationally generated to have systematically-varied properties in their spectrotemporal modulation spectrum (i.e. abstract sweeps of various rate and scale ; Venezia, Hickock & Richards, 2016). We will then reverse-correlate the properties of these sounds on the occurrence of markers of arousals in participant's EEG and cardiovascular measures (Catcheside et al., 2002, Blume et al., 2018), to reveal what acoustic features (conceptually, *thalamocortical receptive fields*) maximally or minimally evoke arousal during sleep (discriminating if necessary between the different stages of sleep and the presence of EEG morpho-elements such as spindles or slow-oscillations ; see e.g. Blume et al., 2018).

Clinical application: We will use the acoustic features learned during WP1.1 to design new sound fire alarms arranged in the emergency evacuation T-3 temporal pattern (ISO8201, 1987), and measure their auditory arousal thresholds in a standard full-night procedure (N=20 participants ; Bruck et al., 2009) to compare them to standard signals (3000Hz pure tone, 520Hz square-wave).

A note on sample sizes: In all the following, data-driven experiments, which make inferences on large number of trials replicated in small number of participants (Smith & Little, 2018), will use sample sizes of N=10 participants (see Zhan et al., 2018: N=6; Ponsot et al. 2018: N=10). Clinical applications, which use group statistics on within-subject comparisons, will use sample sizes of N=20 participants (see Blume et al. 2018: N=17; Andrillon et al. 2017: N=20).



WP1.2. What sounds evoke arousal under anesthesia? A

We will use the same procedure as WP1.1 with N=10 non-neurological surgical patients undergoing general anesthesia, who will be passively presented sounds using headphones during the 20~30-min. separating induction and surgery (Bispectral index BIS 40 to 60; Kearse et al, 1998).

Clinical application: We will use the acoustic features learned during WP1.2 to design sound stimuli used to monitor hypnotic depth in the emergence phase of anesthesia. We will use the procedure of Yli-Hankala et al. (1994) on N=20 surgical patients to measure how early autonomic reactions to the sounds can detect emergence, compared to the standard criteria used by anesthesiologists (BIS>60 and reappearance of motion).

A note on patient recruitment: All participants for anesthesia experiments in the project are non-neurological patients tested in the context of ambulatory orthopedic surgery (Anesthesia Dept. Hôpital Lariboisière, Paris. Dr Fabrice Vallée, M.D.), with inclusion criteria including normal hearing and no history of brain trauma or cognitive impairments. Anesthesia will be done with propofol. Patients will be informed on the opportunity to participate in the study in the pre-operative interview, will sign a consent statement and be compensated for their participation. In accordance with French regulations, all studies will be subjected to prior approval by the regional clinical ethical committee (*Comité de protection des personnes*) and data-protection agency (*Commission nationale informatique et liberté*).

WP1.3. What sounds reach the comatose cortex? C

We will use the same procedure as WP1.1 in N=10 comatose patients (brain stroke or cardiovascular arrest) in order to compute individual sound stimuli that maximally or minimally evoke arousal reactions measured with EEG and autonomic responses. In addition to abstract alarm sounds, we will also present vocal recordings (own-name) with systematically-varied source-filter vocal parameters (i.e. voices of various pitch and timbre; Burred et al., 2019), and reverse-correlate what type of voice (e.g. female or male, high-pitch or low-pitch) maximally reaches to these patients.

Clinical application (1): We will use the sound features learned during WP1.3 to modify existing medical alarm sounds in order to minimize disturbance in ICU patients, by emphasizing features which did not correlate with arousals. New alarm sounds will be tested in-situ on N=20 DoC patients and compared to standard alarms (Block et al., 2000) on electrophysiological markers of patient arousal and ergonomic performance (Williams & Beatty, 2005). Collaboration discussed with European manufacturer Dräger to, later, commercialise these new alarms.

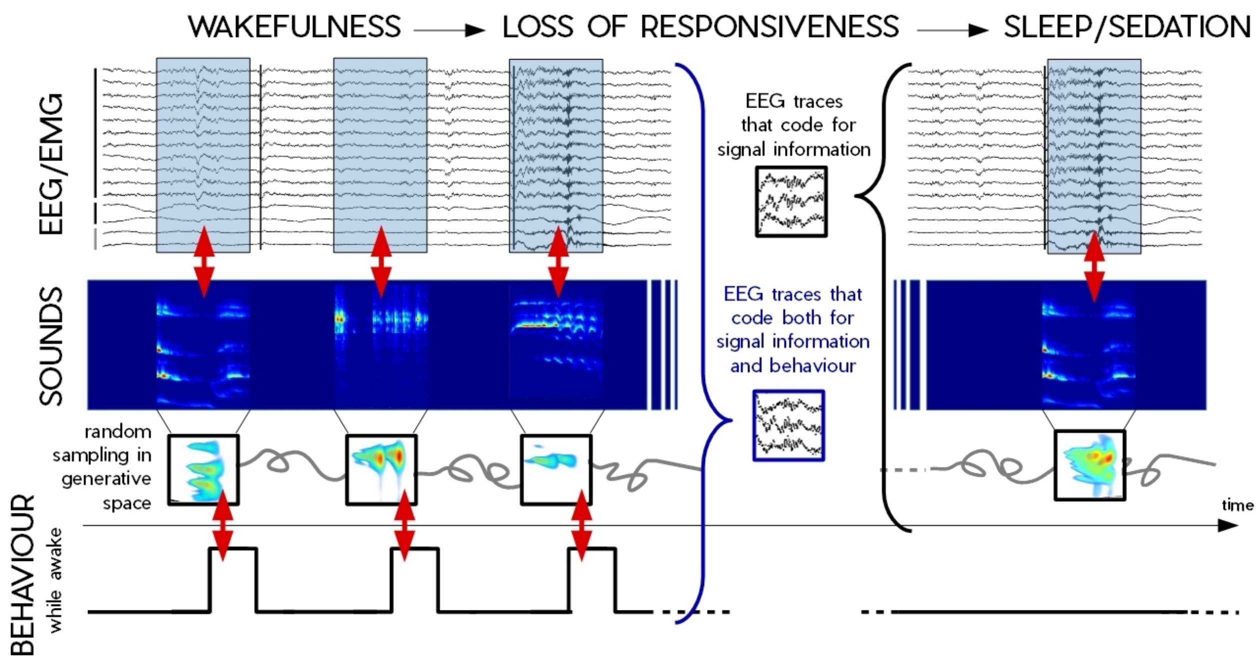
Clinical application (2): We will use the sound features learned during WP1.3 to modify stimuli in standard MMN/P300 auditory testing (replacing tones with optimal abstract sounds, and own-name stock recordings with recordings transformed to have the optimal vocal timbre and pitch) and test their capacity to evoke responses of larger amplitude and smaller latency than standard stimuli, in a sample of N=20 DoC patients (similar methodology as e.g. Perrin et al., 2006).

A note on patient recruitment: All participants for DoC experiments in the project are comatose patients admitted to the ICU for ischemic/hemorrhagic stroke or cardiac/respiratory failure (excluded: traumatic brain injury, epileptic grand mal) and who haven't recovered complete wakefulness or awareness (Glasgow Coma Scale GCS <8) 5 days after withdrawal from sedation. Patients will be tested as part of standard neurophysiological evaluation during their stay at the ICU between day 5-12 (Hôpital Sainte-Anne, Paris. Prof. Tarek Sharshar & Martine Gavaret, M.D.). Functional outcome (Glasgow Outcome Scale GOS) will be assessed 3 months after onset of coma. According to cohort studies in the same population (Luauté et al. 2005), about one third of these patients are expected to recover good functional outcome (GOS 4 and 5) within a year post-coma, while 40% of them will evolve to poor functional outcomes (MCS, VS/UWS and death). In accordance with French regulations, all studies will be subjected to prior approval by the regional clinical ethical committee and data-protection agency.

Personnel involved: 1 PhD student (3 years; profile: neurophysiology M.D.) followed by a 2-year postdoc. Support for clinical study involves one clinical research assistant for data collection and one audio engineer for technical support. Alarm sound design by a music composer or sound designer invited for a 12-month residency after an international call.

WP2. Tracing the perception-action continuum

The objective of W2 is to establish a novel methodology to assess the depth of auditory information processing in the absence of behavioural metrics.



WP2.1. Does the social brain shut down while sleeping?

We will present N=10 healthy awake participants with speech recordings with systematically-varied timbre properties (Ponsot, Arias & Aucouturier, 2018), and ask them to detect with a button-press which of these recordings sound like they were pronounced with a smile, while their own zygomatic muscles are continuously monitored with facial EMG (Arias, Belin & Aucouturier, 2018), and their brain activity measured with scalp EEG. Sound volume will be individually adjusted so stimuli are clearly audible, but participants feel they can sleep despite the stimulation (ISI = 3~7sec., jittered to avoid expectation effects). Participants will be encouraged to fall asleep while they do the task (see e.g. Kouider et al., 2014). We will reverse-correlate what acoustic information is associated with their awake behaviour (ie. what spectral properties of speech drive recognition and facial imitation of auditory smiles) and then use information-theoretic measures (see e.g. Jaworska et al. 2018) to reveal where and when this task-relevant information is processed in the dynamic response of the brain measured with single-trial EEG (e.g. P300), both before and after loss of consciousness. In particular, we will look for overt facial mimicry during sleep, as well as covert EEG antecedents of mimicry indicative of social cognitive processes active in the absence of behaviour.

WP2.2. Residual social interaction under sedation

We will use the same procedure as WP2.1 with N=10 non-neurological surgical patients undergoing general anesthesia, presenting sounds throughout the descent to anesthesia (20–70min.) using headphones (see e.g. Krom et al., 2018). As in sleep, we will look for how cortical integration is disrupted with increasing depth of anesthesia, and discriminate EEG activity indicative of first-order sensory processing (i.e. that codes for acoustic features but not behavior) from that indicative of task-relevant information processing (i.e. that codes both for acoustic features and behaviour).

WP2.3. The smile test of consciousness

Clinical application (1) : We will adapt the passive part of the above procedure to the ICU context (P3/EMG responses to smile & non-smile stimuli, using a familiar voice's recording of patient own-name), and look for similar EEG/EMG patterns as in WP2.1&2, suggestive of overt or covert facial reactions (Fiacconi & Owen, 2016), in N=20 DoC patients.

Personnel involved: 1 PhD student (3 years; profile: computational neuroscientist) followed by a 2-year postdoc. Support for clinical studies involves one clinical research assistant for data collection and one audio engineer for technical support.

WP3. Auditory markers of self-awareness

The objective of WP3 is to use 3D sound stimulations to characterize what remains of a patient's sense of body ownership and self-location after loss of consciousness.

WP3.1. Peripersonal maps of arousal in sleep, sedation and DoCs

We will adapt the passive procedure of WP1.1 and present N=10 unconscious participants in sleep, sedation and DoCs with large sets of sounds (the arousing sounds elicited in WP1) with systematically-varied motion in the 3D peripersonal space (i.e. looming or receding from the participant, at various distances and angles). By reverse-correlating sound motion on EEG/autonomic markers of arousal, we will compute peripersonal gradient fields indicating the topographic properties of the participant's body representations (for inspiration, see e.g. Nummenmaa et al., 2018). We will look for how these fields differ from those computed on N=10 awake healthy controls (in similar lying-down conditions). 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).

Clinical application: If there is sufficient heterogeneity in the peripersonal maps of DoC patients, we will test the procedure as a biomarker of residual consciousness (computing e.g. distance from maps derived from controls), test its coincidence with subsequent MCS diagnosis and its predictive value for awakening in an exploratory cohort of N=20 DoC patients.

WP3.2. Cortical audiotactile integration in sleep, sedation and DoCs

We will adapt the procedure of WP2 and let N=10 sleep and sedation participants engage in a audiotactile integration task before and after loss of responsiveness, in which looming sound sources at various distances of their body are presented shortly before a tactile stimulation. In such tasks, moving auditory stimuli are expected to interact with the processing of tactile stimuli as long as they are perceived at a limited distance from the body, conceptualized as the participant's peripersonal space (Canzoneri, Magosso & Serino, 2012). We will use a passive-listening procedure, in which participants are presented with auditory-only, tactile-only or auditory-tactile stimuli with no overt response (see e.g. Bernasconi et al., 2018), and track scalp EEG/ERP responses to the three types of trials as participants descend into sleep (see WP2.1) or general anesthesia (see WP2.2), looking for evidence of larger multisensory integration at close than far distance, and how such information processing evolves before and after loss of consciousness.

Clinical application: We will adapt the procedure to the ICU context, and look for similar EEG patterns as in WP3.2, suggestive of multisensory integration and self-awareness in an exploratory cohort of N=20 DoC patients.

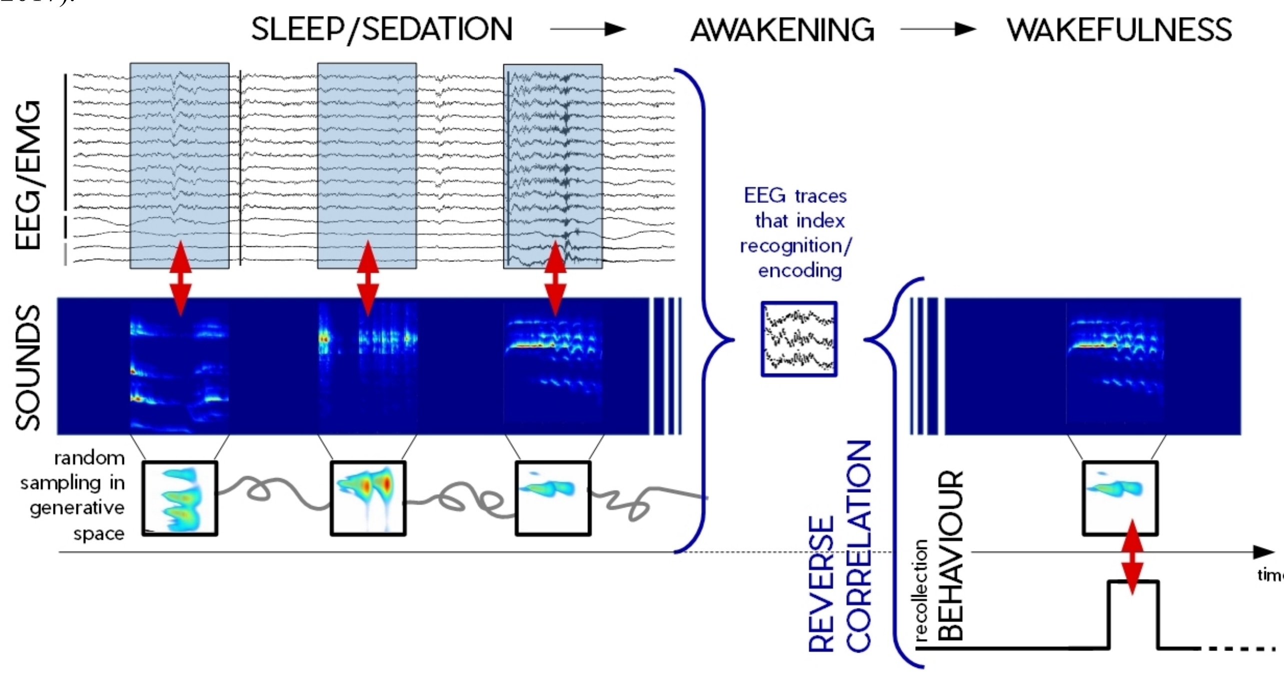
Personnel involved: 1 PhD student (3 years ; profile : psychoacoustician). Support for clinical studies involves one clinical research assistant for data collection and one audio engineer for technical support.

WP4. Rich and memorable auditory experiences

The objective of WP4 is to establish EEG markers of recognition/encoding of auditory events, and how these evolve dynamically during loss of consciousness.

WP4.1. What do people remember of their sonic environment during sleep?

We will present N=10 healthy full-night sleeping participants with continuously varied sequences of environmental soundscapes (e.g. Finney & Janer, 2010) or music (duration: 10s., ISI: 15s.), and test, upon awakening, for their subsequent feeling of familiarity with the same material (to test for sensory encoding) or different material of the same sound sources (i.e., recordings of the same environment, or different extracts from the same song, to test for semantic encoding). Familiarity will be measured in a two-alternative forced-choice procedure, comparing 2 extracts previously presented at different times during loss of consciousness. We will then reverse-correlate stimulus familiarity on the EEG spectra measured during the unconscious exposure of the corresponding stimuli, in order to reveal EEG activity indicative of recognition or encoding (e.g. event-related synchronization/desynchronization in theta band – Schreiner, Göldi & Rasch, 2015). We will also relate subsequent familiarity with sleep phases and EEG morphoelements (spindles, slow oscillations) which occurrences are thought to index mnesic processes (Andrillon et al., 2017; Göldi et al., 2017).



WP4.2. Continuous monitoring of anesthetic awareness under sedation A

We will use the same procedure as WP4.1 with N=10 surgical patients undergoing general anesthesia, presented with sounds during the 20~30-min. separating induction and surgery (BIS 40 to 60), and tested for subsequent familiarity in the post-operative recovery room. As in sleep, we will reverse-correlate stimilus familiarity on the EEG spectra measured during prior exposure, and look for markers of recognition/encoding.

Clinical application : We will test the EEG markers learned during WP4.2. for their ability to monitor hypnotic depth in the emergence phase of anesthesia. Each sedated patient will be presented post-surgery with a continuous playlist of unknown extracts of their favorite genre of music, and EEG spectral indices will be measured to index the occurrence of recognition and encoding of the material while they emerge from anesthesia. We will use the procedure of Yli-Hankala et al. (1994) on N=20 patients to measure how these reactions can detect emergence, compared to the standard criteria (BIS>60 and reappearance of motion). Note that, while the same paradigm would seem appropriate to monitor the rare complication of anesthetic awareness with recall (Sebel et al., 2004), the low-incidence of the condition (1/1000) unfortunately makes a clinical trial to demonstrate its effectiveness prohibitively expensive (over 20,000 patients per group, O'Connor et al., 2001).

WP4.3. Circadicity of auditory recognition/encoding in DoCs C

We will adapt the same procedure as WP4.2 to the ICU context, and present N=10 DoC patients with a personalized, highly-relevant soundscape (e.g. binaural recording of the patient's home and work environment, with familiar voices) or music stream (e.g. favorite music, as indicated by patient's family), streamed continuous over several hours per day. We will then track EEG markers of auditory recognition and encoding similar as those found in sleep and sedation over this period, and look for dynamic variations and how they correlate with cyclic autonomic variables such as temperature (Bekinschtein et al. 2009) and DoC diagnosis.

Clinical application : If significant variations of auditory recognition can be identified at the individual level, we will test whether administrating standard MMN/P300 auditory testing in phases of high-recognition improves evoked responses (larger amplitude, smaller latency) compared to administrating the same tests during phases of low-recognition, in a set of N=20 VS & MCS-level DoC patients (similar methodology as e.g. Perrin et al., 2006).

Personnel involved: 1 PhD student (3 years; profile: neurophysiology M.D.) followed by a 2-year postdoc. Support for clinical study involves one clinical research assistant for data collection and one audio engineer for technical support. Sound design and binaural recordings by a composer / sound designer invited for a 12-month residency after an international call.

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