## Campagne 2020 Contrats Doctoraux Instituts/Initiatives

## Proposition de Projet de Recherche Doctoral (PRD)

## Appel à projet IUIS - Institut univ d'ingénierie en santé 2020

**Intitulé du Projet de Recherche Doctoral : Development of a hierarchical, personalized procedure to determine and track the evolution of states/disorders of consciousness (S/DoC)**

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**Unité de Recherche :**
Intitulé : ICM Paris Brain Institute
Code *(ex. UMR xxxx)* : UMR 7225

**Ecole Doctorale de rattachement de l'équipe & d'inscription du doctorant :** **ED158-Cerveau, cognition, comporteme**

**Doctorants actuellement encadrés par le directeur de thèse (préciser le nombre de doctorants, leur année de 1ere inscription et la quotité d'encadrement) : 3 (2017, 2019, 2020)**

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Ou si ED non Alliance SU :

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**Cotutelle internationale :** ☒ Non ☐ Oui, précisez Pays et Université :

### Description du projet de recherche doctoral *(en français ou en anglais)*

*3 pages maximum – interligne simple – Ce texte sera diffusé en ligne*

*Détailler le contexte, l'objectif scientifique, la justification de l'approche scientifique ainsi que l'adéquation à l'initiative/l'Institut.*
*Le cas échéant, préciser le rôle de chaque encadrant ainsi que les compétences scientifiques apportées. Indiquer les publications/productions des encadrants en lien avec le projet.*
*Préciser le profil d'étudiant(e) recherché.*

## 1. Introduction & background

In the past 2-3 decades, there has been an astonishing prelude into the, by then, obscure science of consciousness. We have been bestowed with fascinating findings on the subtleties and limitations of conscious access, attention, and state transitions (Dehaene 2014). These cognitive discoveries are intertwined with clinical research of Disorders of Consciousness (DoC) patients and have allowed for the application of the fundamental science novelties. This progress could not have been completed without the holistic approach of an interdisciplinary and transdisciplinary collaboration. The holistic and interdisciplinary approach which we have taken is perfectly reflected through the background of the mentors: J.D. Sitt who has an initial degree in electronics, a medical degree (psychiatry) and a PhD in Physics (non-linear dynamics, mathematical modelling), and Benjamin Rohaut who is a neurlogist and in charge of dealing with DoC patients and coordinates the DoC assistance at the Pitie-Salpetriere Hospital. The hosting team, PICNIC, with its members which range from doctors, neurosurgeons, psychologists, engineers, biologists, linguists, also resonates with this approach. For this project we are looking for a student with strong technical competencies but also with an education or experience in interdisciplinary research, specifically in neuroscience.

All human beings experience a transient Loss of Consciousness (LOC) when they fall into a dreamless sleep. Transient LOCs can also occur during general anaesthesia, epileptic seizures, and more. However, more persistent LOCs may follow severe brain injuries, which can drive to DoC. This is a class of neurological conditions, such as coma, unresponsive wakefulness syndrome (UWS) - also known as vegetative state (VS), or minimally conscious state (MCS), which are characterized by extreme disability. Unfortunately,  there are many challenges in determining the DoC class the patients belong to. The error in diagnosis can be as high as 40% (Schnakers et al. 2009) and the elapsed time between a stroke and detection of LIS, is 78 days on average (León-Carrión et al. 2002). Thus, the need arises for novel biomarkers and procedures in order to decrease this unacceptable number. The diagnosis of DoC currently relies on a standardized behavioural assessment (Sergent et al. 2017). The importance of accuracy in such diagnosis cannot be overstated, as it guides critical decisions on treatment (including pain management) and could underlie end-of-life decisions (Dehaene 2014). Despite this importance, current behavioural diagnosis often fails, whether because of the major sensory and motor deficits associated with DoC, or because of the heterogeneous aetiology and pathophysiology associated with the conditions (Sitt et al. 2014; Sergent et al. 2017).

## 2. Project methodology

This project proposes the development of a multivariate, hierarchical, personalized procedure to diagnose and track the evolution of the state of consciousness in patients with brain injury. Based on existing and newly collected data, throughout this project we will develop a multimodal analysis for DoC patients using state-of-the-art computational tools, such as machine learning. Through this improved understanding of the pathophysiological mechanisms in DoC, we aim to better determine the single-patient's current state (diagnosis) and future outcome (prognosis). This will ultimately allow a deeper investigation of the cognitive abilities and the emergence of consciousness of patients belonging to these groups versus healthy controls (HC).

The hierarchical procedure will consist of layers of assessments and cross-modal biomarkers moving from simplest, least invasive, least costly (such as behavioural measures or standard clinical EEG) to ones of higher complexity, invasiveness, and cost (such as fMRI recordings or TMS/EEG evaluations). Each layer of the procedure should give out uncertainty and confidence intervals. The classification efficiency of the markers will be extracted from the different multimodal layers, followed by a development of an algorithm that integrates the multimodal information across layers to obtain an optimal S/DoC assessment tool. In order to combine information across layers, multivariate classification analysis (MVCA) will be used. This will allow a better understanding of the pathophysiology of the DoC by unveiling the interactions of the different aspects of brain activity extracted in the different layers. For the development of the decoder, we will follow the expertise demonstrated in (Sitt et al. 2014; Engemann et al. 2018) and use different multivariate integration strategies (such as mass-univariate analysis, and training of support vector machines or random forest classifiers). In Sitt et al. (2014), the support vector machine provided an efficient way to identify the combination of markers that leads to better discrimination of the patients' states of consciousness (Sitt et al. 2014). This procedure will be validated using cross-validation techniques and generalization across the datasets in the different recording sites. Machine learning procedures will be implemented in Python using scikit-learn (Pedregosa et al. 2011). All codes will be publicly available, as well as we will respect standards to ensure interoperability between the data sets: CDISC for clinical data; DICOM and BIDS for MRI data.

Moreover, such a structure composed of independent and synergic layers should allow for generality and flexibility across hospitals depending on which modalities are available. Previous results indicate that integrating information from different markers within a given layer of evaluation (i.e using EEG or fMRI) can boost diagnostic performance (Sitt et al. 2014; Engemann et al. 2018; Sergent et al. 2017). In addition, the strong focus on the use of multimodal testing of the consciousness level is emphasized by (Dehaene 2014). In his words "no single test will prove whether consciousness is present". This is due to various limitations, such as the fluctuating consciousness level and/or attention by patients, and the inherent limitations of each modality. Through this project, we will rethink these findings and integrate information across evaluation layers and modalities through longitudinal assessments using electrophysiological, neuroimaging and physiological techniques.

Structuring the biomarkers into the categorical layers will provide information on the underlying mechanisms from which they arise. Using the comparison of behavioural, electrophysiological and multimodal neuroimaging data, we can derive conclusions on the subtle differences between levels of vigilance and attention of the patients. Through these contrasts, we can come closer to conclusions on which physical measurements are used by the brain and thus which physical signals act as information for the brain (de-Wit et al. 2016). By employing a holistic approach, we want to investigate the subtleties of body, brain measurements and how their interactions or lack thereof, gives rise to certain behaviour and to consciousness.

As (Dehaene 2014) has argued, there is a need to distinguish between correlates and signatures of consciousness. Correlation does not imply causation, and instead, we are on the search for a systematic signature of consciousness, which is present when conscious perception occurs and absent when there is no occurrence. Through a multimodal comparison, we believe that the distinction can be made between measurements which are correlates and those that are signatures of consciousness. This also implies that the assessment should not be seen as something binary, or step-like. (Sergent et al. 2017) emphasize the importance of establishing a more nuanced profile of residual cognitive capacities of each patient.

Currently, the regular assessment of DoC patients at La Pitié-Salpêtrière Hospital involves a resting state recording and a recording with the local-global paradigm (Tristan A. Bekinschtein et al. 2009). This has contributed to the collection of a large database of EEG, fMRI and electrophysiological recordings of both DoC patients and healthy controls. This database brings an advantage to start building the numerical S/DoC analyses even before the novel data is recorded. For novel data gathering, neurophysiological assessments will be performed in the acute phase (T0), subacute phase (6 months) and chronic phase (12 months) of the patient's clinical evolution employing different techniques. The novel data will be gathered using high-density EEG, fMRI, nasal respiration.

3. Conclusion

This project is innovative compared to other project run by the hosting team from multiple aspects. There is innovation in the recording modalities such as respiration data and TMS/EEG measurements and the hierarchical analysis procedure. Undoubtedly, only through an interdisciplinary approach, this multifaceted challenge can be faced. This project integrates complementary interdisciplinary areas such as neuroscience, neurology, psychology, neuroimaging, neurobiology, computer science, biophysics and clinical research. The interdisciplinary aspect is also reflected in the background of the mentors Sitt (physicist and psychiatrist), Rohaut (neurologist) and their work throughout the academic careers (referenced throughout this proposal). Through this integrative focus, we want to avoid staying within reductionist categories. The power of our approach is in one tool that is nevertheless composed of several very different assessments, and all administered repeatedly across the evolution of the condition within a person. It is this heterogeneity in testing that allows us to tackle the heterogeneity in the condition and the scope of the remaining cognitive abilities (awareness, attention) of each patient.

References

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