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 : Translational and computational approach to study habit formation in healthy and compulsive subjects

Directeur de Thèse porteur du projet (titulaire d'une HDR) :

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Unité de Recherche :
Intitulé : Institut des Systèmes Intelligents et de Robotique (ISIR)
Code *(ex. UMR xxxx)* : UMR 7222

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) : 2 doctorants

Sami BEAUMONT, 1ère inscription : 2018, quotité d'encadrement : 0,5

Elias AOUN DURAND, 1ère inscription : 2019, quotité d'encadrement : 0,5

Co-encadrant :

NOM : **MALLET** Prénom : **Luc**
Titre : Professeur des Universités - Praticien H HDR ☒
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Unité de Recherche :
Intitulé : Institut du Cerveau
Code *(ex. UMR xxxx)* : UMR1127

Ecole Doctorale de rattachement : **ED158-Cerveau, cognition, comportement**
Ou si ED non Alliance SU :

Doctorants actuellement encadrés par le co-directeur de thèse (préciser le nombre de doctorants, leur année de 1ere inscription et la quotité d'encadrement) : 1 doctorante, Lindsay Rondot, 1ère inscription: 2016, quotité d'encadrement: 100%

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.

State of the art

Operant conditioning is a type of learning where the subject learns an association between a stimulus and a specific action to access its goal. Thus, the behavioural strategy used by the subject is called "goal-directed". However, with numerous repetitions, the association between the stimulus and the action increases until it becomes automatic and insensitive to the outcome. There is a progressive shift between the goal-directed behaviour and this so-called "habitual" behaviour. A usual protocol to study the relative dynamic of these learning strategies consists to experimentally extinguish the stimulus-action-goal association. It has been shown that an animal still engaged in a goal-directed behaviour (early during learning), will stop the task with such an extinction. Whereas if the extinction happens late during learning (i.e. over-training) then the animal will keep engaging in the full sequence of the task, meaning its behaviour is now outcome-insensitive and has shifted to habitual. However, Haith & Krakauer (2018) showed in humans that habits are in fact an ensemble of associative (with decision-making step) automatization and motor automatization. The sensori-motor part of habits has been extensively investigated but the associative automatization is yet to be described. The aim of this project is thus to characterise associative habits on a behavioural and a computational aspect using both animal model and humans. Moreover, we will investigate the implication of this process in the context of compulsive behaviors, where dysfunctional habit formation has been proposed as one of the possible cause of the disorder. Indeed, it has been proposed that compulsive disorders could result from an excessive stimulus-response habit learning, but we still need to determine which of the associative or sensori-motor part of the process is impaired.

In the mathematical biology literature, different contradictory computational models of habit learning have been proposed. Initially, computational models of habit learning focused on the automatization of the association between a stimulus and a behavioural response. In these models, any acquired behavioural response has to be triggered by a stimulus, and it is the strength of the stimulus-response association which determines the shift from goal-directed to habitual behaviour. However, a set of alternative models proposed that habit learning consists in acquiring action chains: e.g. if lever pressing is always followed by nosepoking, then having the animal press a lever is sufficient to trigger an automatic nosepoking response, without the need of an intermediate stimulus. While these different models contradict each other, the results of Haith & Krakauer (2018) suggest that both types of mechanisms may co-exist in order to automatize both the associative and the motor components of a habit. To our knowledge, there exists no computational model combining both types of automatization.

Aims

This project will consist in 2 main axes of investigation: (1) Identify associative habits in human and animal model by the means of an original extinction protocol and (2) develop a new integrative computational model of habit formation.

Experimental strategy

The behavioural part of this project will be conducted at the ICM, located at LaSalpétrière Hospital, in the "Neurophysiology of Repetitive Behaviors" team under the supervision of Luc Mallet and Eric Burguière, both experts in behavioural neurophysiology in human and animal models, in particular in the field of compulsive behaviors. The translational approach will be conducted first on healthy human and wildtype mice, as well as on OCD patients and a mouse model expressing compulsive behaviors (SAPAP3-knockout mice).

In both species, we will conduct a cue guided operant conditioning task performed either on a computer for human subject or in an innovative automated operant chambers developed in the lab where animals can perform thousands of trials over weeks. Our task will be an adaptation of a classic two-choice task where the subject has to choose one choice based on a cue to earn a reward. When initiating a trial, the subject will face a visual cue on a screen indicating the side of the expected answer. The subject will then have to respond (button press for humans or nosepoke for mice) on the appropriate side to earn a reward. All subjects will be trained in the same conditions but separated in two groups. Subjects in the early group will be trained until a success rate of 80% of correct responses over 40 trials. The over-trained groups will have to keep performing around the same criteria for 500 trials. Then an extinction protocol consisting in dissociating the reward side from the stimulus (i.e. same reward chance no matter the side/stimulus) will be performed. This protocol aim at extinguishing the association between the stimulus and the outcome. We expect that subject which are still in a goal-directed mode will extinguish in a faster way than subject which automatize the association and became insensitive to such extinction.

In parallel to this experimental work, we will employ our expertise in fitting computational models to animal and human behaviour in order to characterize different degrees (mild training vs. overtraining) and types (associative, motor) of subjects' habits in terms of different model parameter values. This computational part of the project will be supervised by Mehdi Khamassi, expert in computation modelling, who has developed unique model in the past addressing the question of the balance between goal-directed and habitual behaviors. We will propose a new model which combines a standard reinforcement (e.g. reward-based) learning process to acquire stimulus-driven habits with an action chaining (chunking) mechanism, so as to characterize subjects' habitual behaviour as weighted contribution of the two processes. This will allow us to identify possible neural substrates of model-related computations. Finally, we will simulate the winning model in variations of the present experimental protocol in order to derive novel model-drive predictions which could explain emergence of repetitive and compulsive behaviors when the habitual system becomes dysfunctional.

We believe that this multidisciplinary and multi-species approach for studying habitual learning using behavioural observations and computational modelling has a strong potential to mechanistically describe the anatomo-functional basis of habitual learning. We are particularly interested in the role of this habit process in the pathophysiology of compulsive behaviors, characterized by rigid rituals. Not only will we study a fundamental question in neuroscience using both neuroscientific tools and computational models, but we also aim at creating an innovative learning model that could be used in other fields such as personalized medicine to better evaluate the severity of the compulsive state in OCD patients. We therefore believe that our application is in line with the objective of the Institut Universitaire pour l'Ingénierie en Santé (IUIS).

Relevant publication Mehdi Khamassi

- Cinotti, F.*, Fresno, V.*, Aklil, N., Coutureau, E., Girard, B., Marchand, A.§ and Khamassi, M.§ (2019). Dopamine blockades impairs the exploration-exploitation trade-off in rats. Scientific Reports, 9:6770. (* equally contributing authors) (§ equally contributing senior authors)

- Dollé, L., Chavarriaga, R., Guillot, A.* and Khamassi, M.* (2018). Interactions between spatial strategies producing generalization gradient and blocking: a computational approach. PLoS Computational Biology, 14(4):e1006092. (* equally contributing authors)

- Palminteri, S., Khamassi, M., Joffily, M. and Coricelli, G. (2015). The neural computation of value contextualization in reward and punishment learning. Nature Communications, 6:8096.

- Khamassi, M., Quilodran, R., Enel, P., Dominey, P.F. and Procyk, E. (2015). Behavioral regulation and the modulation of information coding in the lateral prefrontal and cingulate cortex. Cerebral Cortex.

- Lesaint, F., Sigaud, O., Flagel, S.B., Robinson, T.E. and Khamassi, M. (2014). Modelling individual differences observed in Pavlovian autoshaping in rats using a dual learning systems approach and factored representations. PLoS Computational Biology, 10(2):e1003466.

Relevant publication Luc Mallet/Eric Burguiere

Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, du Montcel ST, Yelnik J, Chéreau I, Arbus C, Raoul S, Aouizerate B, Damier P, Chabardès S, Czernecki V, Ardouin C, Krebs MO, Bardinet E, Chaynes P, Burbaud P, Cornu P, Derost P, Bougerol T, Bataille B, Mattei V, Dormont D, Devaux B, Vérin M, Houeto JL, Pollak P, Benabid AL, Agid Y, Krack P, Millet B, Pelissolo A. (2009). Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med. 2008 Nov 13;359(20):2121-34.

Burbaud P, Clair AH, Langbour N, Fernandez-Vidal S, Goillandeau M, Michelet T, Bardinet E, Chéreau I, Durif F, Polosan M, Chabardès S, Fontaine D, Magnié-Mauro MN, Houeto JL, Bataille B, Millet B, Vérin M, Baup N, Krebs MO, Cornu P, Pelissolo A, Arbus C, Simonetta-Moreau M, Yelnik J, Welter ML, Mallet L. (2013). Neuronal activity correlated with checking behaviour in the subthalamic nucleus of patients with obsessive-compulsive disorder. Brain Jan;136(Pt 1):304-17.

Burguiere E., Monteiro P., Feng G. P., & Graybiel A. M. (2013). Optogenetic Stimulation of Lateral Orbitofronto-Striatal Pathway Suppresses Compulsive

Behaviors. Science, 340(6137), 1243-1246.

Burguière E, Monteiro P, Mallet L, Feng G, Graybiel AM. (2015). Striatal circuits, habits, and implications for obsessive-compulsive disorder. Curr Opin Neurobiol. Feb;30:59-65.

Benzina N, N'Diaye K, Pelissolo A, Mallet L, Burguière E (2019). A cross-species assessment of cognitive flexibility in compulsive disorders. BioRxiv, https://doi.org/10.1101/542100

Student profile

For this interdisciplinary project, we are looking for a student with either biological and/or computational background. It is important that the student already had some experience in the field of animal and human behavior to collect the data. For the computational part, he will be trained and supervise by Dr Khamassi at the beginning of his PhD to adapt some models already developed in previous studies. Ideally, the candidate will be fluent in spoken and written English and already spent previous training period in experimental laboratories. If the candidate already has legal authorization to work with animal models, it will be a major asset for the project.

Merci de nommer votre fichier pdf :
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à envoyer simultanément par e-mail à l'ED de rattachement et au programme :
cd_instituts_et_initiatives@listes.upmc.fr avant le 30 mars.