SchizApathy: Unveiling the Neuro-Computational bases of Apathy in Schizophrenia

SchizApathy is inter-disciplinary and inter-sectorial, covering system neuroscience, computational neuroscience and clinical sciences, and involves an international collaboration between two labs with complementary expertise.

SchizApathy's rationale. Apathy, marked by a reduced engagement in effortful, reward-driven actions, exhibits a high prevalence in the majority of psychiatric and neurological disorder, including schizophrenia (47%), depression (38%), Parkinson's Disease (40%), and Alzheimer's Disease (49%)[1]. Even when not the core symptom of the disorder, apathy significantly diminishes patients' quality of life and adversely affects their functional outcomes[2]. However, current research on apathy faces two significant challenges. First, subjective reporting of symptoms in psychiatry and neurology does not capture the distinct neural and computational mechanisms underlying apathy across disorders[3,4]. Recent neuroimaging and computational modeling studies reveal that apathy may stem from alterations in either effort processing, reward processing, or a combination of both in different populations[5,6,p1]. This highlights the need for developing neuro-computational biomarkers that offer objective insights into the putative causes of apathy in specific disorders. Secondly, there is a lack of effective therapeutic approaches to improve engagement in effort and alleviate apathy in patients, as many treatments fail to target the specific neuro-computational alterations mentioned above, leading to mixed clinical outcomes[7]. Importantly, these two challenges are particularly prominent in schizophrenia, a disorder where apathy emerges as a significant manifestation of negative symptoms. Recently, Dr. Knolle and her collaborators showed that schizophrenia is associated with an alteration of reward processing in reinforcement learning tasks, quantified through computational modeling of behavior[p2,p3] and neuroimaging data[p4,p5]. SchizApathy will test the hypothesis that schizophrenia involves an alteration of reward processing extending beyond reinforcement learning, affecting effort-based decision-making and contributing to the emergence of apathy in this population.

SchizApathy's objectives. WP1, conducted at TUM, aims to identify neuro-computational biomarkers of apathy in schizophrenia, focusing on potential reward processing alterations. 40 patients will be classified as apathetic or non-apathetic based on the Apathy Evaluation Scale. They will complete an effort-based decision-making (EBDM) task, an incentive motivation (MID) task, and a reinforcement learning (Go/NoGo) task. In addition, multimodal neuroimaging (structural MRI, DTI and rs-fMRI) will be employed to quantify alterations in morphometry, and in structural and functional connectivity within effort and reward processing networks. Computational modeling parameters of effort and reward processing will be associated with potential neurobiological alterations and compared between the apathetic and non-apathetic groups[2,p1]. WP2, conducted at UCBL, aims to test the role of the ventral striatum, a key node of the reward system, in effort-based decision-making among apathetic patients, investigated through assessing the impact of non-invasive brain stimulation on effort engagement. 20 apathetic patients will undergo temporal interference stimulation (TIS) of the ventral striatum[8], a non-invasive electrical stimulation approach previously employed by Dr. Derosiere and his former PhD student (P. Vassiliadis)[p6]. E-field modeling and fMRI will quantify the impact of TIS on striatal activityp[6]. Two separate sessions will involve TIS during the EBDM task using an intermittent theta burst stimulation protocol increasing striatal activity[9] and a sham stimulation, enabling the measurement of the stimulation's impact on the decision to engage in effort, as well as on effort and reward processing through computational modeling of behavior[2].

Proposed working plan: Months 1-5 (UCBL): Develop task battery and computational models for WP1 and 2. Punctual secondments at TUM for code development on reinforcement learning tasks. Months 6-18 (TUM): Conduct data acquisition and analysis for WP1. Months 19-36 (UCBL): Conduct data acquisition and analysis for WP2 and thesis writing. PhD supervisor Dr. Derosiere has successfully supervised 19 Master and 2 PhD students, including through international co-supervision programs, on topics related to effort-based decision-making[p1], reward processing[p7,p8] and brain stimulation[p9,p10]. He holds the Habilitation to Direct Research (HDR) and currently co-supervises 1 PhD student (current supervision rate: 50%).

[pX] Personal contributions

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The PhD student working on SchizApathy will be supervised by Dr. Gerard Derosiere (PhD, HDR), INSERM researcher at UCBL in France. The project will involve a tight collaboration with Dr. Franziska Knolle (PhD), group leader at TUM in Germany, where the student will realize secondments.

Main ArchiFun theme involved:

- ☐ Host-pathogen interactions;
- ☐ Mechanisms of bacterial resistance and cancer onsets;
- ☑ Neurodegenerative and autoimmune diseases;
- ☑ Translational research in prevalent diseases;
- ☐ Physiology and ecology;
- ☑ Neurosciences and cognition.