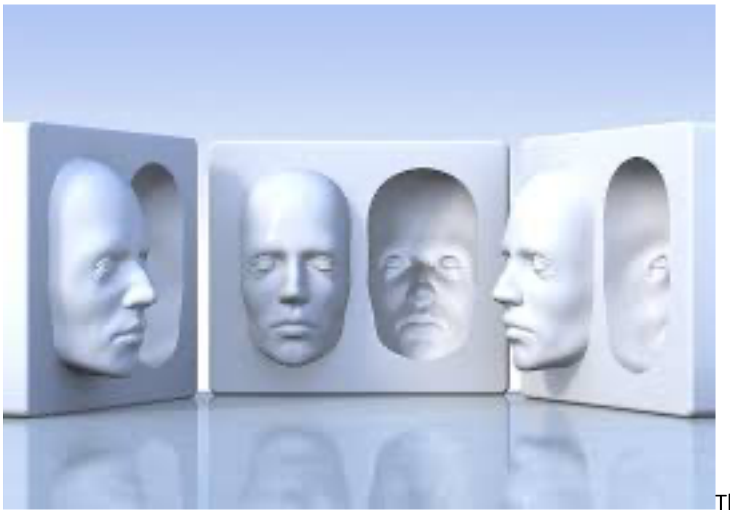
0000000101- MInDSwitches

1. EXCELLENCE (4 pages max)

1.1. Pre-proposal's context, positioning and objective(s)

The visual perception of the world around us is nothing like a passive and static photographic impression. Perceiving is essentially an active and dynamic decision process of the brain, relying on the momentary noisy sensory signals as well as on predictions based on some internal model (VonHelmholtz, 1896). Indeed, the information about our environment is often noisy or ambiguous at the sensory level, and it must be processed and disambiguated to yield a coherent perception of the world. For instance, in vision we only have access to two-dimensional (2D) projections of the surrounding 3D environment, which leads to an intrinsic ambiguity for perception. On the other hand, the expectancies, or beliefs, related to the internal model of the world do also come with some uncertainty and possibly with biases: the famous "hollow face illusion" illustrates well the common bias to interpret an ambiguous stimulus coherent with a human face as a convex, rather than concave, face (see Figure below). Since both sources of information are corrupted by noise and possibly biased, an efficient agent needs to take into account these limiting factors and reduce their impact as much as possible across time. There are good reasons to think that the brain computations underlying perceptual decisions are akin to recurrent probabilistic inference, whereby internal beliefs influence the early processing of visual information and, in turn, sensory prediction errors refine the internal model (Van Helmotz, 1896, Friston 2018, Kording 2014).



The « hollow face illusion » adapted from Science Photo Gallery

One of the limits of this approach is that most studies (when quantitative at all) have focused on homogeneous groups of healthy volunteers and shown a good correspondence between model predictions and experimental data only at the group level. Yet the inter-individual variability in these kinds of behavioural paradigms is very large. Rather as a nuisance, it could be an opportunity to study the underlying mechanisms for such variability, both across neurotypical populations and across pathological conditions. This computational psychiatry approach (Valton et al, 2017) is the one that we will adopt for the translational part of the PhD project. We will combine computational approaches, collection and analysis of behavioural and EEG data from schizophrenic and neuro-typical populations, as well correlational assessment of personality traits.

The phenomenon of multistable perception offers a particularly favourable condition to study dynamic perceptual decision. In this condition, the sensory ambiguity inherent to some visual stimuli pushes the agent to select one among multiple competing, mutually exclusive interpretations (percepts) associated with the single physical stimulus presented. It is also particularly amenable to computational approaches based of probabilistic models of perceptual decision-making. We will focus in particular on a moving bistable stimulus, known as kinetic depth effect (KDE) paradigm, or as Structure from Motion (SFM). The community has clustered for some time around two (non-mutually exclusive) explanations of percept reversals, one favouring neuronal processes (mutual inhibition, neural fatigue and noise in early sensory areas), and the other favouring higher-level mechanisms such probabilistic inference models. In the MInDSwitches we will in fact combine the two approaches. Our framework, while "high level" and normative, is also neuro-mechanistic since it is based on propagation for activity/evidence within recurrent, hierarchical brain networks. It accounts for inter-subject variability as different levels of inhibitory controls on this propagation (see section on circular inference).

1.2. Interdisciplanary and intersectoral dimension of the project

Axis 1: Computational approach.

We previously proposed a model of perceptual inference based on circular inference (CI) (Deneve and Jardri, 2013). This general approach views neural propagation of activity in the hierarchical brain as a form of propagation of sensory evidence and prior information, until the circuit converges to a coherent interpretation/percept of the visual scene. We showed that the capacity of such networks to reach a rational decision is directly linked to its capacity to maintain a tight balance between excitation and inhibition. E/I balance prevents uncontrolled reverberation of information in the circuit, where our own expectation could be mistaken for sensory evidence or vice-versa (i.e., CI). We hypothesized that the level of E/I balance varies from subject to subject, and is more severely affect in psychiatric disorder with a psychotic dimension, such as schizophrenia. We validated the model by fitting it to neurotypical and schizophrenic patient's behaviour in probabilistic choice task and bistable perception tasks (Jardri et al , 2017, Leptourges et al, 2020). This part of the project will continue this line of work by applying the model to dynamic aspects of bistable perception, incorporating eye movement control (see axis 2), and identifying features in data that can differentiate it from other predictive coding approaches. Finally, mesoscopic neural modelling of CI (Bouttier et al, 2022) will generate predictions testable with EEG recordings during a bistable perception task, allowing parametric analysis of behaviour and neural activity linked to perceptual inference (see axis 3).

Axis 2: Behavioural studies.

We will make use of bistable visual stimuli to access the temporal dynamics of ongoing perceptual decision processes and address the causes of perceptual reversals in the broader context of perceptual decision making as an inferential process. To do so, we will manipulate experimentally the expectation in favour of one of the possible percepts, by means of non-ambiguous priming stimuli, as well as the amount of sensory information available (Damasse et al., 2018; Pasturel et al. 2020; Wu et al. 2021). Perceptual dynamics and reversals will be measured both by the subject's own reports, but also by their eye movements while tracking the (apparent) motion of the (3D structural interpretation of) the moving stimuli. That is, we will exploit the incessant rotations of our eyes, or voluntary orienting eye movements (essentially saccades and smooth pursuit), which align the region or object of interest in the scene with the highest resolution part of our retina, the fovea. Note that Eye movements have not been appropriately exploited so far in this field, reinforcing the novelty of the approach. This part of the project will be reinforced by a current ANR project (Vision-3E, PI Anna Montagnini) on the correlational and causal role of eye movements in perceptual switched, where we obtained encouraging results suggesting that eye movements can be used as time-continuous markers of ongoing decision processes. This allows to punctually avoid verbalization or explicit motor responses to communicate the perceptual switches. Eye movements can be recorded with a completely non-invasive setup in all kinds of participants, including psychiatric patients, during tasks with little or no instructions and constraints. Interestingly, recent studies on ambiguous motion direction discrimination (not bistable stimuli) in presence of a probabilistic bias favouring one direction over the other, have revealed an unexpected dissociation (Wu et al. 2021). Whereas anticipatory eye movements were observed in the expected direction, and more so when the probability of occurrence of that direction increased, the perceptual choice was coherent with a bias favouring the rare direction. We are currently exploring whether this dissociation is also observed in the bistable KDE paradigm. Depending on these results, eye movements will be introduced as a cue, a prior or a response, in the CI model for bistable perception.

These protocols will be adapted to be tested on a cohort of psychiatric patients (and controls), and combined with EEG recordings in the group of **Pr Renaud Jardri**, **PUPH in University/CHU Lille**, with who we have an ongoing collaboration. We expect that the schizophrenic patients, exhibiting more of a specific form of CI (namely, reinforcement of sensory evidence at the detriment of the prior) will have less stable perception of weaker influence and prior and sensory cues, and that it will correlate with the severity of positive symptoms (PNASS-P). The student will analyse data collected in Lille, but also visit Renaud Jardri's team regularly to have training ad participate in patient testing and EEG recording protocols.

Finally, in collaboration with **Peggy Series** in the **Computational Psychiatry Lab, Edimburgh** We will test large cohorts of neurotypical subjects and relate the fitted model parameters (e.g. the amount of CI) with the subject's personality traits (e.g. assessed using questionnaires), relying on the expertise of Peggy Series. In a prior study, Deneve and Jardri found an interesting link between the amount of circularity/perceptual stability and the tendency to believe in conspiracy theory, as well as a reverse correlation with stress (Leclerq et al, 2024). However, another related study in P Series did not find such a corrlation with autistic traits (Angeletos et al, 2021).

Axis 3: Neuroimaging studies.

Behavioral and EEG data during bistable perception in neurotypical and schizophrenic patients are already (i.e. currently) being collected in Renaud Jardri's laboratory. After collecting these data from our collaborator, the student will perform of model free and model-based analysis of these behavioural data and EEG data, to investigate the neural basis of bistable perception and perceptual inference in general. We hope to go far beyond the classical ERP (event-related potential)-based approach using a 3-pronged approach. *First*, we will reverse correlate the behavioural model parameters to the neural activity in different channels, identifying which area of interest could encode different components of the model. *Second*, we will fit neurally plausible, mesoscoptic neural models where network activity is interpreted as representing an update on the current state of beliefs from sensory to higher-level areas and back. We will assume that the balancing inhibitory control is delayed, leading to oscillatory dynamics and the multi-component response observed in ERP in response to unpredictable events (or, in this case, presentation of the stimulus but also perceptual switches). And *third,* we will use AI-methods to apply innovative data analysis methods developed in our, Renaud Jardri's and Peggy Series's group. For example, we may use variational autoencoder (VAEs) to detect the perceptual switches and relate them to the neural model dynamics. We will also use all areas outside on the window of interest (unmodulated by the percept) to predict and cancel the activity of the area of interest (modulated by the percept), thus keeping only the part of the part of the response modulated to the task. This method gave very promising results on Voltage dye, intrinsic imaging and calcium imaging data collected in animal subjects, but we have yet to apply them to human data and EEG data. We expect that correlates of the percept will be present in the entire visual hierarchy and propagate from mid-level to high level and low-level area. The functional connectivity between sensory and high level areas should correlate with the stability of the percept on a subject-by-subject basis and be degraded in schizophrenic patients.

Gender dimension

The MInDSwitches project aims at elucidating the computational mechanisms underlying the dynamics of perceptual decision across time. One of the objectives of the project is to estimate the individual best-fit model parameters which can account for the observed inter-individual differences in the combination of ambiguous visual information and the predictions of the internal model. We will do that to identify possible group differences (e.g. between schizophrenic patients suffering of hallucinations and the healthy population) in those informative parameter. Our working hypothesis is that the sensory input is overweighted (or even *reverberated*) in schizophrenia. In addition, we also aim at correlating more subtle variations of the same parameters with a multifactorial characterization of a relatively homogenous population of healthy volunteers. One of these factors will naturally be the participant's gender, although at this stage the correlational analysis will be purely exploratory, as we do not have a specific hypothesis about the effect of gender on the integration of internal expectations and sensory inputs. We will constitute gender-balanced samples of participants, as much as possible, for all the experimental tasks

2. IMPACT (2 pages max)

2.1. Expected impact of the project on the candidate's career

The candidate will take advantage of the diverse competence of the supervisors and collaborators of the project, ranging from visual psychophysics and eye movements, to models of probabilistic coding, recurrent networks and neuronal population dynamics and to clinical screening and diagnosis of psychiatric diseases. This enriched portfolio, at the crossroad between physics, mathematics, biology and medicine will be a crucial plus for the PhD student's career. On the one hand the theoretical understanding and the computational modelling of brain functions have become increasingly valuable skills for the new generation of neuroscientists and they are highly requested in the calls for postdoc positions in the best international laboratories. On a longer term scale, these skills constitute probably an essential mindset to avoid that massive computing resources drive the future of research rather than the scientists' choices (e.g. Summerfield & Miller, 2023).

On the other hand, despite the fact that the research career in neuroscience and the clinical practice remain unfortunately very compartmentalised in France, at the international level new profiles of clinicians seem to emerge, with a strong interest and know-how in the biological and computational fundamental processes underlying the normal function and the dysfunction of the brain. Fostering the dialogue between researchers and clinicians, on the ground of a large shared knowledge is one of the challenges of the European scientific policy and of the next generation of researchers and medical doctors. The PhD student involved in the MInDSwitches project will be trained exactly with this strong motivation.

2.2. Expected impact for the thematic axis

The project is deeply integrated in the *Health and Well-being* thematic axis, I particular for the perspectives on the assessment and early diagnosis of psychiatric diseases. Psychiatric diagnosis and therapies suffer dramatically of a lack of global understanding of the general underlying neurofunctional mechanisms. We hope that our study will help clarifying those kinds of mechanisms, within a solid theoretical framework and the possibility to quantify individual deviations from the average performance. As a speculative example, if our study will provide insight, as we hope, to understanding hallucinations in schizophrenia as a manifestation of aberrant recurrent signals in the circuits sustaining visual perception, we believe that this result will shed new light on this psychiatric disorder and facilitate the development of novel treatments, including behavioural ones.

Furthermore, taking into account in a principled way the interindividual differences in healthy and pathological behaviour is a major challenge for the health and well-being axis in the near future: we think that thorough computational modelling and individual fitting of data is the best methodological approach to this challenge. The MInDSwitches project follows exactly this line.

2.3. Dissemination, exploitation and communication activities planned

Publishing three original scientific articles in peer-reviewed international specialistic journals is one of the main objectives of the project. These articles will be integrated in the final PhD thesis which will be made freely available on the HAL repository.

The original results will also be presented at national and international conferences either focusing on vision/oculomotor research (GDR Vision, VSS, ECVP…) or on theoretical/computational cognitive neuroscience (CNS, CCN, Cosyne…), or more generalist ones (Neurofrance, SfN, FENS…). Likewise, the student will be encouraged to present the results to the teams of the non-academic partner, at Lille hospital, as well as at the host department of the international partner, at Edinburgh University.

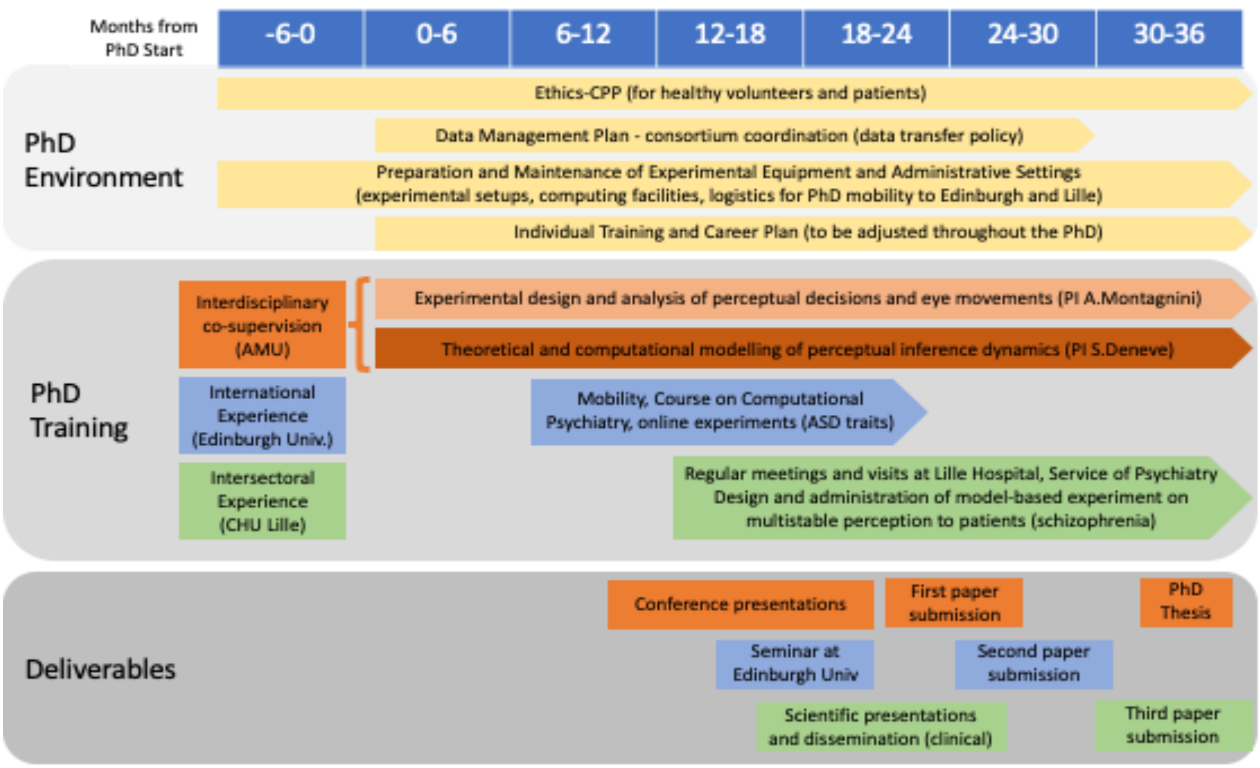
The supervisors are regularly involved in initiatives of dissemination to the general public (Brain Awareness Week, Open days for middle school pupils…). Dr A.Montagnini is the co-director of the PhD program in Neuroscience of Aix-Marseille University which, among other training events, organizes on a regular basis a thematic clinical day (one on ASD and neurodevelopmental disorders is planned for 2026 and schizophrenia for 2027). Therefore, the PhD student will have multiple chances to present the results of her/his project to an audience with a large panel of expertise, in the clinical and fundamental research

3. IMPLEMENTATION (2 pages max)

3.1. Work plan

The material, numerical, ethical and administrative environment necessary for the smooth development of the PhD project will be prepared in advance of the PhD starting date. In particular, all partners will make sure that the required ethical approval is available from the very beginning of the project. Note that in Marseille we already have a valid ethic approval for the visual psychophysics and eye movement experiments on human volunteer: this document is valid until the end of 2027, thus we will need to apply for a prolongation to cover the whole PhD duration. The clinical partner in Lille hosts routinely psychiatric patients and administers several behavioral and physiological tests to them, under the ethical approval of the national health system. All partners comply with the local and EU rules for data management and for the confidentiality obligation concerning personal information of participants. The sharing of human data among the project's partners will in all cases occur in anonymized form.

The graphic Gantt chart below illustrates the foreseen (yet approximative) timeline of the project. The PhD student will first familiarize with the relevant literature in the two domains of expertise of the supervisors, A.Montagnini and S.Deneve, in parallel, with the objective to root the design of the sensorimotor paradigms on a solid knowledge of the theoretical framework and on specific computational predictions. The secondment at Edinburgh University (ideally occurring within the first year of the PhD) will strongly contribute to this aim, providing a unique methodological and theoretical training in computational psychiatry to the PhD student. The foreseen participation of the PhD student in a large-sample online experiment (coordinated by Prof. Seriès) aiming at correlating



personality traits (along the dimension of Autistic Spectrum Disorder) with human visual perception will be completed during the 2nd year of PhD, hopefully leading to the submission of a manuscript by the first half of the third year. The first set of model-based experiments will be completed and results analyzed, under the main supervision of A.Montagnini, between 12 and 18 months after PhD onset (with a manuscript submission right after that). At this point, depending on the results, we expect to proceed with 1) the design and implementation of a novel experimental paradigm to test schizophrenic patients at CHU-Lille, in close collaboration with Prof. Jardri and/or 2) a refinement of the model, under the supervision of Dr S.Deneve and the elaboration of new predictions to be tested experimentally in healthy participants and patients. We expect that this second phase will be completed between 24 and 30 months. In the worst-case scenario this timing will allow enough time to write the third manuscript to be submitted for publication and the final thesis manuscript. Alternatively, if the second set of experiments is completed by 24 months, the PhD student will have the chance to participate in the analysis of EEG recordings collected at CHU Lille, enriching her/his portfolio of competences, and potentially providing a novel, electrophysiological validation of the theoretical framework of probabilistic inference for perceptual decision.

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