PERCEPTION ET INTÉGRATION SENSORIELLE DANS LES PHASES PRÉCOCES DES TROUBLES PSYCHOTIQUES

PERCEPTION AND SENSORY INTEGRATION IN THE EARLY PHASES OF PSYCHOSIS

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Description de la problématique de recherche - Project description

Les troubles psychotiques sont parmi les troubles mentaux qui ont le plus d'impact du fait des dommages personnels et familiaux élevés qu'ils engendrent. Mener des recherches dès le début du processus psychotique est essentiel pour avoir accès aux principales caractéristiques physiopathologiques de la maladie, avant que tous les processus pathologiques ne soient fixés et que les médicaments n'aient des effets sur les fonctions cérébrales. Il y a désormais un consensus scientifique sur la nécessité de poursuivre les recherches fondamentales et thérapeutiques sur les troubles psychotiques en appliquant une stratégie par stades, qui différencierait les premiers stades, tels que l'Etat Clinique à Haut Risque de Psychose (ECHR-P) et le Premier Episode de Psychose (PEP), de stades plus avancés tels que la schizophrénie. L'application directe de cette perspective physiopathologique consiste à identifier les meilleurs marqueurs permettant de prédire la progression de la psychose. Cependant, bien que les aspects physiopathologiques aient été largement explorés dans la schizophrénie, un effort de recherche important est encore nécessaire pour comprendre les mécanismes neuronaux sous-jacents et mieux prédire le risque de progression de la psychose aux stades les plus précoces.

Les troubles de la perception sont éléments clés de la compréhension des psychoses. En plus des hallucinations et distorsions sensorielles observées cliniquement, il existe désormais une littérature très large démontrant des atteintes neurocognitives auditive et visuelle dans les psychoses chroniques. Toutefois, dans les phases précoces de psychoses, si les distorsions sensorielles ont une haute valeur clinique pour évaluer le risque de transition, il existe encore peu de données sur la neurocognition auditive ou visuelle.

Ce projet a pour objectif d'explorer les traitements perceptifs d'entrée et intégrés chez des patients CHR-P, en comparaison à des patients en premier épisode psychotique et des volontaires sains. Nous faisons l'hypothèse de perturbation neurocognitives dès les premiers stades, en lien avec les distorsions sensorielles. Nous explorerons les fonctions visuelles à l'aide de tests mesurant le traitement de l'information dès son entrée dans le système visuel, mais aussi sa transformation en un tout cohérent, comme dans un visage, ainsi que la manière dont elle est interprétée en fonction de nos attentes. Nous étudierons aussi la perception auditive, à l'aide de tests mesurant la perception auditive d'entrée du signal mais aussi la manière dont certains sons sont interprétés dans un contexte émotionnel. Enfin, nous nous intéresserons à la manière dont le temps est perçu . Un suivi d'un an chez les patients avec ECHR-P mesurera si certains marqueurs sensoriels prédisent le risque de progression de la psychose.

Ce projet repose sur le recrutement d'une cohorte de patients sur quatre centres d'intervention précoce tous adossés à des équipes de recherche reconnues pour leurs travaux sur la perception. Nous utiliserons des marqueurs du fonctionnement sensoriel éprouvés, pour lesquels il existe des données préliminaires dans les psychoses chroniques. Le consortium de recherche est adossé au RHU Psycare dont il utilisera les standards de recrutement.

Psychotic disorders are among the most impactful mental disorders due to the significant personal and familial consequences they entail. Conducting research from the very onset of the psychotic process is essential to accessing the core pathophysiological characteristics of the disease, before pathological mechanisms become entrenched and before medication influences brain function. There is now a scientific consensus on the need to pursue both fundamental and therapeutic research on psychotic disorders using a staging approach.

This strategy differentiates early stages, such as the Clinical High Risk for Psychosis (CHR-P) state and the First Episode of Psychosis (FEP), from more advanced stages such as schizophrenia. The direct application of this pathophysiological perspective involves identifying the best biomarkers to predict the progression of psychosis. However, while the pathophysiological aspects of schizophrenia have been extensively explored, significant research efforts are still needed to understand the underlying neural mechanisms and improve the ability to predict psychosis progression at its earliest stages.

Perceptual disturbances are key elements in understanding psychosis. Beyond the hallucinations and sensory distortions clinically observed, a vast body of literature has now demonstrated auditory and visual neurocognitive impairments in chronic psychosis. However, in the early phases of psychosis, while sensory distortions have high clinical value for assessing transition risk, there is still limited data on auditory and visual neurocognition.

This project aims to explore both early-stage and integrated perceptual processing in CHR-P patients, comparing them to individuals experiencing a first episode of psychosis and to healthy volunteers. We hypothesize the presence of neurocognitive disruptions from the earliest stages, linked to sensory distortions. We will investigate visual functions using tests that measure information processing as it enters the visual system, its transformation into a coherent whole (such as face perception), and how it is interpreted based on prior expectations. We will also study auditory perception through tests that assess both the initial processing of auditory signals and the way certain sounds are interpreted in an emotional context. Lastly, we will examine how time perception is altered. A one-year follow-up of CHR-P patients will assess whether specific sensory markers predict the risk of psychosis progression.

This project is based on the recruitment of a patient cohort across four early intervention centers, all affiliated with research teams renowned for their work on perception. We will use validated sensory function markers for which preliminary data already exist in chronic psychosis. The research consortium is affiliated with the RHU Psycare initiative and will adhere to its recruitment standards.

Thématique / Contexte

Psychosis is one of the mental disorders with the largest impact due to high personal and family costs. This pathology occurs in adolescence and early adulthood. The earliest possible identification of the first disturbances is a major clinical and scientific challenge. Observing the clinical and neurocognitive events that precede the emergence of psychosis is essential to identify the factors that precipitate the transition from a vulnerable state to a pathological state. Promoted in the scientific literature for more than 20 years, the early intervention approach aims to identify vulnerable individuals and facilitate their engagement in care. Research on risk assessment in the first stages of psychosis led to a distinction between an earlier state called Clinical High Risk for Psychosis (CHR-P), and the full blown First Episode of Psychosis (FEP). CHR-P is consensually defined as an association of risk factors for psychosis, including attenuated psychotic symptoms and functional impairments in help seeking individuals. Recent consensus work points to the need for further basic and therapeutic research into psychoses by applying a staging strategy that would differentiate the earliest stages such as RHC-P and FEP from later stages such as schizophrenia. Building research at the very beginning of the psychotic process is crucial to give access to core pathophysiological features of the disease before all the pathological processes are fixed and before medication has side effects on brain function. The direct application of this pathophysiological knowledge is to identify the best markers predicting the transition from CHR-P to FEP. As it stands, only 30% of the individuals with CHR-P will develop a FEP, and markers are critical to predict which individuals will make the transition and thus best adapt early intervention care. Basic sensory processing, especially visual and auditory processing, is increasingly recognized as a key feature of psychosis. In addition to their critical role in hallucinations, sensory functions are in fact involved in the personal experience of psychosis, as distorted perceptions of the world have been largely reported by patients and psychiatrists. Besides, there is strong experimental evidence concerning sensory neurocognitive deficits in chronic psychosis. In schizophrenia, behavioral and neurophysiological studies repeatedly showed visual deficits from the retina to the integration of visual information into complex percepts and also alterations of early auditory processing, from basic functions to higher order integrated functions such as attention, memory, language, cognitive control, working memory and processes involved in social interaction. Basic sensory perturbations, which also include how perception is timed, can impinge on more complex visual abilities such as visual or auditory emotion recognition. Such difficulties would affect the individuals' ability to connect to and perceive their environment. Finally, scientific evidence in chronic psychosis positions sensory deficits as intermediaries between neural mechanisms and clinical symptoms of psychosis. However, despite the considerable evidence of impairment of basic sensory functions in schizophrenia, less is known about the state of these functions in the early stages of psychosis.

Objectifs

The project aims to compare the basic and integrated visual and auditory processing in early stages of psychosis (Clinical High Risk for Psychosis CHR-P and First Episode Psychosis FEP). We will explore the auditory and visual sensory processing to investigate three dimensions:
- understanding of the pathophysiological mechanisms of psychosis using the two sensory processes as models of information processing;
- implication of sensory processing in symptomatology such as sensory distortions or hallucinations;
- use of sensory processing as a potential marker of the risk of progression to psychosis. One-year follow-up of individuals with CHR-P will allow us to evaluate which sensory dysfunctions predict the progression of psychosis.

Méthode

Using behavioral computerized tasks, we will investigate visual functions using tests that measure information processing as it enters the visual system, its transformation into a coherent whole (such as face perception), and how it is interpreted based on prior expectations. We will also study auditory perception through tests that assess both the initial processing of auditory signals and the way certain sounds are interpreted in an emotional context. Lastly, we will examine how time perception is altered. A one-year follow-up of CHR-P patients will assess whether specific sensory markers predict the risk of psychosis. progression. See below for behavioral tasks details:

- Early visual processing
This task aims to compare the low level achromatic luminance contrast perception using the pulsed pedestal paradigm. This robust behavioural task aims to discriminate the functioning of mano- and parvocellular perception, which convey information from the retina to visual cortex. Based on previous literature, we hypothesize that patients in the early phase of psychosis are hyperactive to stimuli biased toward the magnocellular pathway. Participants will have to detect a briefly presented (45ms) low-contrast Gabor patch in two different conditions. In the pulsed pedestal condition, the target is preceded by an adaptation period consisting of the presentation of a high luminance background field. During the target presentation, the luminance of the background field is suddenly decreased in order to saturate the magnocellular pathway and to favour the parvocellular processing. During the steady pedestal condition, there is no sudden change of the luminance of the background, and briefly presented targets are preferentially processed by M-pathway. Four spatial frequencies will be tested (0.25, 0.5, 1 and 4 cycles/degree) in a two alternative forced choice staircase procedure. After checking the compatibility of the data with parametric analyses, contrast sensitivity values will be compared with an ANOVA with group as between subject factor and presentation conditions and spatial frequency as within subject factor. A complementary measurement conducted on the sample of participants recruited at the Nancy centre (N=25) aims to measure retinal functioning in the early phases of psychosis. We will measure retinal functioning by flash and pattern ERG according to ISCEV standards with a Metrovision MonPackOne system. Data will be analysed in relation to the subsequent visual processing.

- Facial affect recognition task
This task 2 intends to substantiate a downstream visual process, i.e. aptitude in decoding emotion in faces, in order to determine how this critical impairment documented in schizophrenia relates to early visual processing specifically, and basic perceptual disturbances in general, in the context of early stages of psychosis. Partner 2 has a large experience in conducting facial affect recognition tasks in patients with schizophrenia, both behaviorally and in imaging. Here, we propose to use a novel ecological facial affect recognition task based on various intensities of facial affect (0% to 100% of affect expression), as previous work has shown that moderate intensities are more sensitive and discriminative to identify cognitive biases. The task includes a total of 240 stimuli presented in a randomized order, 8 identities per emotion (4 males and 4 females). The stimuli are obtained by morphing between neutral (0% expression) to expressive (100%) faces from Ekman's validated databases. The task offers a basic (and therefore robust) and precise evaluation of abilities to decode emotion in faces which the team has used in several neuropsychiatric conditions. The largest effect sizes were observed in schizophrenia. Specifically, the task was previously performed with a sample of patients with schizophrenia (n=49) compared to healthy controls (n=35). Groups were matched on gender, age and level of education. Our preliminary findings confirmed the overall deficit in facial affect recognition in patients with schizophrenia (U=199; p=0,003; d= -0,492). The impairment was most significant with the emotion of sadness, disgust and fear and most apparent for the 40% and 60% intensities. A correlation was found in patients between the deficit in facial affect recognition and the desorganisation PANSS dimension.

- Circular inference
This task aims at exploring the relative corruption of priors and visual inputs in the final perceptual representation built by three populations of participants: CHR-P, FEP and control subjects. To do so, we propose to use a bistable task able to maximise perceptual uncertainty. We will manipulate sensory evidence and prior knowledge at different time scales to explore the interaction between prior and likelihood that could be best accounted for by the Circular Inference (CI) model. Based on past works from the team, we will refer to different Necker Cubes to induce bistable perception, in which the 2D figure is perceived as a 3D cube with either the left or the right side located closer to the observer. Sensory evidence will be manipulated by adding visual cues in the form of contrasts. A further manipulation of the prior will be achieved by providing correct or wrong information to the participants about which interpretation was generally stronger (explicit prior). During each run, one version of the cube will be continuously presented to the participants, who will be asked to discontinuously report their dominant percept by pressing a button every time a sound is heard. Each run will consist of 25 sound trials (mean inter-sound interval = 1.5 seconds). The experiment will consist of 30 runs separated into six blocks of five runs each. Adopting a computational phenotyping approach based on CI, the fitted parameters will be used to better characterise how CHR-P, FEP and healthy participants process information to reach perceptual decisions. After checking for normality of the residuals, an analysis of covariance will be used to compare the impact of the CI parameter values on visual stability, with clinical features as covariates.

- Early auditory processing
A large body of evidence has demonstrated impairments in early auditory processes in schizophrenia using behavioural “tone-matching” paradigms. This computerised task consists in presenting to subjects 300 pairs of non-verbal short basic “beeps” tones (300 ms) in series with a brief silent interval between tones of each pair (500 ms). The pairs were divided into 9 randomized blocks (3 blocks per basic feature : frequency, length, loudness). The sounds are presented through headphones. Within each pair, tones are either identical or differ in one basic feature by specified amounts in each feature (Δ1.5%, Δ2.5%, Δ5%, Δ10%, Δ20%, and Δ50%). Participants have to respond by pressing “same” or “different” on a 2-button press. Behavioural performance outcomes (percent correct responses, time reaction) will be used in innovative computational analyses (e.g., drift-diffusion model). Early auditory testing procedure lasts approximately 30 min, with several minutes breaks between each task. The absence of severe hearing impairment is confirmed by a simplified audiogram. We also exclude participants who are professional musicians, as musicians display superior ability to discriminate fine auditory changes.

- Auditory emotion processing
Emotional auditory stimuli will be chosen from the validated, standardized and published Montreal Affective Voices battery. A battery of 90 interjections (non-verbal) was built, corresponding to different emotions. The interjections from the battery were recorded by 10 different actors, 5 men and 5 women. Each emotion was recorded at varying degrees of intensity. For the task, the following basic emotions will be used: joy, sadness, disgust, anger, fear and neutral. For each of the 6 stimuli the subject will have to make a forced

choice among these 6 stimuli. Then he will have to rate on a Likert scale his level of certainty about the selected emotion.

- Temporal dynamics of perception
The aim of this task is to explore the ability of CHR-P and FEP to prepare in time, by benefiting from the passage of time and from the prior history of 'when' the to-be-detected target occurs. The link between time and self, together with the description of self disorders prior to psychotic conversion, justifies this exploration. We will manipulate inter-trial -stimulus intervals in the facial-affect recognition and auditory tasks that are well adapted to examine time expectation in CHR-P and FEP. This manipulation is incidental and does not change the task. We will randomize the delay between the initial warning signal of the trial and the target that follows, within an interval of 700 to 1200 ms. We will randomize the delays between the two successive stimuli. The unidirectional flow of time automatically provides a degree of predictive power. The 'hazard function' measures the increasing conditional probability (and, hence, increasing sense of temporal expectation) over time that an event will occur, which translates into faster RTs at longer intervals. It is precisely this ability to increase the sense of temporal expectation that appears to be impaired in chronic patients with disorders of the sense of self. In preliminary results in CHR-P and FEP, the ability to benefit from prior experience appeared to compensate for a fragile hazard function. It is this possibility that we will evaluate by measuring trial-to-trial influences: we expect FEP and CHR-P to be more surprised than controls when a target occurs earlier than expected. We also expect FEP and CHR-P to benefit less than controls from the passage of time. The results are expected to be related to disorders of the sense of self, and thus possibly to index mechanisms that are complementary to perception per se. The measures may thus improve the sensitivity of the tests considered as a whole. Additionally we will verify whether the use of stimuli with an emotional valence (faces, auditory stimuli) aggravates timing difficulties (this issue is not straightforward given our measure is incidental).

Résultats attendus - Expected results

We hypothesise the existence of basic perceptual disturbances in early stages of psychosis, in relation to sensory distortions and independently of medication.

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Conditions scientifiques matérielles et financières du projet de recherche

The MOTISCHIZ project is positioned at the local level at the Grenoble Institute of Neurosciences (U1216, BASTIN team) and the support of local psychiatric hospital structures (University Psychiatry Service of CHU Grenoble Alpes and CH Alpes-Isère for the recruitment of study subjects). The project also occupies a strong position at the national level because the subjects will be recruited from 5 university centers: (Grenoble, Lyon-Saint-Etienne, Nancy-Strasbourg, Paris, Lille).

The project is already funding for the practical implementation (equipment, compensation for subjects, cost of behavioral explorations). The project are currently being examined by the Ethics board (Committee for the Protection of Persons).

Objectifs de valorisation des travaux de recherche du doctorant : diffusion, publication et confidentialité, droit à la propriété intellectuelle,...

The role of the PhD student who will work on this project will be to invest in these different missions:
- Pilot testing and optimization of the behavioral battery of tasks, and interactions with other study centers for tasks homogenization.
- Collaboration in motivation data collection: assistance in welcoming the patient, performing the tasks.
- Statistical analyses of the various judgment criteria of the study using frequentist statistical methods. Bayesian approaches and computational models developed within the research team attached to this project (U1216, Brain Behavior and Neuromodulation team) can be used by the PhD student.
- Oral communications and writing of scientific articles with an international dimension related to the study with the objective of publication in journals with high impact factor and large reading committee.

In total, the PhD student will receive training and develop comprehensive expertise in the acquisition and processing of behavioral data, which is a particularly important tool in neuroscience research. To do this, everything will be done so that the PhD student can collaborate closely with the researchers and methodologists involved in the study, at each investigator center. If the PhD student wishes, he / she can attend the behavioral sessions which will take place in the associated investigative centers (Lyon-Saint-Etienne, Nancy-Strasbourg, Paris, Lille).
The PhD student will be encouraged to join working groups and national research networks in psychiatry (example: Research Group of the Institute of Psychiatry https://institutdepsychiatrie.org/gdr-psychiatrie- et-addiction /) and in connection with modern visions of research in neurosciences (example: Open Science) in order to enhance one's research activity and prepare for one's future.

Profil et compétences recherchées - Profile and skills required

La/le candidat(e) sélectionné(e) doit avoir des connaissances théoriques et pratiques scientifiques validées par une maîtrise dans le domaine des neurosciences, des sciences cognitives, de l'ingénierie et/ou de la neuropsychologie.
La/le candidat(e) sélectionné(e) devra avoir des compétences en programmation informatique, statistiques, modélisation informatique et traitement du signal (Matlab, R, SPSS ou Python).
La/le candidat(e) sélectionné(e) développera des paradigmes comportementaux expérimentaux, collectera des données comportementales, analysera et interprétera des données, contribuera à des présentations et publications scientifiques.
Applicants should have science knowledge and practice validated by a Master's degree in the field of neurosciences, cognitive sciences, engineering or neuropsychology. The selected candidate should have skills in computer programming, statistics, computational modeling and signal processing (Matlab, R, SPSS or Python). The selected candidate will develop experimental behavioral paradigms, collect behavioral data, analyze and interpret data, contribute to scientific presentations and publications.

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