The general aim of our research project is to study the pathophysiological mechanisms of schizophrenia. Schizophrenia is a major public health concern. One percent of the whole population suffers from this illness (about 600,000 patients in France) and this figure amounts to five percents if the related impairments are taken into account. The disease starts at adolescence or at early adulthood and has a chronic course. It induces a decrease in social and professional skills, which results in considerable human cost both for the patients and for their families. The illness also has a considerable financial cost for the community. Schizophrenia is now thought to result from the interaction of a genetic vulnerability and epigenetic and environmental factors that may be metabolic, toxic, lesional, psychological and sociological and exert their role at critical periods of development such as the prenatal, postnatal and adolescent periods. It is still unclear whether schizophrenia is a single disease or a group of conditions.

Our research project relies on the hypothesis that schizophrenia might be related to a pathophysiological mechanism common to the different clinical and etiological forms i.e., abnormalities of functional integration in the brain due to a disconnection among widely distributed brain areas. The project should enable us to build up an integrated pathophysiological representation of schizophrenia, taking into account the developmental origin of the illness, cognitive impairments and clinical symptoms, and a dysfunction of the striatal dopaminergic and thalamocortical systems. We use both clinical and experimental approaches.

**Clinical pathophysiology.** Our previous studies have contributed to reformulate traditional clinical psychiatry with the help of the concepts and methods of cognitive neuroscience. Updating of the clinical symptoms is a prerequisite to the development of the pathophysiology of schizophrenia. We have investigated cognitive impairments associated with schizophrenia. The strength of this approach derives from the introduction of an intermediate level of analysis, namely cognitive processes, making it possible to bridge the gap between the biological and clinical levels of analysis and carry out complementary clinical and experimental studies based on the notion of a continuum between
animals and humans. Our clinical studies have contributed to establish the existence and to understand the mechanisms of cognitive impairments in patients with schizophrenia. The studies all suggest schizophrenia is characterized by a difficulty to bind information, whenever attentional top-down processes are involved. This in turn would appear to lead to impaired coherent conscious representations, probably in relation with abnormalities in functional connectivity, which we contributed to show in fMRI studies.

Our work has identified several general principles that can guide rehabilitation of patients’ cognitive deficits. However, if we are to improve these techniques we require a better understanding of the relationships between the various cognitive and clinical symptoms. We shall explore which mechanisms it is that disturb the initiation of strategies and the building of coherent conscious representations. This will be done at different levels of analysis, in visual perception, episodic memory and metamemory. Concerning clinical symptoms, we will explore autobiographical memory impairments in relation with the sense of self and delusions. Cognitive disorders will also be explored in relation to their neurobiological substrate. We shall measure cognition simultaneously with functional and anatomical connectivity using fMRI, diffusion tensor imaging and EEG-MEG recordings. Clarifying how connectivity is altered in patients (interhemispheric vs antero-posterior, for example) is critical for the development of innovative treatments aimed at remediating altered synaptic plasticity.

Experimental pathophysiology. Animal models are used to gather proof of therapeutic concepts. We use animal models characterized by connectivity alterations. These models are explored by combining in vivo voltammetry (measure of neurotransmitter secretion) electrophysiological recordings (EEG with juxta- and intracellular recordings/marking), histology techniques and behavioural explorations. Two models are developed in the laboratory. In the first, functional dysconnection follows injection of NMDA antagonists in adult rats. In the second, reversible (TTX) blockade of the hippocampal formation in 8-day-old pups results in abnormalities in adult rat, i.e. altered liberation of dopamine in the nucleus accumbens and behavioural disturbances, especially on latent inhibition, that reflects the impact of memory and affect on behaviour. We use a third model, the STOP KO mouse model, which lacks a protein that stabilizes microtubules, and is characterized by altered synaptic plasticity. Very low doses of epothilone reverse synaptic plasticity abnormalities in the STOP KO mouse model. We shall check whether this drug reverses the electrophysiological and behavioural abnormalities observed in other models of modified connectivity in rats. Lastly, we shall explore the impact of deep brain stimulations on corticothalamocortical systems as an alternative therapeutic possibility.

Therapeutic implications

Our research project should contribute to develop innovative treatments. We will aim at improving cognitive remediation techniques and will explore possible therapeutics targeted at connectivity disorders.

Main publications of the laboratory


