

Thesis Title: “The centrality of both hippocampal-cortical structure and memory to negative symptoms after a First Episode of Psychosis”

Abstract

This thesis presents a series of longitudinal studies of First Episode of Psychosis (FEP) patients, emphasizing the dynamic nature of clinical, cognitive, and neuroanatomical changes in the one to two years following psychosis onset. Chapters 1 and 2 provide a general introduction and background information on the current state of knowledge from neuroimaging studies of patients with psychosis across different stages of the disorder. They also cover critical gaps in treatment strategies, particularly for negative symptoms, that largely stem from unknown biological mechanisms. Chapter 3 introduces the neuroimaging methodology that is used throughout the dissertation to study neurobiological alterations that underlie negative symptoms after a FEP. Chapter 4 includes the first pair of published studies to investigate the trajectories of limbic-neocortical maturation shortly after a FEP, where patients are stratified by negative symptom presentation. These studies demonstrate that patients with persistent negative symptoms not only vary greatly in terms of their clinical presentation but also have significantly altered neuroanatomical trajectories with age in the amygdala, hippocampus, prefrontal and temporal cortices. Chapter 5 investigates the source of such trajectories, introducing a novel white-gray matter contrast measure alongside a more commonly used measure of cortical thickness, to better understand the influence of changes in myelin proximal to the white-gray matter boundary. Relationships with verbal memory are also explored, adding an important cognitive factor that relates to negative symptoms. Findings from this chapter suggest that verbal memory is more strongly associated with expressivity deficits than another negative symptom dimension, amotivation. The intersection of expressivity and verbal memory is related to alterations in both white-gray matter contrast and cortical thickness in language-related regions of fronto-temporal cortices. This study demonstrates the presence of neuroanatomical changes near the inner edge of the cortex, positioning peri-cortical myelin as a key measure of interest for the final investigation in Chapter 6. This last manuscript chapter provides evidence that the coupling of intracortical and hippocampal microstructure, particularly apparent in myelin-rich hippocampal output regions, is reduced in patients with a FEP compared to healthy controls. Importantly, results from this chapter provide a biological mechanism with the hippocampus at the epicenter of neuroanatomical abnormalities associated with negative symptoms after a FEP. These symptoms also interact significantly with changes in verbal memory deficits, which is found to be a mediator of the significant relationship between hippocampal centrality and changes in negative symptoms after psychosis onset. Chapter 7 provides a final summary of these findings.

Altogether, this thesis provides evidence for dynamic changes that occur within fronto-temporo-limbic structures alongside changes in negative symptoms after a FEP. Neuroimaging measures that index myelin content were found to be sensitive in detecting such changes within a critical time window for therapeutic intervention. Specifically, Chapter 6 bridges findings from the first three investigations of this thesis and posits compromised hippocampal connectivity as a key factor underlying the course of negative symptoms after psychosis onset. Such a clear anatomical target holds promise for altering the pathophysiological course of closely related cortical targets that underlie the dysconnectivity aspect of psychotic disorders, which in turn may have an impact on clinical outcomes.

Résumé

Cette thèse présente une série d'études portant sur les patients ayant subi un premier épisode de psychose (PEP) et mettant l'accent sur la nature dynamique des changements cliniques, cognitifs et neuroanatomiques qui surviennent suivant un PEP. Les chapitres 1 et 2 sont une introduction générale et la mise en contexte de l'état actuel des connaissances sur les études en neuroimagerie