

## Abstract

More than a century has passed since a clear definition for schizophrenia was established, yet, the etiology, neuropathological and pathophysiological mechanisms of this psychiatric disorder still, to a large extent, remain to be elucidated. In the theoretical part of this dissertation, we review current classification and pathophysiology of schizophrenia, paying a particular attention to the findings from structural and functional imaging techniques. These techniques demonstrate that patients with schizophrenia tend to have reduced volume of grey matter, reduced integrity of white matter and a disrupted inter-regional functional connectivity (FC). The temporal association between structural changes, already detectable on imaging before symptoms appear, and development of disrupted FC remains to be uncovered. At the same time, current knowledge does not fully explain the link between disrupted FC and disturbed experience of self-awareness, a core symptom of schizophrenia. In addition, it is necessary to develop novel effective methods to prevent relapse and prevent the progression of neurobiological changes in the brain.

In the practical part of this dissertation, we designed a study with three different groups of subjects aiming to fulfil three key aims that would help us to fill the gaps in current knowledge. The first group contained only subjects who had experienced their first episode of schizophrenia (FES) – here, we evaluated the association between morphological changes in grey and white matter of the brain and FC. In the same population we then examined changes in regional FC in the context of disturbed self-awareness. Subjects in group 2 had more advanced stages of the disorder and were monitored by our telemonitoring system in order to prevent relapse episodes. Based on the obtained longitudinal data, we were able to detect when first prodromal symptoms appeared, aiming to intervene early and thus prevent a relapse episode and its accompanying neurobiological changes. The third group contained subjects with chronic schizophrenia and drug-resistant hallucinations. In this group, we assessed the effect of low-frequency, repetitive transcranial magnetic stimulation (LF-rTMS) on the intensity of auditory hallucinations (AHs) and dynamic EEG changes with FC evaluation (lagged phase synchronisation).

In the FES group, we confirmed relative reduction of grey and white matter volumes but not global connectivity. In the subsequent “task-related” functional MRI (fMRI) study we proved disrupted coordination in default mode network (DMN) and central executive network (CEN) during self-paced states aimed at identifying self-agency. Therefore, we shed some light on the pathological mechanisms behind experiencing disturbed sense of self, associated with first-rank symptoms in schizophrenia. In the second group, our longitudinal data analysis clearly demonstrated that relapse episodes can be successfully predicted by increased intensity of warning signs, which we were able to detect as early as 10 weeks before hospitalisation, that is, twice as early as had been assumed. In those with chronic schizophrenia, we established that a two-week course of LF-rTMS therapy decreased intensity of AHs, and was associated with depressed fast beta wave EEG activity (10.5 – 21Hz). At the same time, we proved the positive influence of active LF-rTMS therapy on connectivity in the same regions. These results confirm the assumption that LF-rTMS applied to regions in the brain associated with speech production reduces the intensity of AHs by modulating local aberrant electrical activity and depressing regional FC.

Overall, this study examined three different groups of schizophrenia subjects with different level of chronicity and confirmed morphological changes in brain at the initial stages of the disorder, disruption in coordination of the main neural networks associated with the sense of self as well as dynamic changes in functional connectivity with rTMS therapy. In addition, we have identified a suitable time point for effective tertiary prevention of relapse episodes and the morphological and functional changes associated with them.

**Keywords:** Schizophrenia, First-Episode Schizophrenia, Auditory Hallucinations, Grey Matter, White Matter, Functional Connectivity, Functional Magnetic Resonance Imaging, repetitive Transcranial Magnetic Stimulation, Electroencephalography, Relapse in schizophrenia