Neuroimaging markers of major depressive disorder: orbitomedial prefrontal cortex and beyond

Summary

Major Depressive Disorder (MDD) is a psychiatric syndrome characterized by various affective, cognitive and somatic symptoms which cause significant loss of functioning and distress in patients. MDD is multifactorial and among other factors, genetic load influences the development of the syndrome. Immediate (first-degree blood) relatives of MDD patients are at increased risk of developing MDD themselves. Neurobiologically, MDD is a connectivity disorder in which the functional communication within an extended cortical region, the orbitomedial prefrontal cortex (OMPFC) is disturbed. It is also a disorder characterized by abnormalities in affective processing regions, the function of which can be effectively studied using facial emotional expressions as stimuli. Early diagnosis and individually tailored treatment is instrumental for the alleviation of MDD. In order to improve current prevention, diagnosis and treatment strategies, it is important to discriminate between predisposing factors, precipitating conditions, manifestations of the current depressive episode and possible adaptation-to-disease or compensation processes. By studying large cohorts of patients, at-risk individuals and healthy controls, we can distinguish brain imaging MDD vulnerability markers (i.e. objectively measured biological processes present at both patients and at-risk individuals which precede the onset of the disease state) and MDD disease markers (i.e. objectively measured biological processes observed solely during the acute phase).

The aims of the current thesis were threefold: a) validate and extend data-driven methods based on MRI functional connectivity and graph theory to parcellate the cortex, b) apply these methods to systematically and in an unbiased way delineate functional connectivity markers of MDD vulnerability and MDD disease within an extended cortical region and c) identify trait biomarkers of BOLD changes during face processing in MDD. We achieved these goals by testing a cohort of participants with Major Depressive Disorder, first-degree family relatives of MDD patients and healthy controls. We used a non-invasive technique of in vivo cortical mapping based on MRI connectivity, as well as low frequency BOLD co-fluctuations during rest and BOLD activations during processing of affective face stimuli.

Chapter 1 introduces the basic concepts and tools used in the research described in the current dissertation. Some clinical and theoretical background of MDD is also presented together with the aims and outline of the thesis.

Chapter 2 describes the first study in which a novel parcellation method based on the intrinsic connectivity of voxels and the state-of-the-art Louvain modularity detection algorithm was applied to the study of the OMPFC, a cortical region significant for functions of reward, emotion and decision making. The study revealed that the left hemisphere OMPFC is

organized in 19 functional cortical fields in healthy controls. The way the fields were delineated replicated known cytoarchitectonic trends such as the cortical variation along two spatial gradients in the orbitofrontal cortex and the anterior versus mid-cingulate differentiation in the medial PFC. In addition to being neuroanatomically plausible, the delineated fields of the functional connectivity-based parcellation map were shown with agglomerative hierarchical clustering to be organized in large-scale systems in line with anatomical studies suggesting the existence of a medial and an orbital network of individual regions. Finally, this study underscored the usefulness of including measures of MRI quality, replicability (across runs and hemispheres) and inter-run stability of functional connectivity metrics in neuroimaging studies.

Chapter 3 is concerned with the application of the map developed in the first study to psychiatric disorders. It details the second study of this dissertation in which we used the left-hemisphere parcellation map mentioned above in order to systematically and in an unbiased way examine alterations of connectivity within the OMPFC, an area important for MDD. This study is the first illustration of how data-driven delineated maps can aid the elucidation of dysfunction in entire cortical patches and the first to distinguish between OMPFC connectivity abnormalities that precede the onset of the disease versus those that are present only during the acute MDD phase. The results of this study highlighted that the rostral cingulate and the anterior insula should be the focus of investigation for endophenotypes of vulnerability and biomarkers of the acute MDD phase.

Chapter 4 presents the last study of the thesis in which we examined which of the various abnormalities in BOLD activation during face processing previously reported for the MDD acute phase also characterize the MDD vulnerability state. The results underscored that a series of regions with deviant BOLD responses found in MDD patients are also dysfunctional in the vulnerability state. These deviant responses follow a pattern of enhanced reactivity in limbic and lateral visual areas combined with diminished response in primary visual, striatal, thalamic and frontal regions. Abnormal facial processing in these regions does not occur exclusively in the presence of intense emotional stimuli but is uniform during processing of faces irrespective of valence. These findings suggest that abnormalities in general face processing might predispose at-risk individuals to perceive social interactions in a distorted way and might be, thus, etiologically implicated in MDD.

Finally, ***Chapter 5*** summarizes the main conclusions drawn in the context of this thesis and discusses the implications of our findings for parcellation approaches and neuroscience applications in psychiatry. The discussion is extended by considering open issues and future directions.