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Framing depression in a SN(a)Pshot

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English summary

Understanding the mechanisms underlying major depressive disorder (MDD) is key for developing personalized treatment programs. Getting closer to this understanding can amongst others be established by identifying genetic risk factors that are associated with intermediate phenotypes of (subtypes of) MDD (e.g. PCLO genotype with altered emotion processing). The overall aim of the studies presented in this thesis was to identify imaging characteristics associated with the occurrence and recurrence of depression. This was investigated from two perspectives: Using a neuroimaging genetics approach in this thesis we identified the PCLO risk allele to modulate amygdala function during fearful facial processing in MDD, which may increase the vulnerability for the development and prolonged course of MDD. In addition, susceptibility for depression may also be increased by the PCLO risk allele by modulating local brain in responses to salient stimuli (i.e. insula) and processing novel negative information. Using a longitudinal design in this thesis we identified subjects at risk for non-remitted outcome using regional volume and EF abnormalities as predictors (i.e. smaller inferior frontal, and cingulate volumes as well as increased dlPFC activity).

Summary

MDD is characterized by affective symptoms and cognitive impairments, and has been associated with biased memory formation for mood-congruent information, which in turn may reflect changes in limbic and prefrontal activity as well as altered monoaminergic neurotransmission. The piccolo (PCLO) gene, involved in monoaminergic neurotransmission, has previously been linked to depression in a genome-wide association study. In chapter 2 we showed that the PCLO risk allele is associated with increased activity in the left amygdala during processing of negative faces, but not positive faces. No association with executive function or its neural substrate was found. The paradigms used in this chapter are considered to represent 'pure' examples of tests probing emotion processing and executive function, respectively. Hence, PCLO is probably mainly involved in primary emotion processing, and not in tasks that recruit brain areas involved in executive functioning, emotion regulation, or in implementing action programs important for motivational problems of depression. This indicates that PCLO may act as a risk factor for MDD predominantly through stronger amygdala

reactivity and, possibly, altered serotonergic neurotransmission in brain areas related to emotional information processing. A combined cognitive-emotional paradigm was employed in chapter 3 to further investigate whether the PCLO risk allele was associated with the neural substrate of memory processing of positive and negative information. During negative word encoding, risk allele carriers showed significantly lower activity relative to non-risk allele carriers in the insula, and trend-wise in the anterior cingulate cortex and inferior frontal gyrus. Moreover, depressed risk allele carriers showed significantly lower activity relative to non-risk allele carriers in the striatum during negative word encoding, an effect which was absent in healthy controls. Finally, amygdala responsiveness during processing new positive words vs. known words was blunted in healthy PCLO+ participants and in MDD patients irrespective of genotype, which may indicate that signalling of salient novel information does not occur to the same extent in PCLO+ subjects and MDD patients. The PCLO risk allele may increase vulnerability for MDD by modulating local brain function with regard to responsiveness to salient stimuli (i.e. insula) and processing novel negative information. Also, depression-specific effects of PCLO on dorsal striatal activation during negative word encoding and the relative absence of amygdala salience signalling for novel positive information further suggest a role of PCLO in symptom maintenance in MDD. Summarizing, the results obtained in part I emphasize the modulating role of PCLO during emotion processing in MDD. Moreover, PCLO may modulate the responsiveness to salient stimuli in an emotional context, whereas it does not influence executive dysfunction in MDD. The second part of this thesis aimed to provide insight into the course of neuroanatomical and functional brain abnormalities in MDD in a longitudinal study. Recurrence of depressive episodes in MDD is a burden for both patients and society and executive impairments may increase the risk for recurrent depression. Early prediction of recurrence is therefore key for prevention. Non-remitted MDD patients showed smaller right inferior frontal, rostral anterior cingulate, and posterior cingulate volumes than healthy controls at both baseline and after two-year follow-up. These smaller volumes were not observed in remitted patients (chapter 4). Investigation of the role of executive function (EF) abnormalities in predicting unfavourable course (chapter 5) revealed increased right dorsolateral prefrontal (dlPFC) activity as predictor for non-remitted outcome. No evidence for aggravation of EF abnormalities associated with

unfavourable course was found. Taken together, volume abnormalities could potentially serve as biological markers for poor clinical outcome, and increased right dlPFC activity may distinguish those at risk for non-remission from those with a more favourable course. These results indicate a possible step in MRI-based complementary MDD staging but future long term follow-up functional neuroimaging treatment studies are necessary to investigate the role of increased dlPFC activity on treatment response prediction for improvement of individual-based treatment programs.