Using novel imaging approaches in affective disorders : beyond current models

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English summary

Introduction

Depressive and anxiety disorders are amongst the most prevalent of all psychiatric disorders, and also co-occur frequently. Separately, they are associated with an increased risk for suicide, subjective suffering, impaired social and work functioning, and the resulting disability is in turn responsible for a high economic burden. Depression and anxiety disorders often have an onset during adolescence, and an early onset is associated with more disease severity and disability.

Patients with anxiety disorders often report symptoms of depression, and vice versa. Having comorbid depression and anxiety is related to a higher symptom severity, lower response to treatment, and poorer prognosis than in patients with only one disorder, and it is even a predictor of suicide. In adults, three of the most frequently co-occurring anxiety disorders with major depressive disorder (MDD) are social phobia or social anxiety disorder (SAD), generalised anxiety disorder (GAD), and panic disorder (PD).

Neuroimaging of depression and anxiety

Exactly because these disorders co-occur so frequently, there is an ongoing debate about whether they share the same aetiology or are, concurring with the current classification system, distinct disorders. Neuroimaging offers a non-invasive way to obtain a better insight into what underlies depression and anxiety. Anatomical characteristics of the brain can be mapped with structural magnetic resonance imaging (MRI), whereas functional MRI (fMRI) measures activity of and connectivity between brain regions. One way of applying fMRI is by asking the individual in the scanner to perform a certain task, such as pressing a button or looking at pictures, in order to see what brain areas are activated during that task. Another possibility lies with so-called resting-state fMRI, where the person in the scanner does not have to do any kind of task, but simply must lie as still as possible without falling asleep. It is understood that when various brain areas show the same pattern of activity during this resting-state, they are engaged in the same process and thus defined as functionally connected to one another.

Results from structural and functional neuroimaging studies have shown that certain brain areas show differences in structure and function in individuals with depression and anxiety when compared to healthy

individuals. In depression, brain regions that are consistently reported include the anterior cingulate cortex (ACC), hippocampus, amygdala, thalamus, cerebellum, posterior cingulate cortex (PCC), and temporal and parietal cortical areas. When looking at anxiety disorders, in PD, studies point to the involvement of the hippocampus, amygdala and the brain stem, but also highlight roles for the ACC and PCC as well as other cortical areas such as the insula and the prefrontal cortex (PFC). In SAD, frequent mention is made of the amygdala and frontal cortical areas, as well as the precuneus. GAD appears to be understudied in comparison to other anxiety disorders, but the few studies that are available show involvement of the amygdala and the PFC.

Neurobiological models on depression and anxiety

Over the past decades, there has been an accumulating interest in the underlying neurobiology of depression and anxiety, which has led to the development of several theories.

Helen Mayberg created a neurobiological model on depression in 1997, in which she suggested that an array of brain regions and, more specifically, maladaptive functional interactions of cortico-limbic brain regions are involved in depression. Since such interactions are critical for the normal regulation of mood and associated processes, dysfunctional interactions are proposed to underlie depressive symptomatology. The three elements that form the basis of her model include a dorsal, ventral and rostral component.

Similarly, Mary Phillips and colleagues proposed their functional neuroanatomical model of emotion perception in 2003. Building upon the notion that two systems, a ventral and dorsal system, are responsible for emotion perception, as well as the production and regulation an affective state, their model relates distinct patterns of structural and functional abnormalities in these systems to specific symptoms of psychiatric disorders including MDD.

In his influential original neuroanatomical hypothesis on PD from 1989 and its revision in 2001, Jack Gorman proposed that panic originates from an abnormally sensitive fear network including the amygdala, thalamus, PFC, and insula, as well as amygdalar projections to the brainstem and hypothalamus.

It should be noted that no neurobiological models on SAD and

GAD have been proposed. This underlines the need for further studies and a better understanding of these anxiety disorders. The existing neurobiological models of depression and anxiety have been built around dysfunctional mechanisms that rely upon the proper functioning of and communication between certain brain areas. Since the development of those models, neuroimaging techniques have been much improved and advanced.

Aim of this thesis

The studies presented in this thesis aimed to address gaps in the current limited knowledge of the neurobiology underlying depression and anxiety in adults and adolescents, by employing novel imaging approaches. Adult participants were derived from the Netherlands Study of Depression and Anxiety (NESDA), and adolescent participants from the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA). Very little is known about the network interactions between brain regions in depression and anxiety, despite the importance of such connectivity for an understanding of these disorders. The objective of this thesis was to investigate whether novel imaging approaches such as resting-state fMRI would confirm results from previous studies using other neuroimaging modalities, or uncover neural pathways implicated in depression and anxiety that have not been linked to these disorders before.

The unique resting-state characteristics of PD were examined in Chapter 2. We demonstrated altered resting-state functional connectivity (RSFC) in the limbic and salience networks in a sample of 11 PD patients without any other psychiatric comorbidity, compared to 11 healthy control subjects. For the limbic network, patients showed increased RSFC between the right amygdala and the bilateral precuneus and lateral occipital cortex. This effect may be linked to typical panic symptoms such as derealisation and depersonalisation, which refer to sensations of being detached from reality or oneself. However, as we did not find a relationship between this increase in RSFC and the severity of symptoms, these speculations could not be confirmed. For the salience network, PD patients had decreased RSFC between the left dorsal ACC (dACC), and the bilateral frontal pole and superior/medial frontal gyrus compared to healthy controls. In contrast, PD patients showed an increased RSFC with the bilateral precentral and

postcentral gyrus, right supplementary motor cortex, and right ACC. Furthermore, an increased RSFC between the right dACC and the right superior parietal lobule, lateral occipital cortex, angular gyrus, and central opercular cortex in PD patients was found. These findings could be related to panic symptoms such as a heightened awareness of bodily sensations, or disturbances in self-awareness that could be reflected in symptoms such as the feeling that one is going crazy or loses control.

We investigated RSFC in medication-naïve SAD patients without psychiatric comorbidity in Chapter 3. For the limbic network, SAD patients showed increased negative right amygdala RSFC with the left middle temporal gyrus, supramarginal gyrus, and lateral occipital cortex compared to healthy controls. These areas have been linked to the perception of faces, and an abnormal RSFC could be interpreted as though SAD patients have an enhanced sensitivity for facial expressions of other people. For the salience network, increased positive connectivity was reported between the bilateral dACC seeds and the left precuneus and lateral occipital cortex in SAD patients. This could underlie a disturbed self-awareness and biased information gathering in SAD patients.

Chapter 4 discussed the shared and unique RSFC characteristics of substantial groups of patients with only MDD, patients with only anxiety, and patients with comorbid depression and anxiety, compared to healthy control subjects. Using the data-driven independent component analysis (in combination with dual regression) approach, differences were found between the comorbid group and healthy controls in the limbic network, where comorbid depressed and anxious patients showed increased connectivity in a cluster containing the bilateral precuneus, intracalcarine cortex, lingual gyrus, and posterior cingulate, as well as a cluster including the right precentral gyrus, inferior frontal gyrus, and middle frontal gyrus. It was suggested that the deviant RSFC pattern found in the current study is specific to comorbid depression and anxiety, only becoming evident when patients have both disorders and not in patients with a single diagnosis of either.

Our next RS study was conducted in a sample of treatment-naïve adolescents with a clinical diagnosis of depression and matched healthy controls. Chapter 5 describes the RSFC differences we found between these groups. For the limbic network, depressed adolescents showed increased RSFC between the left amygdala and the right middle frontal gyrus, inferior

frontal gyrus, precentral gyrus, and postcentral gyrus. These findings could be related to a disturbed cognitive control over emotion processing in adolescent depression. There was also a reduced RSFC in the clinical group between the right amygdala and the left frontal pole, right ACC, paracingulate gyrus, and superior frontal gyrus, as well as with the left angular gyrus, lateral occipital cortex, and supramarginal gyrus. Altered connectivity between the amygdala and the ACC is typical for depression, and could be associated with abnormalities in emotion regulation. For the salience network, decreased RSFC was found in the clinical group between the bilateral dACC and the right middle frontal gyrus, frontal pole, and inferior frontal gyrus. Altered connectivity between the dACC and prefrontal areas may be associated with a bias towards negative emotional stimuli and disrupted assessment of affective stimuli.

In addition to RSFC study that was discussed in the previous chapter, grey matter volume in clinically depressed adolescents was studied in Chapter 6. A region-of-interest VBM (voxel-based morphometry) revealed a smaller ACC volume by 14.4% in the patient group compared to matched healthy controls. This is consistent with literature on adult depression. The ACC has been linked to higher cognitive functions, and problems with inhibiting the processing of negative material are common symptoms of depression. Abnormalities in grey matter volume of the ACC could be related to such problems. The emergence of psychiatric illnesses in adolescence has been linked to abnormalities in brain maturation in combination with psychosocial, biological environmental factors. Our results may be interpreted as a result of abnormal maturational processes.

Panic disorder

According to Gorman's revised version of his original neuroanatomical hypothesis of PD, panic originates from an abnormally sensitive fear network including the insula, PFC, thalamus, amygdala, and projections from the amygdala to the brainstem and hypothalamus. Within the context of a limbic network, we reported abnormalities between the amygdala and the precuneus and lateral occipital cortex. Whereas the amygdala plays a central role in Gorman's theory, the precuneus and lateral occipital cortex are not considered; the hypothesis does not include any posterior regions.

The differences we reported for the salience network are also new to models on PD. The left and right dACC showed altered RSFC with

frontal and occipito-parietal areas that are involved in the processing of somatosensory information, attentional control, and self-awareness. With the salience network serving as an assessor of relevance of internal and external stimuli, an exaggerated significance attributed to such stimuli is much in line with the typical symptoms of PD.

Our finding that a more widespread set of brain regions is involved in PD than what is currently described in models, is consistent with other contemporary neuroimaging studies. Based on the currently available body of literature on PD, potential amendments of Gorman's hypothesis were suggested. The emphasis on the amygdala might be tempered, since findings on its involvement in PD are not univocal. Simultaneously, the role of several cortical areas such as the insula and ACC seems to be underestimated in the hypothesis. However, it is evident that much more research is needed before a model can be proposed that is based on conclusive findings.

Social anxiety disorder

The need for further studies in SAD is widely recognised, and was reflected in the number of resting-state fMRI studies that appeared around the time of our own publication. Our results are largely consistent with such studies also reporting altered amygdala and ACC functional connectivity in SAD patients, as well as other cortical regions. The particular importance of the connectivity between the amygdala and frontal cortical regions is not just emphasised in functional but also in structural connectivity studies. Contemporary studies recognise the role of multiple brain regions in emotion, which is highlighted in the use of neuroimaging modalities that point to the involvement of neural networks rather than singular brain regions in SAD.

It is evident that brain areas involved in facial perception and facial processing are heavily involved in SAD. The sensitivity for others' approval and fear of negative judgement is reflected in cognitive theories on SAD, and we speculate that the idea of how one is perceived by other people relies to a great extent on information derived from their facial expressions. Unfortunately the recent growth in number of neuroimaging research, particularly connectivity studies, has not yet resulted in a neuroanatomical model of SAD. However, it may be an indicator that such a model may be

developed in the near future.

Generalised anxiety disorder

Whereas the unique contributions of PD and SAD were discussed in Chapters 2 and 3 respectively, GAD was not separately addressed in this thesis. The Netherlands Study of Depression and Anxiety (NESDA) sample, from which the participants were drawn for Chapters 2, 3, and 4, did not include participants with GAD alone, preventing us from addressing this explicitly in our research. We have therefore not been able to contribute to the literature on GAD alone.

Depression

Depression has attracted much attention over the past decades with a growing amount of neuroimaging research. Providing support for Mayberg's and Phillips' theories, many studies have investigated the roles of separate brain regions in anatomical and functional studies, with findings consistently highlighting abnormalities of the hypothalamus, pituitary, hippocampus, amygdala, and prefrontal regions as the ACC, dorsolateral and orbitofrontal cortex. Particularly the ACC has received much attention, and our finding of reduced ACC grey matter volume in clinically depressed adolescents confirms findings from the vast majority of structural studies in depressed subjects reporting ACC volume reductions.

Our resting-state study in the same adolescent sample also showed abnormalities of the ACC in depressed subjects. Confirming previous literature as well as Mayberg's model and Phillips' theory on emotion perception, we reported decreased resting-state functional connectivity between the amygdala and the pregenual ACC. This provides further support for disturbances in the ventral system in which such deviations are proposed to underlie depressive symptomatology by both models. It is plausible that frontocingulate dysfunction contributes to key cognitive and affective abnormalities in depression, such as emotion dysregulation and rumination: a tendency to engage in and enhance negative information.

Comorbid depression and anxiety

With the topic of the shared or separate etiology of depression and anxiety disorders still hotly debated, the available literature is not yet able to provide a definitive answer. The results from Chapter 4 of this thesis, reporting

altered RSFC in a limbic network in comorbid depressed and anxious adults compared to healthy controls, but no differences in depression or anxiety alone, suggested that the effect is specific to comorbid depression and anxiety, only becoming evident when patients present with both disorders and not in patients with a single diagnosis of either.

Considerations

The longitudinal and multi-centre design of NESDA enables the monitoring of a large, well-characterised sample presenting with an extensive variety of symptoms over a long period. Despite these obvious advantages, there are also some limitations. Patients for the NESDA sample were recruited through general practitioners, primary care practices, and outpatient clinics of mental health organisations. It is therefore possible that the most severely affected patients were not included. It is also likely that patients with the severest symptomatology were not motivated to partake in the extensive assessments, with an additional two-hour MRI scanning session and interview for the neuroimaging study. A consideration regarding the scanning sequence lies with the position of the resting-state fMRI run at the end of the protocol. It is possible that the preceding task-related functional MRI sessions have influenced the resting-state scan.

This was not an issue in the EPISCA study, with the resting-state scan positioned at the beginning of the scanning protocol. However, one consideration that should be made regarding EPISCA is the relatively small sample size.

A big advantage of resting-state fMRI is that it offers an unbiased approach to investigate functional connectivity of the brain. This is of especially great importance in clinical groups, where persons suffering from, for example, neurodegenerative or (neuro)psychiatric disorders are less capable or even incapable of dealing with the cognitive demand that functional tasks often require. One of the difficulties with resting-state fMRI is that in contrast to task fMRI, it is more complicated to interpret, because functional connections between brain regions are correlations, and do not imply causality or directionality. These correlations are also more susceptible to being influenced by confounders, such as physiological noise caused by breathing and heart rate variability. Fortunately, technical advances

are continuously improving the ways to minimise or even eliminate the influence of such artefacts.

Concluding remarks

Structural and functional magnetic resonance imaging have provided important insights into the involvement of candidate brain regions in depression and anxiety. It is unlikely that simple increases and decreases in brain activity alone are sufficient to explain the complex diversity of symptoms that define depression and anxiety. Combined efforts using various research modalities (for example: MRI, (epi)genetics, neuroendocrinology, and environmental studies) could significantly improve knowledge about the neurobiology and pathophysiology of depression and anxiety disorders. Performing such complementing multimodal studies would be a promising next phase of neurobiological research on affective disorders.