Using novel imaging approaches in affective disorders : beyond current models

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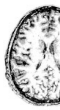
Chapter 1
Introduction



Prevalence and clinical characteristics

Depression and anxiety are among the most prevalent psychiatric disorders worldwide. Whereas major depressive disorder (MDD), with lifetime prevalence estimates of over 20%, classifies as the most common disorder with the heaviest burden and disability, anxiety disorders are the most common class of disorders with a combined lifetime prevalence of 28% (Kessler *et al*., 2005a, Ressler and Mayberg, 2007). The average age of onset for MDD is in the mid-20s but the median age is 30 years; however, the disorder may occur at any age (American Psychiatric Association, 1994, Kessler *et al*., 2005a). Notably, anxiety disorders have a much earlier age of onset than MDD with a median of 11 years (Kessler *et al*., 2005a). Depression and anxiety disorders often have an onset in adolescence, and an early onset is associated with more disease severity and disability (Paus *et al*., 2008, van Noorden *et al*., 2011). Studies show that anxiety symptoms predict and often precede depression in adolescence (Wittchen *et al*., 2003, Beesdo *et al*., 2007), which is consistent with evidence of the earlier onset of anxiety than depression.

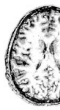
A person diagnosed with MDD will suffer from one or more major depressive episodes, which are characterised by the presence of depressed mood and/or loss of interest or pleasure over a consecutive period of two weeks, as well as five of the following: weight loss that is not a result of dieting, or weight gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or guilt; diminished ability to concentrate; and recurrent thoughts of death or suicide. These symptoms are not due to another psychiatric disorder, secondary to a medical condition, or accounted for by bereavement (American Psychiatric Association, 1994).

MDD is associated with high morbidity, subjective suffering, impaired social and work functioning, and high mortality. The resulting substantial disability that is caused by MDD is in turn responsible for a high economic burden (Cassano and Fava, 2002). Females have a greater risk of developing MDD than males both in adulthood and adolescence, and individuals with a first-degree relative with MDD are more likely to develop MDD than the general population. Furthermore, recurrence of depressive episodes is high and as the number of episodes an individual has experienced increases, so does the chance of having additional episodes (American Psychiatric Association, 1994, Kessler *et al*., 2005a).

Other strong predictors of recurrence and duration of the depressive episode are severity and comorbidity with other psychiatric disorders (Melartin *et al*., 2004).

Indeed, MDD frequently co-occurs with anxiety disorders (Gorman, 1996, Ressler and Mayberg, 2007). Presence of anxiety disorders in depressed patients is associated with increased symptom severity, lower response to treatment, and poorer prognosis than in patients with only one disorder, and it is even a predictor of suicide (Fawcett, 1992, Gorman, 1996). Conversely, patients with anxiety disorders often report symptoms of depression, and it is estimated that more than 30% of patients with an anxiety disorder will meet the criteria for a clinical diagnosis of depression during their illness (Gorman, 1996).

In adults, three of the most frequently co-occurring anxiety disorders with MDD are social phobia or social anxiety disorder (SAD), generalised anxiety disorder (GAD), and panic disorder (PD) (Gorman, 1996, Kessler *et al*., 1996). Social anxiety disorder is characterised by a distinct fear of social or performance situations in which embarrassment or humiliation may occur. Exposure to the feared social situation will invariably lead to an anxiety response. Individuals with SAD will typically fear that others perceive them as weak, crazy, or stupid, and that others will notice their anxiousness, for example due to trembling hands or voice. There is recognition that the fear is excessive or unreasonable. Feared situations will be avoided or otherwise endured with intense anxiety or distress, and the fear significantly interferes with the person's normal routine and daily functioning (American Psychiatric Association, 1994).
The most essential feature of generalised anxiety disorder is excessive general anxiety and worrying about a number of events, and difficulty to control the worry, which will occur more days than not for at least 6 months. Other symptoms include restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and disturbed sleep. Individuals with GAD report subjective distress and impaired daily functioning due to constant worry. The symptoms do not result from another psychiatric disorder or substance abuse (American Psychiatric Association, 1994).
Panic disorder is marked by recurrent unexpected panic attacks and at least one month of persistent concern about having additional attacks and their possible consequences. These panic attacks cannot be induced by substance use or be better accounted for by another mental disorder. The



unexpected panic attacks are not associated with a situational trigger, and are thus defined as spontaneous and uncued. A minimum of two attacks is required for diagnosis; however, many individuals experience more. Typical characteristics of a panic attack are a discrete period of intense fear and a number of the following symptoms: palpitations, sweating, trembling or shaking, shortness of breath, feeling of choking, chest pain, nausea, feeling dizzy or faint, derealisation (feeling of unreality) or depersonalisation (being detached from oneself), fear of losing control or going crazy, fear of dying, numbness or tingling sensation, and chills or hot flushes. Individuals with PD may or may not present with agoraphobia, which is characterised by anxiety about being in places or situations from which escape and in which getting help might be difficult, in the event of having a panic attack. Such situations are avoided or endured with marked distress (American Psychiatric Association, 1994).

Diagnostic classification

Clinical diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) means that a disorder is either present or absent, and based on whether diagnostic criteria are met. It is of note that upon the start of the current project, the fifth edition of the DSM was still under development, and diagnoses according to the DSM in the project were based on the DSM-IV.

Initial research on depression and anxiety disorders has mostly proceeded along different tracks, reflecting the diagnostic separation between the two classes of disorders. However, with regard to the distinction between depression and anxiety, there is a longstanding and ongoing debate as they co-occur so frequently, have overlapping symptom criteria and phenomenology, respond to similar types of treatment (including pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) as well as cognitive behavioural therapy CBT)), and the same brain circuits are involved in both types of disorders (Gorman, 1996, Ressler and Mayberg, 2007). In this light, some researchers advocate that depression and anxiety disorders share the same aetiology (Ressler and Mayberg, 2007) and should be best conceptualised by a continuum (Stavrakaki and Vargo, 1986), or using a dimensional approach (Simms *et al*., 2008). The ways in which these disorders are diagnosed and classified have important implications for clinicians and patients, in terms of prognosis and treatment (Simms *et al*., 2008).

Neuroimaging

One of the approaches to study the neurobiology underlying depression and anxiety is neuroimaging, which provides the opportunity to investigate the brain in vivo in a safe and non-invasive way. This enables studying the anatomical and functional characteristics of the brain and or specific regions of the brain. Technical advances in neuroimaging methods, magnetic resonance imaging (MRI) and functional MRI (fMRI) in particular, have contributed greatly to our knowledge of the human brain. This young field of research is still rapidly expanding. Studies of healthy individuals give an ever-increasing insight in the morphology and functioning of the 'normal' brain, and facilitate comparison with the brain of persons with a (neuro)psychiatric disorder. Similarly, MRI research in healthy youngsters helps create an understanding of the normally developing brain, which provides a frame of reference for developmental difficulties that can have far-reaching consequences for psychological functioning.

Structural MRI enables the examining of the anatomical characteristics of the brain, and the structural connections between brain regions (Ashburner and Friston, 2000, Basser *et al.*, 1994). Functional MRI is based on the assumption that active brain regions require more oxygen and thus have an increased blood flow. The ratio between oxygenated and de-oxygenated haemoglobin changes with brain activation. In other words, an increased amount of oxygenated blood is delivered to active brain regions because they have a higher energy demand. With fMRI, images sensitive to changes in the concentration of de-oxygenated haemoglobin are mapped, which is known as the blood oxygenation level-dependent (BOLD). This is reflective of increased activity of the site (Ogawa *et al.*, 1990). By measuring the changes in oxygen consumption during sensory or cognitive processing using fMRI, it can be inferred what areas of the brain are activated during the presumed function. Therefore, the execution of specific sensory, cognitive and motor tasks are widely employed to investigate the function of brain regions.

More recently it was observed that the BOLD signal is not only useful for studying task-related brain activity, but it also provides information about the brain when it is not engaged in goal-directed behaviour (Biswal *et al.*, 1995, Raichle *et al.*, 2001). Technical advances have allowed the application of fMRI to the resting brain; that is, measuring brain activity whilst the individual is in the scanner, but in the absence

of stimuli or tasks. So-called resting-state fMRI has become a powerful tool to examine the unconstrained, spontaneous activity of, and connectivity between, brain areas (Biswal *et al.*, 1995, Fox and Raichle, 2007). When various brain regions simultaneously show the same spontaneous fluctuations of the BOLD signal during resting-state, they are defined as functionally connected. Such collections of correlated brain regions are known as functional connectivity networks. Studying network interactions are not only important for an understanding of the brain in general, but also for an understanding of the abnormalities that accompany mental illness. Resting-state fMRI also allows researchers to study brain connectivity as a whole rather than just the brain regions that are activated during task fMRI. Additionally, overcoming potential limitations of task-related fMRI for severely ill patients who are less capable or even unable to cope with the cognitive burden of tasks, RS-fMRI can provide an outcome in studying debilitating neuropsychiatric disorders.

Neuroimaging in depressed adults and adolescents

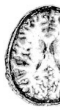
Volumetric studies indicate that several brain areas show anatomical abnormalities in MDD patients compared to healthy control subjects. Reductions in grey matter volume have been most consistently reported in the anterior cingulate cortex (ACC) and orbitofrontal cortex, as well as the hippocampus, putamen, and caudate nucleus (Koolschijn *et al.*, 2009). Structural findings from studies on adolescent depression are scarce, but point to similar brain regions and also report volume differences in the amygdala (MacMillan *et al.*, 2003, Caetano *et al.*, 2004, Rosso *et al.*, 2005). These areas are known to be involved in stress and emotion regulation.

Widely used paradigms in task fMRI studies of MDD involve the presentation of pictures, scripts of autobiographical memory, words, and faces. These stimuli have an emotional content and are used to induce a positive (happy) or negative (sad) emotion. Studies focusing on happy stimuli reported altered activation in depressed subjects of the cerebellum and various frontal, posterior and temporal cortical regions. Studies that used negative stimuli found altered activity of frontal, temporal, parietal and posterior cortical regions, the cerebellum, insula, and the amygdala (Fitzgerald *et al.*, 2008). Frequently reported resting-state functional connectivity differences in adult depression include decreases in pregenual anterior and posterior cingulate, middle frontal gyrus, insula, and

superior temporal gyrus. Areas showing hyperactivation include the thalamus, amygdala, and superior frontal and middle temporal gyrus (Fitzgerald *et al.*, 2008). Additionally, increased thalamic and subgenual ACC connectivity was reported in depressed subjects (Greicius *et al.*, 2007). Remarkably, only one preliminary resting-state study has been performed in depressed adolescents compared to healthy controls. However, in addition to a primary diagnosis of MDD most of the patients had one or more comorbid diagnosis and were treated with medication. Decreased connectivity was found in the depressed group in a subgenual ACC-based neural network including the supragenual ACC, right medial frontal cortex, left inferior and superior frontal cortex, superior frontal gyrus, and insula (Cullen *et al.*, 2009). This network is involved in emotion processing (Kober *et al.*, 2008, Cullen *et al.*, 2009).

Neuroimaging in adults and adolescents with anxiety disorders

In adult PD, structural studies pointed to a reduction of grey matter in temporal regions, particularly the hippocampus (Vythilingam *et al.*, 2000, Uchida *et al.*, 2003, Massana *et al.*, 2003a, Kent and Rauch, 2003) and amygdala (Massana *et al.*, 2003b, Hayano *et al.*, 2009). However, grey matter abnormalities were also reported in the ACC (Uchida *et al.*, 2008) and brain stem (Protopopescu *et al.*, 2006). Initial functional studies in PD have used positron emission tomography (PET) and single photon emission computerised tomography (SPECT), and most consistently indicated alterations of blood flow of hippocampal regions (Reiman *et al.*, 1986, Nordahl *et al.*, 1990, De Cristofaro *et al.*, 1993, Kent and Rauch, 2003, Sakai *et al.*, 2005). Task fMRI studies have also found altered activity in cortical regions as the anterior and posterior cingulate (Bystritsky *et al.*, 2001) and the amygdala (Pillay *et al.*, 2006). Symptom-provocation paradigms, where an anxiety state is intentionally induced through the use of pharmacologic or behavioural manipulations, point to reduced activity in widespread cortical regions including the prefrontal cortex (PFC), and increased activity in insular and motor striatal regions (Kent and Rauch, 2003). To date, no resting-state studies in PD have been done. Taken together, neuroimaging findings in PD suggest that abnormalities in the hippocampal regions may be a trait marker for the disorder. However, symptom provocation studies have also indicated the more global involvement of widespread cortical regions, including the PFC.



For SAD there is only one volumetric study, which did not report any grey matter differences between patients and healthy controls (Potts *et al.*, 1994). Functional studies in SAD, the majority of which employed emotional faces tasks or symptom provocation paradigms involving the anticipation of public speaking, consistently report increased amygdala activation and decreased frontal cortical activation (Kent and Rauch, 2003, Etkin and Wager, 2007). To date, there are only two resting-state studies in SAD. The first, using SPECT, did not report any differences in regional cerebral blood flow (Stein and Leslie, 1996). The second, more recent SPECT study reported increased resting perfusion in the frontal cortex and right cerebellum, and decreased perfusion in the pons, left cerebellum, and right precuneus (Warwick *et al.*, 2008). No resting-state fMRI studies have been done in SAD. In sum, the most prominent and consistent findings in SAD are an exaggerated amygdala response to human face stimuli or to the stress of public speaking.

There is very little neuroimaging data available for GAD. The first two volumetric studies were in a paediatric sample, reporting increased right and total amygdala volumes (De Bellis *et al.*, 2000) and larger total, white matter, and grey matter volumes of the superior temporal gyrus in children with GAD (De Bellis *et al.*, 2002b). One study in adults found increased grey matter of the centromedial nucleus of the amygdala (Etkin *et al.*, 2009). Findings of functional studies include increased activation of the ventral PFC in adolescents with GAD compared to healthy control subjects, whilst viewing angry faces (Monk *et al.*, 2006). The same group also reported that disturbed amygdala activation was associated with dysfunctional ventral PFC activation in adolescents with GAD (McClure *et al.*, 2007, Monk *et al.*, 2008). In adults, relative to healthy controls, GAD patients showed an increased response to angry versus neutral faces in the middle frontal gyrus, inferior temporal cortex, and the culmen. They also showed decreased amygdala activation during fearful versus neutral faces (Blair *et al.*, 2008b). By contrast, one study did not report differences in amygdala activity between GAD patients and healthy controls (Whalen *et al.*, 2008). One resting-state study investigated functional connectivity of subregions of the amygdala, and found less distinct connectivity patterns of the basolateral and centromedial nuclei in GAD patients, as well as increased grey matter in the centromedial nucleus. Additionally, increased connectivity was found with a frontoparietal executive control network,

and decreased connectivity with an insula- and cingulate-based salience network (Etkin *et al*., 2009). Compared to other anxiety disorders, GAD is notably understudied. However, the few existing research findings point to a disruptive activation of the amygdala and to a lesser extent of the ventral PFC.

Neurobiological models of depression

MDD is characterised by a variety of symptoms of a cognitive (e.g. attentional and concentration problems), emotional (e.g. depressed mood, anhedonia, feelings of worthlessness) and somatic (fatigue, psychomotor agitation, sleep disturbances) nature (American Psychiatric Association, 1994). It is therefore unlikely that depression is the result of dysfunction of one particular brain area. Rather, as in an influential model by Mayberg (1997), it is 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 (Mayberg, 1997, Seminowicz *et al*., 2004). Mayberg's model comprises three components and dysfunction of each of those is related to specific symptom sets. An effective collaboration between the three components is key to the maintenance of an intact mental state. The dorsal component, encompassing neocortical and midline limbic elements such as the PFC, dorsal ACC and striatum, is linked specifically to attentional and cognitive features of depression. A ventral component includes paralimbic (sub)cortical regions (such as the hypothalamic-pituitary-adrenal axis, insula, and subgenual cingulate) and brainstem regions. This element is hypothesised to mediate the vegetative and somatic aspects of depression. Thirdly, a rostral cingulate component is considered to have a regulatory role in the overall network by facilitating the interactions between the other two components (Mayberg, 1997) (Figure 1).

In her functional neuroanatomical model of normal emotion perception, Phillips and colleagues (2003) describe three processes that are key for emotion perception: the identification of the emotional significance of a stimulus (i.e. salience); the production of an affective state in response to the aforementioned; and regulation of the affective state. The authors

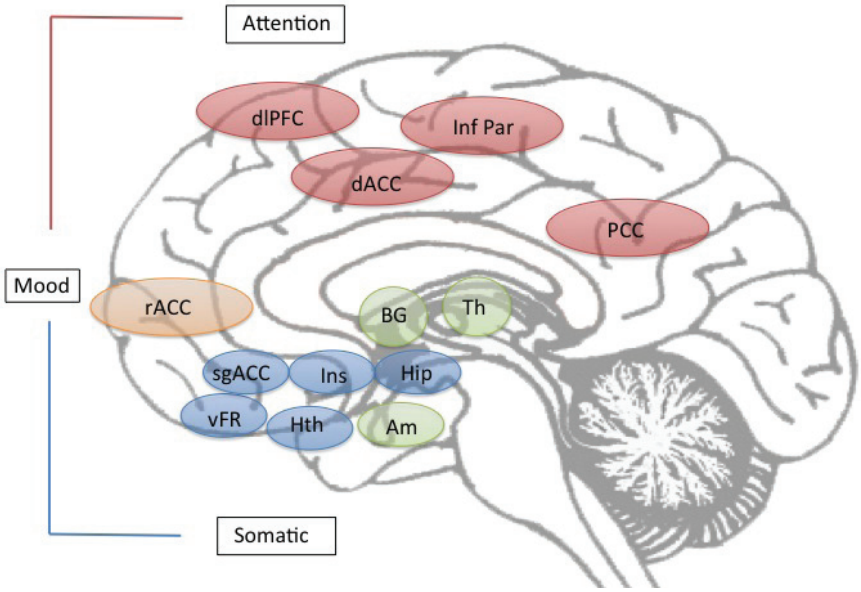


Figure 1. Representation of Mayberg's model on depression
The three systems (dorsal, red; ventral, blue; rostral, orange) are depicted. Correct regulation of each of these systems as well as an effective collaboration between them is critical for the maintenance of an intact mental state.
Abbreviations: dlPFC, dorsolateral prefrontal cortex; dACC, dorsal anterior cingulate; Inf Par, inferior parietal cortex; PCC, posterior cingulate; rACC, rostral anterior cingulate; BG, basal ganglia; Th, thalamus; sgACC, subgenual anterior cingulate; vFR, ventral frontal cortex; Ins, insula; Hth, hypothalamus; Hip, hippocampus; Am, amygdala.
Simplified schematic representation of the original model.
Adapted from: Mayberg, 1997.

further argue that two neural systems are responsible for these processes: a ventral system including the amygdala, insula, ventral striatum, and ventral regions of the ACC and PFC, which is involved in salience assessment and the production of an affective state; and a dorsal system including the hippocampus and dorsal regions of the ACC and PFC, known to play a role in higher cortical functions and a more top-down controlled regulation of affective states (Phillips *et al.*, 2003a). In a subsequent review, Phillips relates distinct patterns of structural and functional abnormalities in these systems to specific symptoms of psychiatric disorders including MDD. It is suggested that dysfunction

of particularly the ventral system, with a key role for the amygdala, leads to an identification bias towards negative emotion, resulting in the production of depressed mood and anhedonia (Phillips *et al*., 2003b).

Whilst both models emphasize the involvement of similar neural systems in depressive symptomatology, an important difference is the explicit role for the amygdala in Phillip's model. Even though Mayberg acknowledged the role of limbic structures in the pathogenesis of depressive disorders, she pointed out that their involvement was not known at the time (Mayberg, 1997) (Figure 2).

Neurobiological models of anxiety

A comprehensive and highly influential neuroanatomical model of PD was proposed by Gorman (1989), integrating biological and psychological views on the origin of the disorder (Gorman *et al*., 1989). In the original hypothesis, three components of panic disorder are discussed. The first, an acute panic attack, is proposed to originate in the brainstem, where stimulation of the locus ceruleus produces physiological and autonomic signs of panic, causing the sudden onset of an attack. The second component is anticipatory anxiety and it is suggested that limbic sites play a role in the fear of having additional panic attacks; a typical symptom of PD. The third component, phobic avoidance, involves a conscious cognitive capacity, and is linked to activation of the PFC (Gorman *et al*., 1989). A decade later, the authors revised their original hypothesis incorporating new research findings. In their updated model, Gorman and colleagues (2000) attributed a central role to the amygdala and its key function in the so-called fear network. Panic was proposed to originate from an abnormally sensitive fear network, including the amygdala, thalamus, PFC, and insula, as well as amygdalar projections to the brainstem and hypothalamus (Gorman *et al*., 2000).

There is no extensively defined neurobiological model describing the involvement of neural pathways in the symptomatology of SAD as there is for PD. However, Mathew (2001) builds upon predominantly non-human preclinical neurobiological models by reviewing pharmacological and neuroimaging research. Whilst emphasizing the many unanswered questions regarding the neurobiology of SAD, he notes impaired dopaminergic function in striatal regions as preliminary findings of

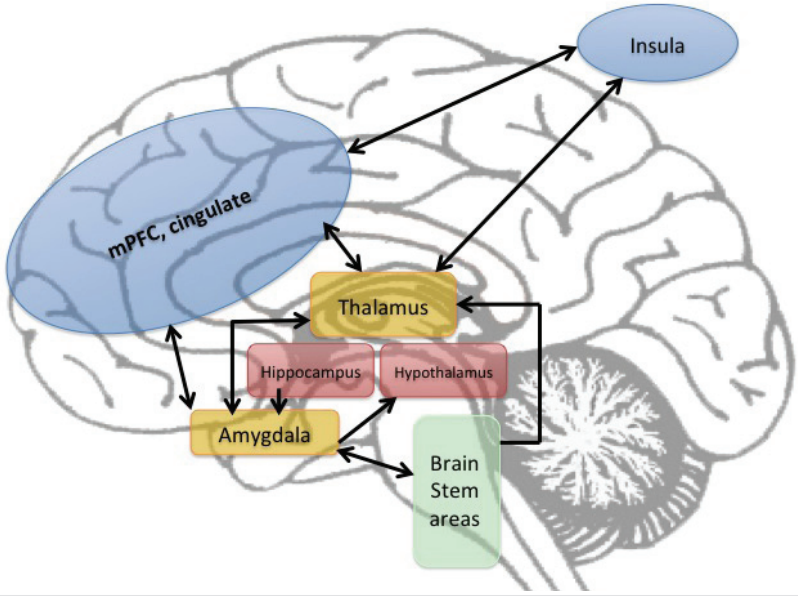


Figure 2. Representation of Gorman's neuroanatomical hypothesis of Panic Disorder
Upstream (cortical) and downstream (brain stem) sensory information is relayed to the amygdala via the thalamus. Contextual information is stored in the hippocampus and transferred directly to the amygdala, which in turn projects back to the brain stem, hypothalamus and prefrontal cortical structures.
Simplified schematic representation of the hypothesis.
Adapted from: Gorman *et al.*, 2001.

neurobiological studies on SAD. The amygdala and interactions with cortical structures and the hippocampus are also mentioned. Furthermore, the author stresses the importance of developmental studies for a better understanding of the underlying neurobiology of SAD (Mathew *et al.*, 2001).

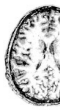
If SAD is understudied compared to PD, the paucity of available data on GAD is, as mentioned above, even more pronounced and limits the development of a comprehensive neuroanatomical model. What emerges from the few studies that do exist is that a disrupted interaction between the amygdala and regions in the PFC appear to underlie the symptomatology of GAD (McClure *et al.*, 2007, Etkin *et al.*, 2009). It is suggested that a defective coupling between these regions is consistent with cognitive theories of GAD, which suggest that the use of

compensatory cognitive strategies, such as worry, are employed to decrease the impact of emotions and regulate excessive anxiety (Etkin *et al*., 2009).

Taken together, the markedly smaller number of neurobiological studies of anxiety disorders is reflected in the limited comprehensiveness of neurobiological models of anxiety disorders compared to depression. Nonetheless, it is noteworthy that the amygdala has been given a more central role in models on anxiety than on MDD. Fear and anxiety, of course, are central features of anxiety disorders and only to a much lesser extent of MDD. The amygdala has also been implicated in other emotional states than fear as well as in the regulation of cognitive functions such as attention, perception and explicit memory. However, less is known about the circuitry involved in these functions (LeDoux, 2007).

Aim of this thesis

The constant development of new neuroimaging techniques, together with the improvement of existing methods, makes neuroimaging a highly dynamic and continuously evolving field. New ideas are generated and existing theories are adapted when new research findings point in a different direction. Consequently, neuroimaging studies have greatly contributed to the development of neurobiological models of depression and anxiety. However, it is evident that much is still unknown about the neural circuits that underlie these debilitating disorders. Various anxiety disorders are particularly understudied and have not been investigated with the newest neuroimaging approaches such as resting-state fMRI. This is surprising, since anxiety disorders are amongst the most prevalent psychiatric disorders worldwide, and it is repeatedly stressed that more research is needed. Due to its independence of externally applied stimuli or tasks, resting-state fMRI provides an unbiased research strategy that can help bridge the gaps in the knowledge of what underlies depressive and anxiety disorders. A lack of insight into the neurobiology has prevented the realisation of integral neuroanatomical models on SAD and GAD. Such models are important in providing a framework for a thorough understanding of depression and anxiety by researchers and clinicians, and inherently contribute to improved prevention and treatment strategies and the wellbeing of patients. Also to this end, insights in adolescent depression and anxiety, when the brain is still developing and malleable, are vital.



In addition, despite the ongoing discussion on whether depression and anxiety should be seen as distinct disorders or have a shared etiology, the shared and unique characteristics have not been explicitly addressed in neuroimaging studies.

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. There is very little known about the network interactions between brain regions in depression and anxiety, despite the importance of such connectivity for an understanding of these disorders. Resting-state fMRI studies in PD and SAD have not been done before. Also, neither this technique nor structural MRI has been used in depressed adolescents that are free from other psychiatric comorbidities with the exception of anxiety. Finally, the shared and unique characterisations of depression and anxiety have not been studied with the use of resting-state fMRI.

The objective of this thesis is to investigate whether novel imaging approaches such as resting-state fMRI will 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.

In Chapter 2, the unique characteristics of PD will be examined using resting-state fMRI in a sample of PD patients without any other psychiatric comorbidity, compared to healthy controls. In Chapter 3, resting-state functional connectivity in medication-naïve SAD patients without psychiatric comorbidity compared to control subjects will be discussed. Chapter 4 discusses the shared and unique resting-state functional connectivity characteristics of substantial groups of MDD patients without comorbidity, anxiety patients without comorbidity, and comorbid depressed and anxious patients, compared to healthy control subjects. Chapters 5 and 6 focus on developmental issues. Chapter 5 covers a resting-state fMRI study of a sample of treatment-naïve adolescents with a clinical diagnosis of depression, and pair-wise matched healthy controls. Grey matter volume in clinically depressed adolescents compared to healthy control subjects is discussed in Chapter 6. Finally, in Chapter 7, the results of Chapters 1 to 5 will be discussed in the light of existing models on depression and anxiety disorders.