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## **The Affective Amygdala : towards a better understanding of adolescent depressive and anxiety disorders**

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## CHAPTER 1

General introduction



## Introduction

### *Scope*

The transition from childhood to adolescence is a vulnerable developmental period in which many external changes prevail: adolescents change schools, often start a part-time job and get new friends which become very important while they also become less dependent on their parents. Besides external changes, alterations at the biological level are remarkable as well, like the increase in pubertal hormones (Blakemore, Burnett, & Dahl, 2010) and the ongoing development of the brain (Giedd et al., 1999). For most adolescents, including myself, these changes just happen and have no further detrimental implications for their daily lives. Of course the majority of adolescents experience some struggles, for example having arguments with their parents about what time they need to be home or feeling extremely sad because their first relationship broke. For most adolescents, these feelings all pass by and do not cause ongoing problems. For some adolescents, however, this period is not without consequences and includes the onset of depressive and anxiety disorders. They struggle much more with their feelings and behaviors and experience problems in daily life. Although we know quite a lot about the development and persistence of depressive and anxiety disorders during adolescence and several randomized controlled trials indicated that the current treatment and intervention approaches are quite effective (Compton, Burns, Helen, & Robertson, 2002; Compton, March, Brent, Albano, Weersing, & Curry, 2004), there are many adolescents who do not benefit from treatment. Conducting research to examine the underlying neurobiological mechanisms of adolescent depression and anxiety can provide us with better insights about the exact mechanisms of these disorders and eventually might provide guidelines for the development of better treatment and intervention strategies (cognitive behavioral therapy or medication therapy).

Quite some studies have indicated that the amygdala is an important brain region related to emotion processing (Fusar-Poli et al., 2009; Wha-



len, Davis, Oler, Kim, Kim, & Neta, 2009) and it is shown that depressed and anxiety participants (both adults and adolescents) show increased amygdala activation when processing emotional faces when compared to healthy controls (Beesdo et al., 2009b; Monk et al., 2008a; Monk et al., 2008b; Perlman et al., 2012; Thomas et al., 2001a). The results of these studies suggest that the amygdala is a target region when performing research into the neurobiological mechanisms of depression and anxiety. Because depression and anxiety often have their onset during adolescence, it is important to further investigate differentiating patterns of amygdala activation within this specific period. Furthermore, efforts should be made to examine longitudinal changes in amygdala activation. Only these studies provide with important information about individual differences in the development of depressive and anxiety disorders. Therefore, we conducted a large longitudinal study examining cross-sectional and longitudinal differences in amygdala activation and connectivity in a sample of adolescents with depressive and anxiety disorders.

### *Depression and anxiety*

Depression and anxiety are two of the most diagnosed psychiatric disorders during adolescence. Studies investigating prevalence rates indicated that approximately 10% of adolescents develop a depressive disorder and about 20-24% any anxiety disorder (Kessler et al., 2012a). The comorbidity between depressive and anxiety disorders is found to be high: for example a study by Essau (2008) investigate the comorbidity of depressive and anxiety disorders in adolescents and showed that about half of the adolescents with a depression diagnosis also fulfills the criteria for an anxiety disorder. This high comorbidity and the large overlap in emotion related symptomatology increases the need to examine both disorder groups together.

The presence of a depressive or anxiety disorder all too often causes substantial problems in the lives of adolescents. Research indicated that depression and anxiety lead to a decrease in the rating of quality of life and af-

ffects the thoughts, feelings and behaviors of these adolescents, which influences their daily life (Zisook et al., 2007). When taking comorbidity between depression and anxiety into account the perspectives are even worse: Lewinsohn and colleagues (Lewinsohn, Gotlib, & Seeley, 1995) reported poorer global functioning, more academic problems and a higher risk for attempted suicide in a comorbid depressed-anxious group compared to a 'pure' depression group. Depression and anxiety not only cause problems during adolescence, but also continues to affect people into adulthood: Adolescents with a depressive or anxiety disorder have a 2- to 3-fold increased risk for having a depressive or anxiety disorder during adulthood (Pine, Cohen, Gurley, Brook, & Ma, 1998). This suggests that these disorders are relatively complicated and are hard to treat, which makes it even more important to conduct studies that include both depressed and anxious adolescents.

One often used form of treatment for depression and anxiety in adolescents is cognitive behavioral therapy (CBT). Individuals with a depression or anxiety disorder often have maladaptive thoughts, feelings and behaviors. By changing and exploring individuals can learn how to adapt their thoughts, feelings and behaviors. It challenges an individual to replace the maladaptive thoughts, feelings and behaviors with adaptive ones. Techniques that are applied within CBT include exposure and cognitive restructuring (Compton et al., 2004). Research has shown that CBT is a quite effective form of treatment for both depression and anxiety, with comparable levels of effectiveness as treatment with medication (Compton et al., 2002; Compton et al., 2004). However, not everyone benefits from CBT and more research is necessary to further investigate why some individuals do benefit while others do not. One way of doing that is by examining the neurobiological mechanisms of depression and anxiety with the use of functional Magnetic Resonance Imaging (fMRI).

### *Depression and anxiety in the brain*

When conducting research on the neurobiological mechanisms of de-





pressed and anxious adolescents, it is important to take brain development into account. Research indicated that there are ongoing changes in gray matter and white matter that continue into adulthood (Giedd et al., 1999) and are related to enhanced plasticity in cognitive and emotional functioning (Steinberg, 2005). Furthermore, it is known that several brain regions or networks follow distinct maturational trajectories: the cognitive control regions in the prefrontal cortex develop at a slower pace than regions related to the processing of affective information in the limbic system (Gogtay et al., 2004). Because of these distinct maturational trajectories, an imbalance arises in which the limbic 'emotional' regions are further developed than the prefrontal 'control' regions (Somerville, & Casey, 2010). It appears that this imbalance is largest during adolescence and possibly plays a role in the onset of depression and anxiety during adolescence (Casey, Jones, & Hare, 2008; Somerville, & Casey, 2010).

One brain region within the limbic system that is important for the processing of emotional stimuli is the amygdala. The amygdalae are two almond shaped groups of nuclei located deep in the brain. It is known that the amygdala is involved in the processing of emotional stimuli, more specifically emotional faces (Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Fusar-Poli et al., 2009; Whalen et al., 2009). Furthermore, the amygdala is part of the social information-processing network and the overlapping face processing network (Scherf, Behrmann, & Dahl, 2012). Finally, research indicated that the amygdala is important for learning associations between a stimulus and its emotional significance, for example learning the association between seeing a spider and being afraid and careful (Tottenham, Hare, & Casey, 2009a). Early on, it was thought that the amygdala only was involved in the processing of negative stimuli. However, nowadays the amygdala is known to be involved in the processing of both negative and positive stimuli (Davis, & Whalen, 2001; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; Van Den Bulk et al., 2013). Meta-analyses by Costafreda and colleagues (2008) and Fusar-Poli and colleagues (2009) showed that the amygdala is

most strongly activated in response to fearful and disgusted faces, but also in response to happy and neutral faces. Studies investigating developmental differences in amygdala activation in response to emotional faces indicated that there is an increase in amygdala reactivity during adolescence (Baird et al., 1999; Guyer et al., 2008; Pfeifer et al., 2011). For example, a study by Hare (Hare, Tottenham, Galvan, Voss, Glover, & Casey, 2008) indicated that adolescents showed higher levels of amygdala activation compared to children and adults when performing an emotional go no-go task. These findings seem to correspond to the theory of an imbalance in the development of prefrontal cortex regions and limbic regions (Somerville, & Casey, 2010).

Overall, the amygdala is important for the processing of emotional stimuli. Because it is thought that in depression and anxiety the primary emotional response is exaggerated and not effectively controlled by prefrontal cortex regions (Mayberg, 1997), the amygdala might be important target regions when examining the neurobiological mechanisms of depression and anxiety. There are some studies that investigated amygdala reactivity to emotional stimuli in adolescents with depressive and anxiety disorders (Hulvershorn, Cullen, & Anand, 2011; Monk, 2008). In general these studies reported heightened patterns of amygdala response to emotional faces. The results of studies including depressed adolescents are somewhat more inconsistent than those including anxious adolescents. For example, a study by Roberson-Nay and colleagues (2006) found an increase in amygdala response for depressed adolescents compared to healthy controls while another study including depressed adolescents reported a decrease in amygdala response (Thomas et al., 2001a). Studies including adolescents with an anxiety disorder show much more consistency: when using an emotional face processing task several studies reported an increase in amygdala activation in response to emotional faces for the anxious adolescents when compared with healthy controls (Mcclure et al., 2007b; Monk et al., 2008b). Even though the results of studies including depressed adolescents are somewhat inconsistent, in general increased patterns of amygdala activation in response to



emotional stimuli are found for depressed and anxious adolescents. These findings suggest that increased amygdala activation might be an underlying neurobiological mechanism of depression and anxiety. This suggestion is supported by some research that investigated the relation between differentiating patterns of amygdala activation and levels of self-reported anxiety symptoms, symptom severity and diagnoses (Ball et al., 2012; Monk et al., 2003a; Stein, Simmons, Feinstein, & Paulus, 2007; Thomas et al., 2001a). These studies indicated that there is a positive relation between levels of self-reported anxiety symptoms and amygdala activation.

Although some research has indicated that adolescents with depressive and anxiety disorders show heightened patterns of amygdala activation, more research is necessary to further investigate the neurobiological mechanisms of depression and anxiety. Up till now, most research has been performed in adults and the amount of research performed in adolescents is still relatively low. Furthermore, not much is known about longitudinal changes in amygdala activation in depressed and anxious adolescents: most studies used data of just one fMRI session and compared a depressed/anxious group with a healthy control group (Canli et al., 2005; McClure et al., 2007a). Performing longitudinal research provides us with the opportunity to examine individual differences and changes in amygdala activity and depression/anxiety symptomatology and thereby provides us with better insights in individual trajectories and the influence and effectiveness of treatment.

## **Objectives and approach**

### *Goal*

Because of the large increase in depression and anxiety diagnoses during adolescence and the persistence of these disorders into adulthood it is worthwhile to further investigate the underlying neurobiological mechanisms of adolescent depression and anxiety. Possibly, these studies will provide further insight in the mechanisms of these disorders and directions for future studies that might lead to better treatment and intervention strategies.

In this thesis we investigate the neurobiological mechanisms of depression and anxiety with a focus on amygdala functioning. The main objectives for this thesis were three fold. First, to further examine whether adolescents with depressive and anxiety disorders show increased patterns of amygdala activation compared to healthy controls when performing an emotional face-processing task. In addition, we also investigated whether depressed and anxious adolescents show less habituation of amygdala activation in response to emotion faces. Second, to examine the test-retest reliability of the fMRI signal in brain regions related to face processing (bilateral amygdala, bilateral lateral prefrontal cortex and visual cortex). Third, to study longitudinal changes in amygdala activity (task based activation) and connectivity (based on resting state analyses) in a sample of depressed and anxious adolescents who were referred for cognitive behavioral therapy based treatment. Within these studies we also explored the relation between changes in brain activity/connectivity and change in self-reported symptomatology.

### *Approach – the EPISCA study*

All studies described in this thesis were part of the larger EPISCA study. EPISCA stands for ‘Emotional Pathways’ Imaging Study in Clinical Adolescents’ and is a large longitudinal study in which three clinical settings collaborated: Curium-LUMC, ‘GZZ kinderen en jeugd Rivierduinen’ and ‘het kind en jeugd trauma centrum Haarlem’. The study included a group of treatment naïve adolescents with a DSM-IV depression or anxiety disorder, a group of adolescents who experienced childhood sexual abuse and who were seeking help for trauma related symptomatology and a group of normally developing adolescents without psychopathology. They all were between 12 and 19 years old.

The overall goal of EPISCA was to examine differences between these groups in the neurobiological mechanisms related to emotion processing and emotion regulation. To do this, all adolescents were scanned three times



in a six-month period. In between scan sessions the adolescents from the two clinical groups received treatment as usual which was based on cognitive behavioral therapy or EMDR (eye movement desensitization reprocessing). Adolescents from the control group were scanned within the same time interval but did not receive treatment. During a scan session several MRI parameters were collected: task based fMRI (emotional face processing task), resting state fMRI, high-resolution structural scan and Diffusion Tensor Imaging. Besides the scan sessions, we also administered several interviews (session 1 and 3), questionnaires (each session; both for the adolescents and their parents) and subtests of an intelligence test (session 1).

## Outline of the chapters

The first part of this thesis describes two task-based fMRI studies examining group differences in amygdala activation during an emotional face-processing task. In **chapter 2**, we included a group of adolescents with depressive and anxiety disorders and a healthy control group. All adolescents were scanned with fMRI and while in the scanner they performed an emotional face-processing task. This study aimed to investigate the underlying neurobiological mechanisms of depression and anxiety in relation to emotional face processing. By using an emotional face-processing task we were able to investigate differentiating patterns of amygdala activation and its relation to individual differences in self-reported depression and anxiety symptoms.

**Chapter 3** concerns a study including three groups of participants: a group of depressed and anxious adolescents, a group of adolescents who experienced childhood sexual abuse and a healthy control group. In this study we focused on group differences in the habituation of amygdala activation in response to emotional faces. We included two clinical groups to be able to investigate whether these groups showed different patterns of amygdala habituation in response to emotional faces. Depression/anxiety and childhood sexual abuse (CSA) share a lot of clinical features mainly related to mood and anxiety symptomatology. However, CSA also has a unique component namely the experience of a traumatic event.

**Chapters 4 and 5** describe longitudinal fMRI studies using an emotional face-processing task. Performing longitudinal fMRI studies provides us with the opportunity to examine individual changes in brain and behavioral functioning, which is important to understand the influence of development and treatment on brain functioning and the development and persistence of psychiatric disorders. We first examined the test-retest reliability of brain activation in a sample of healthy adolescents (**chapter 4**). These adolescents were scanned three times in a six-month period and during each scan session they performed an emotional face-processing task. More specifically, we focused on the within-subject reliability of amygdala, lateral prefrontal



cortex and visual cortex activation during an emotional face-processing task. These analyses provide us information about whether activation in a specific region at time point 1 is comparable to activation in that same region at time point 2 and 3 within individuals.

Next, we performed a longitudinal study investigating changes in amygdala and prefrontal cortex activation in depressed and anxious adolescents and a healthy control group, which is described in **chapter 5**. In this study we examined whether amygdala and prefrontal cortex activation changed over a six-month period during which the depressed/anxious adolescents received treatment as usual. Furthermore, we were interested in the relation between changes in brain activation and changes in self-reported symptomatology. We reasoned that brain activation might change under the influence of treatment: when treated adolescents report fewer symptoms which might be visible in the brain by means of a change in activation in important brain regions related to depression and anxiety like the amygdala and prefrontal cortex.

In **chapter 6** we shifted focus to resting state fMRI. The main objective of the study presented in **chapter 6** was to examine longitudinal changes in resting state functional connectivity in a sample of depressed and anxiety adolescents who were referred for treatment and a sample of healthy controls. We used a seed-based approach and focused on connectivity between the bilateral amygdala and the rest of the brain. Performing these analyses gives us more information about the connectivity between the amygdala and other brain regions and whether these changes are related to changes in self-reported symptomatology.

The last chapter (**chapter 7**) does not describe an empirical study but summarizes the findings of **chapters 2-6** (concluding remarks), provides some general considerations in relation to the studies described in the thesis and discuss the results in relation to the main goals stated in the introduction.

## The following papers have resulted from this thesis

**van den Bulk, B.G.**, Meens, P.H.F., van Lang, N.D.J., de Voogd, E.L., van der Wee, N.J.A., Rombouts, S.A.R.B., Crone, E.A., Vermeiren, R.R.J.M. *Amygdala activation during emotional faces processing in adolescents with affective disorders: the role of underlying depression and anxiety symptoms*. *Frontiers in Human Neuroscience*, 8, #393. (**chapter 2**)

**van den Bulk, B.G.**, Somerville, L.H., van Hoof, M.J., van Lang, N.D.J., van der Wee, N.J.A., Crone, E.A., Vermeiren, R.R.J.M. *Habituation effects during emotional face processing in adolescents with internalizing disorders, sexually abused adolescents and healthy controls*. Submitted. (**chapter 3**)

**van den Bulk, B.G.**, Koolschijn, P.C.M.P, Meens, P.H.F., Lang, N.D.J., van der Wee, N.J.A., Rombouts, S.A.R.B., Vermeiren, R.R.J.M. & Crone, E.A. (2013). *How stable is activation in the amygdala and prefrontal cortex in adolescence? A study of emotional face processing across three measurements*. *Developmental Cognitive Neuroscience*, 4, 65-74. (**chapter 4**)

**van den Bulk, B.G.**, Cousijn, J., van Lang, N.D.J., van der Wee, N.J.A., Rombouts, S.A.R.B., Crone, E.A., Vermeiren, R.R.J.M. *Amygdala reactivity to emotional faces in depressed and anxious adolescents: a longitudinal fMRI study across treatment*. Submitted. (**chapter 5**)

**van den Bulk, B.G.**, van der Werff, S.J.A., Aghajani, M., Granettia, M., van Lang, N.D.J., van der Wee, N.J.A., Rombouts, S.A.R.B., Crone, E.A., Vermeiren, R.R.J.M. *Longitudinal changes in resting-state functional connectivity in depressed and anxious adolescents in relation to treatment*. Submitted. (**chapter 6**)

