Neuroticism and the brain
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General introduction
1.1 General introduction

There are differences in the way individuals deal with emotions evoked by daily life events. Some stay cool and collected in case of a negative event, such as being rejected after a job interview, while others feel emotionally overwhelmed for a long period of time. Such emotional response patterns are part of an individual's personality, which can be described by a set of traits. In this thesis, we focus on the personality trait neuroticism that is characterized by a predisposition to experience increased negative emotions, such as sadness and fear, and to express heightened emotional reactivity to daily hassles (Costa and McCrae, 1992; Eysenck, 1967; Gray, 1982, 1991; Watson et al., 1994). Individuals with neurotic tendencies see their glasses half empty, make mountains out of mole hills and believe that after rain comes more rain (Suls and Martin, 2005). These kind of perspectives are generally not healthy and can lead to the development of a variety of psychiatric disorders, specifically depression and anxiety disorders (Lahey, 2009; Ormel et al., 2013b). The aim of the current thesis was to investigate the neural mechanisms underlying neuroticism to gain insight into why individuals scoring high on this personality trait are more vulnerable to develop psychopathology. To this end, we examined differences in brain function in relation to neuroticism with functional magnetic resonance imaging (fMRI) during rest as well as a number of emotion processing tasks. Furthermore, prior studies have shown that neuroticism is moderately heritable (=50%) (Boomsma et al., 2000; Canli, 2008; Distel et al., 2009; Flint, 2004; Hansell et al., 2012; Riese et al., 2009), therefore we examined whether genes, that have previously been suggested to be of relevance, moderate the association between neuroticism and brain function.

1.2 Neuroticism

1.2.1 Measurement and description

As mentioned above, neuroticism is generally defined as the tendency to experience increased negative affect and to react with a negative emotional response to daily life events (Ormel et al., 2013b; Suls and Martin, 2005). Methods that are usually applied to assess neuroticism are self-report questionnaires, followed by parent, teacher and peer reports. Objective behavioral tests (e.g. the self-introduction test wherein participants are seated in front of a camera and asked to introduce themselves, for more examples, see Back et al., 2009) are rarely used and their results are only weakly associated with scores on questionnaires, because the targeted behaviors do not fully represent the personality trait neuroticism (Ormel et al., 2012; Ormel et al., 2013b). Prior research has shown that women, younger individuals and individuals with lower social economic status score higher on neuroticism compared to men, older individuals and individuals with higher economic status, respectively (Lahey, 2009). Compared to individuals scoring lower on neuroticism, individuals scoring higher experience more feelings of anxiety, depression and anger, such as fear, tension, sadness, hopelessness, irritability and frustration. Furthermore, they experience more guilt and blame themselves more easily for making mistakes or failing to complete a task. In addition, these
individuals are more self-critical and highly sensitive to criticism by others (Watson et al., 1994). Moreover, high compared to low neurotic individuals tend to appraise the environment as more threatening and negativistic, leading to increased levels of stress. It has been proposed that these stress levels take longer to return back to baseline and possibly cause mood to spill over into the next time period, due to the application of maladaptive coping strategies (e.g. excessive worry and escape or avoidance) (Bringmann et al., 2013; Lee-Baggley et al., 2005; Muris et al., 2005; Suls and Martin, 2005; Watson et al., 1994; Watson and Hubbard, 1996). Lastly, high compared to low neurotic individuals experience more stressful life events, specifically interpersonal conflicts. The reason for this is that they tend to use ineffective interpersonal coping styles (e.g. hostile reactivity) (Bolger and Schilling, 1991; Bolger and Zuckerman, 1995; Gunthert et al., 1999; McCrae and Costa, 1986). In contrast, individuals scoring lower on neuroticism are emotionally more stable, down-to-earth, calm and even-tempered, compared to individuals scoring higher (Watson et al., 1994).

1.2.2 Personality theories

Neuroticism is part of a variety of widely accepted personality taxonomies of which three of the most influential ones will be discussed here. The first is the three factor model and the underlying arousal theory of Eysenck (Eysenck, 1967; Eysenck and Eysenck, 1991). According to Eysenck, there are three higher-order traits, named extraversion, neuroticism and psychoticism. He believed that these traits are highly heritable, have an identifiable biological substrate, are universal across cultures and have a relationship with psychological (mal)functioning. In his model, trait neuroticism is described as the expression of heightened emotional reactivity to stressors, which is caused by rapid arousability. Eysenck's theory (1967) links this tendency to a more excitable viscerocortical loop, interconnecting frontal (e.g. prefrontal cortex, PFC) and limbic (e.g. amygdala) brain regions, that is involved in regulating subjective and autonomic emotional responses, specifically during the experience of stressful events (Eysenck, 1967; Eysenck and Eysenck, 1991; Matthews and Deary, 1998).

The second taxonomy is the model of Gray and the underlying reinforcement sensitivity theory (Gray, 1982, 1991). Based on animal research, Gray proposed two biological systems in the brain that are important for personality. The first system is called the behavioral activation system (BAS), which is sensitive to reward and controls approach behavior (motivation). The second system is called the behavioral inhibition system (BIS), which is responsive to cues of punishment and non-reward and novel and fearful stimuli. Activation of the latter system results in the inhibition of behavior and the initiation of physiological and behavioral preparatory mechanisms in order to respond adaptively to potential sources of threat. The BIS consists of a number of brain regions that are part of the septo-hippocampal system, limbic system and frontal lobe and is more reactive in individuals with an anxious personality (e.g. neuroticism), leading to increased negative emotions (Gray, 1982, 1991; Matthews and Deary, 1998).
The third taxonomy is the five factor model of Costa and McCrae (1992). This model is based on the work of previous researchers (e.g. Digman, 1990 and Goldberg, 1990) that used lexical as well as statistical approaches to uncover the broad dimensions of personality. Specifically, clusters of personality descriptors were identified by performing factor analyses on personality related adjectives selected from the natural language. The five factors proposed by Costa and McCrae are named neuroticism, extraversion, openness, agreeableness and conscientiousness and are measured with the neuroticism-extraversion-openness personality inventory revised (NEO-PI-R). Each factor consists of six facets, the facets of neuroticism are anxiety, angry hostility, depression, self-consciousness, impulsivity and vulnerability. The factor neuroticism is defined as a dimension that ranges from emotional stability to negative emotionality (Costa and McCrae, 1992; Matthews and Deary, 1998). At present, the NEO-PI-R is the most widely used measurement of personality in neuroimaging research and its psychometric properties can be considered good. Cronbach's alpha ranges from 0.86 to 0.92 for the domain scales of the Dutch version of the NEO-PI-R (Hoekstra et al., 1996). This questionnaire was also used in the current thesis.

1.2.3 A mental and somatic risk factor

High neuroticism is a potent risk factor for a variety of psychiatric as well as somatic problems and disorders (Lahey, 2009). First, there is a strong association between neuroticism and several Axis I and II psychiatric disorders during development. A review of cross-sectional studies - investigating associations between higher-order personality traits (including neuroticism) and particular depressive, anxiety and substance use disorders (SUD) - found higher levels of neuroticism in all examined disorders (Kotov et al., 2010). On average, individuals diagnosed with a mental disorder score 1.65 (Cohen's d) standard deviations higher on neuroticism than individuals without a diagnosis, which can be defined as a large effect (d > 0.80). Specifically, neuroticism was strongly associated with depressive and anxiety disorders (e.g. dysthymia, generalized anxiety disorder, post-traumatic stress disorder, panic disorder and obsessive compulsive disorder), and to a lesser extent with SUD and specific phobia (for more details, see the review of Kotov et al., 2010). Prospective studies point in a similar direction, neuroticism is particularly predictive of depressive and anxiety symptoms/disorders and psychological distress, and less of substance use symptoms/disorders (mean d = 0.54 unadjusted for baseline psychopathology, mean d = 0.26 adjusted; a medium and small effect, respectively) (for more details, see the review of Ormel et al., 2013b). Furthermore, studies have found cross-sectional and/or prospective associations between neuroticism and somatoform disorders, schizophrenia, eating disorders and personality disorders (Lahey, 2009).

Second, neuroticism has been related to medically unexplained complaints and general health problems, such as abnormal cardiac and immune functioning. Moreover, it has been shown to predict longevity in the general population, morbidity and mortality in chronic diseases (e.g. cancer) and risk of committing suicide (for more details, see the review of Lahey, 2009). Besides
being a risk factor for the abovementioned, neuroticism is also related to increased comorbidity between psychiatric disorders and between psychiatric and somatic problems (Khan et al., 2005; Neeleman et al., 2001). This is important because individuals with comorbid disorders show more chronic disease courses and make more use of costly public health services (for more details, see the review of Lahey, 2009). In the Dutch general population, among the 5% highest scorers on neuroticism approximately 60% had a mental disorder at one-year follow-up, 40% a depressive or anxiety disorder and 67% a somatic disorder, compared to approximately 5%, 13% and 40% in the rest of the population, respectively. Furthermore, among the 5% highest scorers on neuroticism approximately 18% had more than three psychiatric disorders at one-year follow-up compared to approximately 1% in the rest of the population (Cuijpers et al., 2010).

1.2.4 Social-economic burden

In the Netherlands, it has been shown that i) neuroticism has a substantial effect on mental health care and public health and that ii) the associated economic costs (e.g. health care costs and costs due to production losses) are higher than those of common mental disorders (Cuijpers et al., 2010). First, the authors calculated the per capita excess costs of neuroticism, that is, additional costs that can be uniquely attributed to neuroticism as costs over the average ‘base rate’ costs per individual. Second, they compared these costs to the excess costs of mood disorders, anxiety disorders, SUD and somatic disorders. Notably, the results showed that the total excess costs per one million inhabitants of the 25% highest scorers on neuroticism (= $1.4 billion) are approximately 2.5 times higher than the costs of common mental disorders (= $600 million) and approximately two-thirds the costs of somatic disorders (= $2 billion). Furthermore, the results demonstrated that there is a positive association between neuroticism scores and the total per capita excess costs, with low costs for individuals with low scores on neuroticism (< $3000) and high costs for individuals with high scores on neuroticism (> $22,000). In conclusion, besides being a heavy burden on the individual and his/her social environment, neuroticism is also an important burden for society in terms of considerable economic costs (Cuijpers et al., 2010).

1.3 Neuroimaging and neuroticism

In the early theories of Eysenck (1967) and Gray (1982, 1991), it was already assumed that differences in brain functioning underlie neuroticism. Furthermore, neuroticism is a clinically relevant concept and it is important to identify and map its underlying neural correlates. By investigating the neural basis of neuroticism, we may be able to elucidate its relationship with psychopathology and possibly develop treatments that prevent individuals with higher levels of neuroticism to transit from a healthy state to clinical state.

1.3.1 Magnetic Resonance Imaging

One of the methods to investigate the human brain non-invasively is magnetic resonance
imaging (MRI). Using MRI, images of high spatial resolution can be produced without exposing the brain to radiation. Originally, this method is based on the fact that protons of certain atoms (e.g. hydrogen) have an axis of rotation, which aligns when placed in a constant magnetic field. When a radiofrequency (RF) pulse is applied, the orientation of the protons is perturbed while they absorb energy. This energy is released when the RF pulse is turned off and the protons return back to their original axes. The MRI device picks up these energy signals, which differ for different tissues in the brain, and constructs a three-dimensional structural image of the brain (Warach, 1995; Ward, 2010). The resulting image is static, however, when one is interested in activation changes over time then functional magnetic resonance imaging (fMRI) can be used. This method is based on the magnetic properties of hemoglobin, a protein that binds to oxygen in the blood. It is known that blood, that has already released its oxygen (deoxygenated hemoglobin), is more sensitive to the magnetic field than blood that is still carrying its oxygen (oxygenated hemoglobin). The ratio between oxygenated and deoxygenated hemoglobin is referred to as the blood oxygen level-dependent (BOLD) effect and increases when brain areas become more active. The MRI device continuously measures the BOLD effect by applying a similar procedure as in traditional MRI. From the returning energy signals, an image can be constructed showing brain activation that can be overlayed on a structural image of the brain to localize the activation pattern (Logothetis et al., 2001; Logothetis, 2002; Ward, 2010).

1.3.2 Structural imaging

Structural studies on neuroticism have investigated differences in brain volume and concentration and cortical thickness and surface, using voxel-based morphometry (VBM) and cortical thickness/surface-based analysis, respectively (Montag et al., 2014). Studies have shown a negative relationship between neuroticism and total brain volume, gray matter volume and the ratio between brain volume and intracranial volume (Bjørnebekk et al., 2013; Jackson et al., 2011; Knutson et al., 2001; Liu et al., 2013). Furthermore, in most studies, a negative association was found between neuroticism and brain volume, cortical thickness or cortical surface in frontal and temporal areas of the brain involved in cognition and emotion, such as the dorsal, ventral and orbital PFC and the inferior, medial and superior temporal lobe (Bjørnebekk et al., 2013; Blankstein et al., 2009; DeYoung et al., 2010; Jackson et al., 2011; Kapogiannis et al., 2013; Liu et al., 2013; Rauch et al., 2005; Wright et al., 2006; Wright et al., 2007). However, no associations (Cremers et al., 2011; Hu et al., 2011; Taki et al., 2013) or positive associations (Blankstein et al., 2009; DeYoung et al., 2010; Kapogiannis et al., 2013; Wright et al., 2007) between neuroticism and brain structure have been reported as well, but to a lesser extent.

Besides brain structure, studies have investigated structural brain connectivity in relation to neuroticism, using diffusion tensor imaging (DTI) (Montag et al., 2014). Notably, these studies showed a negative association between neuroticism and white matter integrity in multiple tracts interconnecting various brain regions, not only PFC regions and the amygdala (as hypothesized
by i.a. Eysenck, 1967) (Bjørnebekk et al., 2013; Xu and Potenza, 2012). Specifically, decreased structural connectivity was found, among others, in tracts interconnecting frontal, occipital, parietal and temporal lobes, orbitofrontal regions and limbic areas, the thalamus and frontal lobes and the two hemispheres. Due to the wide distribution of the observed effects, these studies suggested that general disconnectivity may potentially underlie the predisposition to experience increased negative affect (Bjørnebekk et al., 2013; Xu and Potenza, 2012).

1.3.3 Functional imaging

1.3.3.1 Task-based imaging

Most functional neuroimaging studies on neuroticism targeted one of the following three cognitive-emotional processes. The first is negative emotional biases in information processing. This causes individuals, that score higher on neuroticism, to pay more attention to negative cues in the environment than positive cues (Chan et al., 2007, 2009). Consequently, these individuals may develop negative thought schemas, appraise life events as more threatening, experience more interpersonal conflicts and retrieve more negative memories (Chan et al., 2007, 2009). A variety of paradigms have been applied in neuroimaging research on neuroticism to investigate the negativity bias in emotion processing, such as emotional face and scene processing tasks (Britton et al., 2007; Canli et al., 2001; Chan et al., 2009; Cremers et al., 2010; Cunningham et al., 2011; Harenski et al., 2009; Hyde et al., 2011; Jimura et al., 2009; Kehoe et al., 2012; Schuyler et al., 2014; Stein et al., 2007), emotional conflict tasks (Canli et al., 2004; Fruhholz et al., 2010; Haas et al., 2007; Han et al., 2013), mood-induction paradigms (Koelsch et al., 2013; Park et al., 2013), emotional word categorization tasks (Chan et al., 2008) and emotional prosody tasks (Brück et al., 2011). In high compared to low neurotic individuals, abovementioned studies have demonstrated increased activation in brain regions involved in the identification and interpretation of emotions during the processing of negative emotional stimuli, in contrast to positive emotional stimuli and/ or neutral stimuli. These regions included the amygdala, insula, fusiform gyrus and a number of frontal (e.g. dorsal PFC and anterior cingulate cortex, ACC), temporal (e.g. middle temporal gyrus and temporal pole) and parietal (e.g. superior parietal gyrus) regions. Furthermore, Cremers et al. (2010) have investigated functional connectivity during the processing of negative facial expressions and found that neuroticism was i) negatively correlated with connectivity between the left amygdala and ACC and ii) positively correlated with connectivity between the right amygdala and the dorsomedial PFC. These findings suggest that individuals with higher levels on neuroticism may exhibit reduced top-down emotion regulation and stronger self-referential processing in response to negatively valenced stimuli, respectively.

The second and third cognitive-emotional process are fear learning and anticipation of aversive stimuli. These two related processes have been found to be altered in individuals scoring higher on neuroticism compared to individuals scoring lower. According to the theories of Eysenck
(1967) and Gray (1982, 1991), high neurotic individuals have difficulties in forming adaptive and meaningful associations that lead to the engagement of physiological and behavioral mechanisms in order to prepare for threats and stressors in their environment. Studies have applied the Pavlovian conditioning paradigm to investigate the neural correlates of fear learning and anticipation in association with neuroticism (Brühl et al., 2011; Coen et al., 2011; Drabant et al., 2011; Hooker et al., 2008; Kumari et al., 2007; Tzschoppe et al., 2014). In this paradigm, subjects have to learn the association between a neutral conditioned stimulus (CS, e.g. tone) and an aversive unconditioned stimulus (UCS, e.g. electrical shock) through repeated pairing of the two stimuli. The CS-UCS association has been learned when a conditioned response (CR, e.g. skin conductance response) is generated to the CS in anticipation of the UCS (Sehlmeyer et al., 2009). Different stimuli have been used as UCS in neuroimaging studies on neuroticism, such as screaming sounds, negative facial expressions, emotional scenes, esophageal distention and electrical shocks (Brühl et al., 2011; Coen et al., 2011; Drabant et al., 2011; Hooker et al., 2008; Kumari et al., 2007; Tzschoppe et al., 2014). In high compared to low neurotic individuals, differential activation has been found in the amygdala, hippocampus, striatum, thalamus, middle temporal gyrus, ACC and several frontal (e.g. middle frontal gyrus), parietal (e.g. precuneus and posterior cingulate cortex) and occipital (e.g. middle occipital gyrus) regions during fear learning and anticipation of aversive stimuli (Brühl et al., 2011; Coen et al., 2011; Drabant et al., 2011; Hooker et al., 2008; Kumari et al., 2007; Tzschoppe et al., 2014).

As mentioned above, the majority of research on neuroticism has been focused on negative emotional processing biases, fear learning and anticipation of aversive stimuli. However, there are other key cognitive-emotional processes related to neuroticism that are important and lack investigation, specifically sensitivity to criticism, the use of maladaptive coping mechanisms and social cognition during interpersonal interactions (see section Measurement and description of Chapter 1). In the current thesis, we will focus on these other processes to gain more knowledge on neuroticism and its relationship to brain functioning and psychopathology.

1.3.3.2 Resting-state imaging

Besides task-based imaging, resting-state imaging has been used to discover the neural basis of neuroticism. During a resting-state scan, individuals are instructed to close their eyes and to not fall asleep. They do not have to perform an explicit task, but instead are allowed to let their mind wander. Due to this, intrinsic spontaneous fluctuations in the BOLD signal can be measured that are unconstrained by external task demands (Buckner et al., 2008). Different methods have been used in resting-state research on neuroticism to investigate: functional segregation and integration in the brain (graph theory analysis, GTA) (Gao et al., 2013), connectivity between brain regions (seed-based analysis) (Adelstein et al., 2011), the fractional amplitude of low-frequency oscillations in brain regions (fALFF) (Kunisato et al., 2011; Wei et al., 2014) and the coherence of spontaneous BOLD activity in brain regions (regional homogeneity, ReHo) (Wei et al., 2011). The first two
methods and associated studies will be discussed in more detail below, since we applied both types of analyses in the current thesis.

First, Gao et al. (2013) have applied graph theory analysis on resting-state data to explore the whole-brain functional network organization in neuroticism. To this end, network measures were calculated that provide information on the way information is segregated (i.e. the presence of specialized local networks) and integrated (i.e. the presence of connections between these specialized local networks) (Rubinov and Sporns, 2010). Complex networks - such as the brain - typically show high functional segregation and integration, also called a 'small-world organization'. In this type of organization, an economical trade-off is made between adaptive topological values (e.g. high efficiency) and physical wiring cost; a balance that is often disturbed in neurological and psychiatric disorders (Achard and Bullmore, 2007; Bullmore and Sporns, 2012). Gao et al. (2013) found significant positive correlations between neuroticism and the betweenness-centrality network measure (i.e. a measure of integration that calculates the number of shortest paths that pass through a certain brain region) in the amygdala, precentral gyrus, olfactory cortex and caudate nucleus. The finding of the amygdala being a hub (i.e. a brain region that enables efficient information processing) may explain the observed increased emotional reactivity in individuals with higher levels of neuroticism. Notably, this study is based on a whole-brain network analysis. In the current thesis, besides this type of analysis, we also performed an analysis to investigate the integration of information within and between different functional subnetworks, specifically subnetworks related to emotion processing and cognitive control (e.g. affective subnetwork and frontal-parietal control subnetwork).

Second, Adelstein et al. (2011) have performed a seed-based analysis on resting-state data to investigate whether neuroticism modulates connectivity between two cortical hubs - the anterior cingulate cortex and precuneus - and the rest of the brain. In the seed-based method, a time course is extracted from an a priori region of interest (seed region) and similarity is quantified (e.g. using Pearson correlation) between this specific time course and time courses extracted from other voxels or seed regions in the brain (Margulies et al., 2010). Adelstein et al. (2011) found that neuroticism was positively correlated with connectivity between the precuneus (seed region) and dorsomedial PFC and speculated that individuals scoring higher on neuroticism may demonstrate increased self-evaluation and sensitivity to socio-emotional information during social interaction. In the current thesis, we applied this method to investigate the effect of criticism on functional connectivity in association with neuroticism, using seed regions related to self-referential processing and stress-regulation.

1.3.3.3 Genetic imaging

1.3.3.3.1 Endophenotype approach

Prior research has shown that neuroticism is moderately heritable and that approximately
50% of the variance in neuroticism can be attributed to genetics (Boomsma et al., 2000; Canli, 2008; Distel et al., 2009; Flint, 2004; Hansell et al., 2012; Riese et al., 2009). As is the case with common mental disorders, the genetic basis of neuroticism is complex, that is, it is not caused by a single gene but multiple minor mutations at different gene loci (Canli, 2008; Flint, 2004). Due to this polygenic nature, traditional linkage methods have failed to find risk or disease promoting genes and therefore, a different approach was needed to make gene mapping successful again. This approach was based on the concept of endophenotypes (Cannon and Keller, 2006), which are intermediate phenotypes that lie in between the genotype and phenotype. Examples of endophenotypes are, among others, neural system dysfunction and cognitive-emotional impairment. The assumption is made that endophenotypes are more elementary in nature and because of that, implicate fewer genetic, environmental and epigenetic factors as well as interactions between them in producing phenotypic variation (Gottesman and Gould, 2003). The watershed analogy, describing this concept, states that upstream genes (water sources, e.g. 5-HTTLPR) (in interaction with the environment) impact downstream phenotypes (sea, e.g. neuroticism) via different pathways, that is, endophenotypes (rivers, e.g. dysfunctional amygdala activation during emotional face processing). Hence, investigating endophenotypes may facilitate the discovery of associations between the genotype and phenotype.

1.3.3.3.2 SLC6A4 and COMT gene

Two genes that have been studied extensively in relation to neuroticism and emotion processing are the serotonin transporter gene (SLC6A4) and catechol-O-methyltransferase (COMT) gene (for reviews, see Bevilacqua and Goldman, 2011; Canli, 2008; Domschke and Dannlowski, 2010; Hariri and Holmes, 2006; for a meta-analysis on COMT, see Mier et al., 2010). First, the SLC6A4 gene is an important regulator of serotonergic neurotransmission through the reuptake of serotonin (5-hydroxtryptamine, 5-HT) from the synaptic cleft in, among others, limbic regions of the brain (Bevilacqua and Goldman, 2011; Hariri and Holmes, 2006). A common length polymorphism (5-HTTLPR) is located in the promotor region of this gene and encodes two alleles: a short (S) allele comprising 14 repeat sequences and a long (L) allele comprising 16 repeat sequences (Bevilacqua and Goldman, 2011; Hariri and Holmes, 2006). Carrying the S-allele has been associated with lower serotonin transporter binding and mRNA expression as well as lower serotonin uptake compared to carrying two copies of the L-allele (Lesch et al., 1996). Furthermore, the L-allele is functionally regulated by an A to G substitution in the single-nucleotide polymorphism (SNP) rs25531 located close to 5-HTTLPR, making its transcriptional efficacy more comparable to the low-expressing S-allele (Hu et al., 2006; Wendland et al., 2006).

Second, the COMT gene produces the enzyme COMT that inactivates catecholamine neurotransmitters dopamine, epinephrine and norepinephrine, specifically in the PFC (Mier et al., 2010). Enzyme function is in part influenced by a G to A substitution at codon 158 (rs4680), producing an amino acid change from valine (Val) to methione (Met) (Lachman et al., 1996). The
Met-allele is thermolabile at normal body temperature and has a three-to-four fold reduction in enzyme activity compared to the Val-allele, leading to higher dopamine concentrations and more efficient information processing in the PFC (Chen et al., 2004; Egan et al., 2001; Lachman et al., 1996). Furthermore, other SNPs in the COMT gene have also been shown to be important in relation to neuroticism, specifically SNP rs165599 (Hettema et al., 2008).

Results from studies investigating an association between neuroticism and 5-HTTLPR or COMT rs4680 have been largely inconsistent (Lee and Prescott, 2014; Minelli et al., 2011). Specifically, six meta-analyses have been performed to find evidence for an association between neuroticism and 5-HTTLPR and revealed contradictory results (Minelli et al., 2011; Munafo et al., 2003, 2005, 2009; Schinka et al., 2004; Sen et al., 2004). In neuroimaging studies, based on the endophenotype approach, the genetic influence of 5-HTTLPR and COMT rs4680 on the brain has been investigated during several cognitive-emotional processes (Bevilacqua and Goldman, 2011; Hariri and Holmes, 2006; Mier et al., 2010). For 5-HTTLPR, Hariri et al. (2002) have shown in their seminal paper that carriers of the S-allele exhibited increased amygdala activation in response to fearful and angry facial expressions compared to L-allele homozygotes. Furthermore, Pezawas et al. (2005) and Heinz et al. (2005) have also demonstrated altered functional connectivity between the amygdala and PFC during emotion processing (emotional faces and scenes) in individuals carrying the S-allele. However, a recent meta-analysis on the association between 5-HTTLPR and amygdala activation has revealed a borderline significant result, when unpublished studies were included (Hedge $g = +0.21$, 95% CI 0.00, +0.43, $p = 0.05$) (Murphy et al., 2013). In the current thesis, we updated this meta-analysis with data from our relatively high-powered sample. For COMT rs4680, Egan et al. (2001) have found that Val-allele load was related to increased PFC activation (reduced PFC efficiency) during a working memory task (N-back). This finding was further confirmed in a meta-analysis on this topic, showing a pooled effect size of 0.73 (Cohen’s $d$, 95% CI +0.33, +1.14) with a $p$-value <0.001 (Mier et al., 2010). However, the opposite effect was shown for emotion processing tasks, that is, increased PFC activation in Met-allele carriers ($d = -1.0$, 95% CI -1.38, -.062, $p<0.001$) (Mier et al., 2010). With regard to neuroticism, to our knowledge, no genetic imaging studies have been performed investigating the influence of 5-HTTLPR and COMT rs4680 on the association between neuroticism and brain function. However, studies on other neuroticism-related anxiety traits have shown increased amygdala activation and decreased functional connectivity between the amygdala and PFC during emotional face processing, modulated by 5-HTTLPR (for a review, see Domschke and Dannlowski, 2010). In the current thesis, we shed more light on the relationship between 5-HTTLPR/COMT rs4680, neuroticism and brain function, following the recent perspective that genes have an impact on functional network organization.

### 1.4 Thesis outline

The aim of the current thesis was to investigate the neural mechanisms underlying neuroticism...
to gain insight into why individuals scoring high on this personality trait are more vulnerable to develop psychopathology, using fMRI and genetic imaging. In Chapter 2, we performed a meta-analysis on neuroimaging studies investigating neuroticism and emotion processing to provide a quantitative summary of the existing literature. Based on the meta-analytic findings, we proposed an integrated model of emotion processing in neuroticism. In the next chapters, we focused on other key cognitive-emotional processes that are altered in neuroticism, besides basic emotion processing (negativity bias), fear learning and anticipation of aversive stimuli, that lack investigation in neuroimaging research: i) the use of worry as a coping mechanism (Chapter 3), ii) emotional reactivity to unfairness (Chapter 4) and iii) sensitivity to criticism (Chapter 5). In Chapter 6, we investigated the functional network organization in association with neuroticism using resting-state fMRI. The reason for this was that studies investigating the neural basis of neuroticism have suggested that (widespread) alterations in connectivity may underlie it. Furthermore, besides investigating the whole-brain network (as in Gao et al., 2013), we investigated the properties of the different functional subnetworks to investigate the functional integration of information within and between subnetworks related to emotion processing and cognitive control. In Chapter 7, we investigated the alleged association between 5-HTTLPR and amygdala activation in our sample and updated the recent meta-analysis of Murphy et al. (2013) on this topic. In Chapter 8, we investigated the triadic interplay between 5-HTTLPR/COMT, functional brain network organization and neuroticism. The reason for this was that recent reviews on genetic imaging and psychopathology proposed that psychopathology probably arises from alterations in the functional segregation and integration of neural circuits (i.e. disrupted connectivity), not from altered activation in a few specific brain regions during a particular task. Finally, in Chapter 9, we conclude this thesis with a summary of the chapters, a general discussion of the results and suggestions for future research and clinical implications.
PART I

META-ANALYSIS