The stress connection: Neuroimaging studies of emotion circuits in social stress, personality, and stress-related psychopathology

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CHAPTER 8

General discussion

Chapter 8

SUMMARY OF FINDINGS

Social stress and emotional working memory

In **Chapter 2** the effects of acute social stress on distracter inhibition during working memory were studied. Participants had to keep in mind a set of letters for one and a half second, during which a neutral or emotionally negative picture was shown that had to be ignored. Subsequently, presence of the remembered letters (targets) had to be verified in a second set of letters (probe). Working memory performance, as measured by reaction times to the probes, was slower for negative than for neutral distraction in stressed participants compared with non-stressed controls, together with greater activation in ventral "affective" areas and, reduced deactivation in dorsal "executive" areas during distraction. In addition, smaller distracter interference and reduced activity of the ventral "affective" areas were both associated with higher cortisol levels in the stress group. Together, these results suggest that the brain prioritizes processing of salient information at the cost of cognitive performance in the aftermath of acute stress, while cortisol might play a modulatory role.

Social stress and resting-state functional connectivity

Chapter 3 described the prolonged effects of social stress on amygdala resting-state functional connectivity. Compared with non-stressed controls, increased connectivity was found with the precuneus, posterior cingulate cortex, and ventromedial prefrontal cortex in stressed participants. These midline structures are key nodes of the *default mode network*, and have been implicated in memory, emotion regulation, and social cognition. Differences in cortisol response to the stressor, however, were not associated with the strength of this connection. Although speculative, the stress effects on amygdala connectivity might be reminiscent of the process of reaching (behavioral) homeostasis after stress, which could linger long beyond the initial stress response.

Cortisol and resting-state functional connectivity

In **Chapter 4** it was tested whether amygdala resting-state functional connectivity might be related to individual differences in endogenous cortisol fluctuations under

relatively stress-free circumstances. Steeper cortisol decreases over the course of the experiment were associated with stronger *negative* amygdala functional connectivity with the medial prefrontal cortex, most notably the perigenual anterior cingulate cortex. It is hypothesized that this finding could be indicative of a cortisol-mediated regulatory network, served to adaptively adjust stress- and, more generally, emotional responses.

Resting-state functional connectivity in major depression

Differences in whole brain resting-state connectivity networks were assessed between unmedicated patients with *major depressive disorder* and matched healthy controls in **Chapter 5**. Within a ventral network, comprising key affective regions, depression was associated with reduced functional connectivity with the bilateral amygdala. In addition, reduced *negative* connectivity with the left frontal pole was found in the dorsal *task-positive network* in depressed patients compared with controls, as well as weaker connectivity with the lingual gyrus in a medial visual network. None of the effects were associated with symptom severity, suggesting these to be trait rather than state differences. Overall, these findings could reflect maladaptive emotional processing in ventral affective areas and compromised cognitive processing in dorsal regions, corroborating the current neural network models of depression.

PTSD and medial temporal lobe volumes

In **Chapter 6** differences in volumes of the hippocampus and amygdala were assessed between female *posttraumatic stress disorder* patients with a history of childhood maltreatment and matched healthy controls. Smaller right amygdala volumes were found in patients compared with controls, whereas the left amygdala and bilateral hippocampus did not differ between the two groups. In addition, this volume reduction appeared to be specific to the basolateral and centromedial nuclei groups of the right amygdala. Smaller amygdala volumes were furthermore associated with more severe sexual abuse during childhood. It is hypothesized that traumatic events in childhood might impede normal development of the amygdala, which could render someone more vulnerable to develop psychopathology later in life.

Personality and resting-state functional connectivity

Finally, in **Chapter 7** it was tested to what extent amygdala resting-state functional connectivity relates to interindividual differences in neuroticism and extraversion, personality traits that are associated with vulnerability and resilience, respectively, to affective disorders. Higher neuroticism was related to increased amygdala connectivity with the precuneus, and decreased amygdala connectivity with the temporal pole, insula, and superior temporal gyrus, which could be indicative of less adaptive perception and processing of self-relevant and socio-emotional information in neurotic individuals. Extraversion, on the other hand, was associated with increased amygdala connectivity with the putamen, temporal pole, and insula, which could relate to the heightened reward sensitivity and enhanced socio-emotional functioning observed in extraverts. These trait-specific functional connectivity patterns could potentially provide insights into the neurobiology underlying increased susceptibility or resilience to affective disorders.

INTEGRATION OF FINDINGS

The aim of this thesis was to provide more insight in how stress impacts emotion processing and regulation, how affective brain networks are modulated in the aftermath of a stressful situation, and how changes in functional connectivity within these networks can be related to stress-related psychopathology. Given its important role in the orchestration of stress responses (Ulrich-Lai & Herman, 2009) and (abnormal) emotion processing (Hariri & Whalen, 2011; Phillips, Drevets, Rauch, & Lane, 2003a; 2003b), the majority of the research described in this thesis revolved around the amygdala.

Consistent with the hypothesis that the brain prioritizes processing of salient information under stress, we found that ventral "affective" regions, most notably the amygdala, increased their response to negative pictures that had to be ignored, while dorsal "cognitive control" areas demonstrated relatively decreased activity (Oei et al., 2012). Although this study was designed to assess the effects of stress on inhibition

of distracters rather than on working memory per se, we did find an indication for slower, but not worse, performance for the stress group, yet only as a function of distracter type. This corroborates findings from previous studies in which reduced working memory performance could be measured after psychosocial stress or cortisol administration (Elzinga & Roelofs, 2005; Lupien et al., 1999; Oei et al., 2006; Schoofs et al., 2008), though an absence of behavioral differences (Porcelli et al., 2008; Qin et al., 2009), and even increased performance (Henckens et al., 2011), have been observed as well. Of note, larger cortisol responses were related to better performance and less amygdala activity in our study. On the one hand, these results are at odds with the study of Lupien et al. (1999), but corroborate the beneficial effects of cortisol on working memory (Henckens et al., 2011) and distracter inhibition (Oei et al., 2009). However, the stress-induced cortisol levels sampled in our study were relatively low compared with both other studies in which cortisol was administered, while concurrent stress-induced increases in noradrenaline might further obscure a direct comparison between experiments.

Our finding of increased amygdala activity in response to negatively arousing stimuli after stress is in keeping with the results from a previous study (van Marle et al., 2009). It can be appreciated that the shift from cognitive processing to vigilance towards salient, and potentially threatening, information under stress benefits immediate survival from an evolutionary perspective. However, as observed in our non-stressed participants, we are in general quite capable to actively inhibit intrusive information that could keep us from engaging in goal-directed behavior, which helps us to achieve our aims and objectives in everyday life.

Although adaptive in the short run, this regulatory mechanism might fail in more chronic stress states, and could, as such, form the basis for the pathological anxiety (Kim et al., 2011b), rumination (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002), or trauma-related intrusions (Shin & Liberzon, 2010), symptoms observed in a range of affective disorders. To test this hypothesis directly, we compared posttraumatic stress patients and healthy control participants on the same distracter inhibition task used before, though considering the disorder as a chronic stress condition, given the HPA-axis dysregulation that is typical for PTSD, instead of temporarily inducing

psychosocial stress. In line with our expectations, patients showed increased amygdala responses to emotionally salient pictures that had to be ignored, similar to the effects in healthy controls after stress. This might indicate a chronic state of increased attention towards threatening stimuli and reduced ability to dampen this response in posttraumatic stress disorder (Veer et al., in preparation).

To date, surprisingly few studies have been carried out on the effects of stress on connectivity within affective brain circuits in healthy participants. A recent study tested the whether changes in amygdala functional connectivity could be observed immediately following stress, which was induced by viewing negatively arousing video clips (van Marle et al., 2010). The authors reported increased connectivity with areas of the *salience network*, such as the dorsal anterior cingulate cortex (dACC), insula, and brainstem, which have been found to coactivate in response to a wide variety of both internally and externally generated salient signals (Seeley, Keller, et al., 2007a). Thus, increased connectivity between the amygdala and this network after stress could reflect the neural trajectory through which heightened monitoring and evaluation of information is achieved in the face of a stressful event. This is further substantiated by an earlier finding of increased blood flow within regions of the salience network *during* stress (Wang et al., 2005). Moreover, connectivity of the dACC with either other regions of the salience network (Seeley, Keller, et al., 2007a), or the amygdala (Kim, Gee, Loucks, Davis, & Whalen, 2011a), was found to be stronger when reported state anxiety was higher. Although this provides a potential link to stress-related disorders in which vigilance and autonomic tone is sustained, such relation has yet to be established.

In contrast to the immediate effects described above, we studied whether a stressful event modulates amygdala functional connectivity even long, in our case an hour, after the stress has been terminated (Veer et al., 2011). Instead of expecting connectivity changes related to the acute stress response, it was expected to find altered functional connectivity with regions more associated with regulation of stress responses, and (emotional) memory formation and consolidation. In this study we found increased connectivity with core regions of the *default mode network* (DMN), the posterior cingulate cortex (PCC) and precuneus, and medial prefrontal cortex

(mPFC), which have been implicated in mind wandering (Mason et al., 2007), autobiographical memory processes (Buckner & Carroll, 2007), and self-referential thought (Gusnard et al., 2001; Northoff et al., 2006; Raichle et al., 2001). As such, the network is hypothesized to provide the infrastructure for integrating past, present and future events that are related to the self (Buckner & Carroll, 2007). This would enable us to reflect on and learn from past experiences, which is essential to adaptively cope with future challenges. Given the dense connections between the hippocampus and both the PCC and amygdala (Amaral, 1986; Greicius et al., 2009), the increased amygdala connectivity with the DMN found here could potentially underlie stress-induced increased encoding and consolidation of emotionally salient events (Wolf, 2009).

In this study in healthy young males we did not find an association between the strength of amygdala connectivity and stress-induced cortisol levels. However, it is important to note that stress effects on memory do seem to depend on an interplay between cortisol and noradrenaline (Roozendaal et al., 2009; Strange & Dolan, 2004; van Stegeren et al., 2008), which was not assessed in our study. Perhaps surprisingly, we did find a relation between interindividual differences in endogenous cortisol and amygdala connectivity in our non-stressed controls (Veer et al., 2012). Higher cortisol levels at the start of the experiment, and subsequent steeper cortisol decreases over the course of the experiment, were associated with stronger negative amygdala connectivity with the perigenual ACC (pgACC). Lesions in the dorsal prelimbic cortex, which is considered a homologue of the human pgACC, causes disinhibition of stress responses in rodents (Boyle et al., 2005; Diorio et al., 1993; Furay et al., 2008). Given the hypothesized role of the pgACC in emotional conflict and regulation of autonomic and affective responses in humans (Etkin et al., 2006; Gianaros et al., 2008; Wager et al., 2009), a regulatory pathway between this area and the amygdala might be crucial for the negative feedback of cortisol in terminating stress responses. However, another recent study found diminished negative connectivity between the amygdala and a more dorsomedial portion of the PFC after hydrocortisone intake (Henckens, van Wingen, Joëls, & Fernández, 2012). Future studies are thus warranted to elucidate the effects of cortisol on amygdala-mPFC connectivity, and its relation

to regulation of stress responses, taking into account both the tonic and phasic effects of cortisol.

Similar to our findings after stress, we found an increase in amygdala connectivity with the precuneus in participants who scored higher on the personality dimension neuroticism (Aghajani et al., 2013). Neuroticism has been intimately linked to self-evaluative and ruminative behavior (Trapnell & Campbell, 1999), as well as to increased vulnerability for developing affective disorders (Bienvenu et al., 2001). Therefore, whereas self-evaluation could be an important regulatory feature in the aftermath of stress, especially when the stressful situation encountered was social in nature, higher neurotic individuals could be more susceptible to get stuck in a "ruminative loop". It is this susceptibility that has been proposed to be a major feature underlying depressive symptoms (Holtzheimer & Mayberg, 2011), while perseverative rumination has been linked to prolonged autonomic signs of stress (Brosschot, 2010). In addition, increased activity within cortical midline structures has been reported in a recent study when participants had more worry-related thoughts in response to worry-inducing sentences (Servaas, Riese, Ormel, & Aleman, 2014).

Although depression-related abnormalities in DMN connectivity have been described in literature (Greicius et al., 2007; Sambataro, Wolf, & Vasic, 2013a; Sambataro, Wolf, Pennuto, Vasic, & Wolf, 2013b; Sheline, Price, Yan, & Mintun, 2010; Zhou et al., 2010), we did not observe any differences within this specific network between our sample of depressed patients and healthy controls (Veer et al., 2010). However, we suffered the limitation of having only mildly depressed participants in our sample, of which several were already in remission at the time of scanning. Nevertheless, we did observe altered connectivity within three other networks. Patients showed reduced functional connectivity with the amygdala in a network comprising a set of other regions involved in emotion processing and regulation, such as the mPFC, temporal poles, and insula, which might mediate the affective symptoms of the disorder. We demonstrated a similar decrease in amygdala functional connectivity with the insula and temporal poles in higher neurotic individuals, while the opposite pattern was found for the more extravert participants (Aghajani et al., 2013). Again, this might reveal a neural pathway that underlies the increased susceptibility to develop

affective psychopathology for higher neurotic individuals, whereas at the same time it might be considered a neurobiological marker for extraversion-related resilience to develop these disorders.

Only one study described in this thesis focused on the anatomical integrity of the amygdala, which was assessed in posttraumatic stress disorder patients with a history of childhood maltreatment (Veer et al., submitted). Here we found a smaller volume of the right amygdala compared with healthy controls, specifically in the centromedial and basolateral complex. The centromedial nucleus of the amygdala plays a major role in the stress response, as it initiates and regulates autonomic responses (Ulrich-Lai & Herman, 2009). The basolateral nucleus, on the other hand, has been implicated in responses to psychogenic stressors, regulation of the HPA-axis, as well as emotional memory (Roozendaal et al., 2009; Ulrich-Lai & Herman, 2009). Thus, the smaller right amygdala volume that was found in our study might relate to several hallmark symptoms of posttraumatic stress, including hyperarousal and intrusions of trauma-related memories (APA, 1994; Shin & Liberzon, 2010). A recent study reported *decreased* right amygdala grey matter for risk allele carriers of the brain-derived neurotrophic factor Val66Met polymorphism, associated with increased susceptibility for affective disorders (Montag, Weber, Fliessbach, Elger, & Reuter, 2009), while another study reported an association between *greater* right amygdala grey matter density and higher extraversion scores (Cremers et al., 2011), which could again be hypothesized to be a neurobiological marker for resilience to these disorders.

So far, resting-state functional connectivity studies of the amygdala are relatively sparse in posttraumatic stress disorder, and mostly carried out in male combat veterans, whereas our sample comprised female patients with a history of childhood maltreatment. Increased connectivity has been reported between the basolateral amygdala and the dorsal ACC and dorsomedial PFC (Brown et al., 2014), while another study showed decreased negative amygdala connectivity with the same region, as well as decreased connectivity with the hippocampus (Sripada et al., 2012). Studying the same female PTSD sample as used for assessment of medial temporal lobe volumes, we found results that point in the same direction (Veer et al., in preparation). Of major relevance to our specific patient sample with a history of childhood trauma,

reduced grey matter density in this exact dorsomedial PFC region has been described in participants that reported childhood emotional maltreatment (van Harmelen et al., 2010).

LIMITATIONS

The studies that were carried out for this thesis have several limitations. First, in our stress induction experiment we used the Trier Social Stress Test as stressor (TSST), which has social evaluative threat as its main stress-inducing component (Kirschbaum et al., 1993). However, other forms of stress-induction have been used in literature as well, including cold pressor stress (Cahill et al., 2003), and negatively arousing video clips (Hermans et al., 2011), which might all probe different aspects of the stress response. For example, a meta-analysis of stress-induction studies has shown that negative social evaluation in combination with uncontrollability of the situation, which both are aspects of the TSST, causes the highest increase in cortisol levels by far (Dickerson & Kemeny, 2004). Therefore, when elevation of cortisol levels is the main objective of stress-induction, it could be advised to use the TSST, or other forms of social evaluative threat. However, whereas social stress might be highly commendable in relation to, for example, social anxiety disorder and emotional abuse, videos of violence might be more suited to study similarities with trauma related to sexual or physical abuse and combat experience.

Second, timing of measurements with respect to stress-induction is pivotal. Here, we studied effects directly after social stress (task), and one hour after induction (resting-state). In both cases our results are limited to effects of the stress response that happen on that specific point of time, which renders us blind to effects during other stages of the response. Although challenging to design and carry out, experiments that probe different stages of the stress response (Vaisvaser et al., 2013), or time-dependent effects of stress hormones (Henckens et al., 2010; 2011) are most likely to provide us a more comprehensive picture of the neurobiological sequelae of stress.

Third, not only is it well established that the stress response differs between males and females, but it also does within females, depending on the menstrual cycle (Kajantie & Phillips, 2006). Additionally, these differences are reflected by distinctive neural activity in stress-related brain regions as well (Goldstein, Jerram, Abbs, Whitfield-Gabrieli, & Makris, 2010; Wang et al., 2007). To this end, we decided to only include male participants in our social stress study. Our findings and conclusions with respect to the effects of stress are therefore limited to the male population. Conversely, we only assessed female posttraumatic stress patients, given the difficulty we encountered in finding male patients with a history of childhood maltreatment. To illustrate, physical and sexual abuse, which were two of our criteria, are more prevalent during childhood in females than in males (de Vries & Olff, 2009).

Fourth, in three of the four resting-state functional connectivity studies we employed a seed-based connectivity analysis, choosing the amygdala as seed. Although this type of analysis is well suited to address hypothesis-driven questions, as was the case in these studies, results are inherently limited to the connections of the seeds that are chosen a priori. This means that differences between our groups in neural circuits not associated with the amygdala seeds might have gone unobserved. In contrast, the more data-driven independent component analysis has the potential to explore the breadth of connectivity changes that might occur anywhere in the brain, which was used on our depression data. However, it has been shown that group differences might or might not become evident depending on the model order (i.e., number of components) that was chosen (Abou Elseoud et al., 2011). This suggests that it might even be feasible to run the analysis at a range of model orders, although this could, of course, easily lead to chance capitalization. A similar argument can be made for the number of components tested within a certain model order. Whereas with seed-based analyses one only has to correct for the number of voxels tested, a correction should additionally be carried out for the number of components tested. However, doing this for a typical number of networks, say ten, dramatically lowers the significance threshold to a point that we can be quite confident to have protected ourselves to false positive findings, at the cost of becoming highly susceptible to not finding true effects (i.e., false negatives). A possible solution to this problem has re-

cently been suggested by Abou Elseoud et al. (2014).

Fifth, as was already alluded to in the introduction, the use of global signal regression in seed-based connectivity analyses has become a matter of debate in recent years. Initially, this step was intended to correct for global confounding signal sources in the fMRI data, such as physiological noise. Although global signal regression has been praised for its potential to increase connectivity specificity (Weissenbacher et al., 2009), it has been shown that this analysis step necessarily also introduces negative correlations (assumed negative connectivity) to arise in the data (Murphy et al., 2009), and could potentially even cause spurious effects between groups (Saad et al., 2012). Although elegant techniques exist to correct for physiological confounds, such as RETROICOR (Chang & Glover, 2009; Glover, Li, & Ress, 2000), these typically depend on proper acquisition of the physiological signals (e.g., heart rate and respiration). In our seed-based connectivity studies, however, these data were incomplete, or not available at all, which led us to use global signal regression to try to account for these confounding factors. Importantly, after reanalyzing the data from our neuroticism and extraversion study without global signal regression, the results were highly similar. Nevertheless, future studies should best refrain from using global signal regression, as alternative correction strategies have become widely available in recent years. One such solution is ICA-based denoising of the data, as ICA has the potential to separate apparent neural signal sources from non-neuronal noise (Salimi-Khorshidi et al., 2014). In addition, new acquisition techniques, such as multiplexed fMRI acquisition, can substantially accelerate repetition times (TR < 1 s) between volumes, yielding better temporal specificity and better characterization of higher frequency artifact signal sources in the data (Feinberg et al., 2010; Uğurbil et al., 2013).

Sixth, we cannot infer causality from our connectivity measures, as these are merely correlational in nature. Any conclusions on the directionality of the effects are therefore highly speculative. Nevertheless, tract tracing and in vivo intervention studies in primates and rodents do inform us on the information flow within certain pathways or brain circuits, which can lead us to formulate causal hypotheses based on the connectivity effects measured in humans. Excitingly, recent research has suggested that high-resolution fMRI data acquired on a high field MR system could potentially

reveal causal connectivity patterns between regions in the visual cortex, making use of information from distinct cortical layers (Polimeni, Witzel, Fischl, Greve, & Wald, 2010). The authors describe a correlation in BOLD signal between the output layer of V1 and the input layer of area MT, thus suggesting information flow from the former to the latter region.

Seventh, another limitation pertains to multicollinearity issues in the *general linear model* (GLM), which was used for our seed-based connectivity studies. Estimation of parameter estimates (i.e., betas) of each individual predictor critically depends on which other predictors have been added to the model, and to what extent these predictors correlate among each other. It is this correlation that can influence the estimation of the parameter estimates, and even can cause otherwise uncorrelated variables to show an association (Andrade, Paradis, Rouquette, & Poline, 1999; Kraha, Turner, Nimon, Zientek, & Henson, 2012). In fact, the effects of global signal regression on the data described previously are the consequence of multicollinearity issues, given that the global signal will always correlate with any given voxel to some extent. However, typically a range of other "nuisance" variables are added to the regression model, including regressors for motion, white matter, and cerebrospinal fluid, which through collinearity may all alter the parameter estimate of the seed of interest in their own respect. Therefore, reporting parameter estimates only, as is commonly (though not exclusively; Courville & Thompson, 2001) done in imaging studies, does not reveal the complete picture of relations between the different regression variables. Although several additional metrics have been proposed to better understand and interpret regression results in the face of multicollinearity (Kraha et al., 2012), these have yet to be implemented in fMRI analysis suites. Nonetheless, regression results are statistically valid, but should always be interpreted with respect to the other predictors in the model.

A final limitation relates to the small sample sizes used in most of the studies described in this thesis, especially the posttraumatic stress study. It has been argued that small sample sizes not only could lead to an increase in false negatives due to low power, but will also overestimate effect sizes of the effects that do pass the stringent correction for multiple comparisons (Button et al., 2013; Cremers, 2013; Yarkoni,

2009). As such, small sample sizes also hamper reproducibility of findings across studies. Unfortunately, however, it is not always possible to achieve large sample sizes due to, for example, patients that are hard to find, complicated and extensive research designs, financial limitations, or just lack of time. Detailed overviews of the issues related to reliability and replication of findings in cognitive and affective neuroimaging studies, as well as possible solutions, are offered in a recent special issue of *Cognitive, Affective, & Behavioral Neuroscience* (volume 13, issue 4, 2013).

FUTURE RESEARCH

This thesis concludes with some recommendations for future research. First, as was already argued in the limitations section, when designing a stress experiment the method of stress-induction should be chosen according to the specific research question, depending on, for example, which aspect of the neuroendocrine response is of interest, or to which disorders the type of stress should compare.

Second, the modulating effects of cortisol depend greatly on the timing of cortisol secretion or administration with respect to the stressful situation or the cognitive process to be studied, as well as the height of cortisol levels (Lupien et al., 2007; Sapolsky et al., 2000). Oftentimes, stress-induction methods, achieved cortisol responses, and the time of testing differ widely between studies, which makes it difficult to determine the exact effects of the hormone. Whereas this is difficult, if not impossible, to control for in stress-induction studies, experiments in which cortisol is administered should employ comparable doses. In addition, dose-response studies are warranted to determine level-dependent effects of cortisol on brain and cognition more accurately.

Third, all too often resting-state acquisition is still a byproduct of a larger imaging protocol. If one is truly interested in the unique information that resting-state fMRI has to offer, experiments should rather be designed to target task-independent neural activity specifically. Moreover, although simple group comparisons of resting-state data could inform us, for example, which brain circuits might be involved

in the pathophysiology of a disorder, future studies should strive to manipulate resting-state activity to be able to attach functional significance to these circuits.

Fourth, although symptomatic for the entire field of neuroimaging, more effort should be put into replicating resting-state findings, especially given the power issues related to smaller sample sizes described earlier. In addition, consensus on preprocessing and analysis standards would further improve comparability of findings between studies. Importantly, large-scale data sharing initiatives have emerged in recent years (e.g., the *1000 functional connectomes project*: www.nitrc.org/projects/fcon_1000), which already have resulted in the description of consistencies and discrepancies in resting-state derived metrics over a large collection of data acquired in different labs from all over the world (Biswal et al., 2010).

Fifth, traditionally resting-state activity and connectivity mostly have been studied as a static phenomenon over the period of acquisition. As the BOLD response is already a gross underestimation of the underlying neural dynamics, it is quite unrealistic to assume that functional connections do not change over the course of minutes, or even seconds. In recent years, attempts have been made to capture these dynamic changes over time, which are expected to give a deeper understanding of how connections between brain regions are related to information processing and behavior (Smith et al., 2009). The interested reader is referred to an excellent review providing an in-depth discussion of the concept, current methods, and limitations of time-varying functional connectivity (Hutchison et al., 2013).

CONCLUSION

In sum, in this thesis I have provided an introduction to the effects of stress on cognition, brain structure and function, and the relation to stress-related psychopathology. In addition, the studies that were carried out in the context of this thesis demonstrate how stress can influence information processing and even cause changes in functional connectivity up to an hour after the stress has waned. Moreover, it was shown through which circuit cortisol might modulate stress responses, and how personality dimen-

sions related to vulnerability and resilience to affective disorders can be associated with changes in brain circuits involved in the processing and regulation of emotions. Lastly, volume reductions were reported in specific subnuclei of the amygdala, which might relate to specific symptoms of posttraumatic stress disorder, and reduced integrity of large-scale connectivity networks was described in depression. Taken together, these findings strengthen our knowledge on the effects of stress and stress hormones on the brain, at the same time opening important new avenues for future research.