The stressed brain - discovering the neural pathways to risk and resilience

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Chapter 9

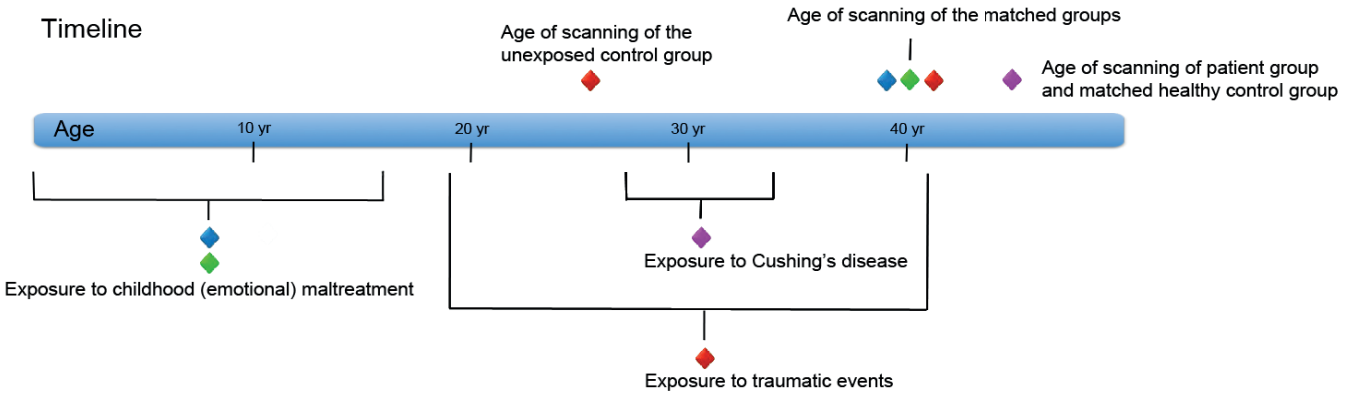
Summary and general discussion

The human body is inherently designed to be able to adapt to challenging situations. However, some experiences are so severe that they can lead to substantial and longer-lasting disturbances in an individuals' behavioral, psychological and physiological functioning. Importantly, there is a degree of inter-individual variation, as not all individuals show similar reactions to severe stress. Neuroimaging techniques can help to unravel the brain characteristics related to vulnerability and resilience to severe stress.

In the research for this dissertation several neuroimaging modalities were used to further explore the brain characteristics related to (dys)function after exposure to severe stress and after exposure to hypercortisolism, such as voxel-based morphometry and diffusion tensor imaging to study the structure of gray and white matter in the brain, and resting-state fMRI to study functional connectivity patterns. We studied brain characteristics in several groups: a group of patients in long-term remission of Cushing's disease and a group of individuals with a history of childhood emotional maltreatment to examine the effects of hypercortisolism and severe stress on the brain. In addition, we studied a group of police officers and a group of individuals with a history of childhood maltreatment to investigate the brain characteristics related to resilience to stress.

Figure 1. Summary of each Chapters findings and timeline

- Chapter 2: Childhood emotional maltreatment: Decreased RSFC between the right amygdala and the bilateral precuneus, and left insula. And between the dorsal ACC and the precuneus, and frontal parts.
- Chapter 3: A history of Cushing's disease: Decreased gray matter in the ACC and increased gray matter in the cerebellum
- Chapter 4: A history of Cushing's disease: Widespread reductions of white matter integrity
- Chapter 5: A history of Cushing's disease: Increased RSFC between the limbic network and the subgenual ACC, increased RSFC between the DMN and the left lateral occipital cortex
- Chapter 7: Resilience to childhood maltreatment: Increased RSFC between the dorsal ACC and the lingual gyrus and occipital fusiform gyrus
- Chapter 8: Resilience to traumatic stress: Increased white matter integrity of the corticopontine tract; and increased RSFC between the putamen and the precuneus.



Summary of results

Section I: Brain correlates related to severe stress exposure and their consequences
A short summary of the most important finding per Chapter is given in Figure 1, along with a timeline showing when the samples we used in each of the Chapters were exposed to stressful events or hypercortisolism and when the MRI scan was conducted.

Resting-state functional connectivity characteristics of adults with a history of childhood emotional maltreatment both with and without depression and anxiety were examined in Chapter 2, using a seed-based correlational approach. Four resting-state networks were examined: The limbic network, the salience network, the default mode network, and a network seeded by a location in the medial prefrontal cortex based on volumetric differences found in previous research (van Harmelen et al., 2010). The resting-state functional connectivity strengths of these networks were compared between a group of adults with a history of repeated emotional maltreatment during childhood (CEM; N = 44), and a control group of adults without a history of emotional maltreatment (N = 44). For the limbic network, the CEM group showed a decreased connectivity between the right amygdala and the bilateral precuneus and bilateral occipital cortex, as well as increased connectivity between the right amygdala and the other parts of the limbic network, including the putamen and the hippocampus in the left hemisphere of the brain. For the salience network, the CEM group showed decreased connectivity between the left dorsal anterior cingulate cortex seed and a region containing the angular cortex and the precuneus cortex, as well decreased connectivity between this seed and the medial prefrontal cortex. We found no differences between groups in connectivity with the default mode network and the left medial prefrontal cortex.

In Chapter 3, the effects of a history of excessive endogenous cortisol exposure resulting from Cushing's disease on gray matter volumes in the brain were investigated. Using a voxel-based morphometry method we found decreased gray matter volume in the anterior cingulate cortex, but were unable to associate gray matter volumes of this area to behavioral and cognitive functioning in the patients with long-term remission of Cushing's disease. In addition, we found an increased gray matter volume of the left posterior lobe of the cerebellum.

The structural connectivity characteristics related to a history of Cushing's disease were examined in Chapter 4, using a tract-based spatial statistics approach on

diffusion tensor imaging scans. All of our a priori hypothesized regions-of-interest showed reduced white matter integrity in the group of patients with a history of hypercortisolism. In addition, we found a relation within the patient group between depression scores and fractional anisotropy values in the left uncinate fasciculus, a white matter tract that has been implicated with major depressive disorder before. The findings of reduced white matter integrity in our regions-of-interest were put into another perspective when we found widespread reductions in white matter integrity throughout the brain, using an explorative whole brain analysis. These results indicated that effects of hypercortisolism on white matter integrity are global rather than localized.

Chapter 5 describes the resting-state functional connectivity characteristics of patients with remission of Cushing's disease. A probabilistic independent component analysis was used to extract data driven independent networks. Using visual checks, three a priori hypothesized networks were identified, which included the limbic network, the default mode network and the executive control network. An increase in resting-state functional connectivity was found in the patient group between the limbic network and the subgenual subregion of the anterior cingulate cortex, as well as an increase in connectivity between the default mode network and the left lateral occipital cortex. These findings were not associated with any of the behavioral measurements.

Section II: Brain characteristics of resilience to severe stress exposure

Chapter 6 describes the state of the art knowledge on the characteristics of brain structure and function related to resilience to stress as published until 2011. Typical regions of interest included the hippocampus, the amygdala, the anterior cingulate cortex and the prefrontal cortex. Most studies used a design that compared trauma-exposed non-PTSD (resilient) individuals with PTSD individuals. One of the most important conclusions of this review is that this design is insufficient to distinguish between characteristics related to PTSD, resilience or mere exposure. Therefore, alternative designs are described that enable disentangling the effects related to PTSD, resilience and trauma exposure, including longitudinally designed studies, and a three-group design with an additional non-trauma-exposed non-PTSD (healthy control) group.

In Chapter 7 we put into practice one of the suggested designs to study the resting-state functional connectivity characteristics of resilience to childhood maltreatment. We compared three groups (all N=11), including a resilient group of adults who

experienced childhood maltreatment without developing psychiatric disorders in later life, a vulnerable group of adults who experienced childhood maltreatment and developed a psychiatric disorder in later life, and a healthy control group of adults without a history of childhood maltreatment and without a history of psychiatric disorders. The same four networks were examined as described in Chapter 2, using a seed-based correlational approach. Increased connectivity was found between the dorsal anterior cingulate cortex seeding the salience network and the lingual gyrus and occipital fusiform gyrus in the resilient group compared to the two other groups. Examination of the other three networks did not reveal any resting-state functional connectivity results specific to the resilient group.

In Chapter 8 we examined the brain characteristics associated with resilience using a similar design but now in a group of Dutch police officers. Police officers are a highly relevant group when studying resilience duo to the frequency of which they are exposed to traumatic events. The results indicated no gray matter characteristics specific to resilience. However, we did find increased white matter integrity of a part of the corticopontine tract adjacent to the putamen, specific for the resilience group. In post-hoc analyses the white matter integrity in this tract was accompanied by increased resting-state functional connectivity between the putamen and the posterior cingulate cortex, and the precuneus. In addition, both white matter integrity and strength of resting-state functional connectivity were associated with positive reappraisal as coping style.

In the next sections the findings of our studies on vulnerability and resilience are integrated and discussed in light of findings of contemporary studies of brain characteristics of stress-related dysfunction and resilience.

Section I: The brain characteristics related to severe stress exposure and its consequences

Gray matter

Cushing's disease is an important research topic from three clinical points-of-view. The first perspective is that of the endocrinologist who treats the patients with Cushing's disease and sees these patients for checkups. After the hypercortisolism is cured patients improve substantially, but they often do not return to their normal level of functioning and most patients keep reporting symptoms despite (in some cases artificial) restoration of hormone levels (Tiemensma et al., 2010a; Tiemensma

et al., 2010b; Tiemensma et al., 2011). This phenomenon clearly warrants further investigation. The second perspective is that of the pharmacologist, as glucocorticoids are used as an immunosuppressive drug for various immune-related diseases. Excessive use of these types of medication can induce symptoms similar to those of Cushing's disease. This is called Cushing's syndrome. More insight into the persistent effects of hypercortisolism on the brain can have consequences for advised dosages and side-effect warnings. The third perspective is the behavioral point-of-view, or clinically speaking that of the psychiatrist or clinical psychologist. The HPA-axis is a hormonal system that plays a central role in many psychiatric disorders, and hypercortisolism can lead to psychiatric symptoms like depression and anxiety. Studying brain characteristics after hypercortisolism and comparing them to brain characteristics related to severe stress exposure might give an indication of the pathophysiological pathway through which increased levels of cortisol may lead to increased vulnerability for psychopathology. In this section we will attempt to integrate our findings with regard to brain characteristics of endogenous hypercortisolism (Cushing's disease) with the findings on brain characteristics related to exposure to severe exogenous stress (childhood maltreatment). It should be noted that cortisol levels in response to exogenous stressors are not as high as those seen in Cushing's disease. In addition, we did not directly compare the two groups. However, most studies in the literature do compare each of the groups with a healthy control group, so we are able to make conclusions related to the differences with the healthy population.

In Chapter 3 we found a decrease in gray matter in the anterior cingulate cortex in Cushing's disease patients. Interestingly, previous research by our group found this area was affected in adults with a history of childhood emotional maltreatment as well (van Harmelen et al., 2010), although the effect was not as large as we found in the Cushing's disease sample. Other studies support the finding of anterior cingulate cortex volume decreases in adults and adolescents with a history of childhood maltreatment (Cohen et al., 2006; Kitayama et al., 2006; Hart and Rubia, 2012). The observation that these decreases in volume are present after long-term remission of hypercortisolism or when individuals have long since passed into adulthood (as in the case of history of childhood maltreatment) indicates that these gray matter decreases are persistent. Another brain structure that is highly sensitive to exposure to excessive cortisol levels is the hippocampus (Starkman et al., 1992; Carrion et al., 2007). In our study, we did not find any abnormalities in hippocampal volume in patients with long-term remission of Cushing's disease. This is in line with previous studies, which suggest that damages to the hippocampus

can restore after hypercortisolism is normalized (Starkman et al., 1999; Bourdeau et al., 2002; Starkman et al., 2003). In line with these findings, studies into the effects of a history of childhood maltreatment on hippocampal volume report that smaller hippocampal volumes in maltreated subjects were related to present psychiatric symptoms rather than maltreatment itself (Bremner et al., 2003; Kitayama et al., 2005; Weniger et al., 2008; Hart and Rubia, 2012). Taken together, this suggests that the abnormalities in the anterior cingulate cortex represent a persistent effect of exposure to hypercortisolism and are possibly part of the pathophysiological pathway through which exposure to hypercortisolism leads to the development of psychiatric symptoms. A decrease in gray matter volume of the hippocampus, however, appears to be a temporary effect of exposure to cortisol excess and/or related to current psychiatric symptomatology. This effect is reversible after normalization of the excesses in cortisol levels.

White Matter

Studies on the effects of hypercortisolism on white matter integrity are scarce. Traditionally studies examined white matter volume using protocols similar to those being used to investigate gray matter volume. However, relatively recently the development of diffusion tensor imaging protocols has enabled the investigation of white matter integrity rather than volume. As white matter tracts are the wiring of the brain networks, the integrity of these tracts are thought to be better estimates of detrimental effects compared to white matter volumes. In Chapter 4, we found widespread reductions in white matter integrity in the patients with long-term remission of Cushing's disease, suggesting a more general effect of cortisol excess on white matter rather than localized effects. This finding is supported by animal studies finding reduced white matter integrity in multiple tracts throughout the brain as a result of early life exposure to severe stress, as well as an association with increased levels of cortisol (Howell et al., 2013). Animal studies also give an indication which microbiological processes might be involved in reducing white matter integrity as they show an association between prolonged exposure to corticosteroids and the inhibition of proliferation of oligodendrocyte precursors throughout the white matter (Alonso, 2000; van Gemert et al., 2006). Importantly, the findings of the study described in Chapter 4 have recently been replicated in a sample of active as well as remitted Cushing's syndrome patients (Pires et al., 2015).

In the context of childhood maltreatment there are few studies using diffusion tensor imaging protocols to investigate white matter integrity, and the results of the few studies that do are not univocal. Studies show reduced white matter integrity

in a wide array of white matter tracts, including the arcuate fasciculus, cingulum bundle, the fornix, the inferior longitudinal fasciculus, the corpus callosum, and the corona radiata (Choi et al., 2009; Teicher et al., 2010; Choi et al., 2012; Daniels et al., 2013). While there is a lack of clarity regarding the localization of the effects it does support the idea that Cushing's disease is associated with more general white matter affecting properties of cortisol excess, as opposed to more localized effects like we demonstrated in examination of gray matter.

With regard to the relation between behavioral symptoms and white matter integrity we found an association within the Cushing's group between depression and white matter integrity of the uncinate fasciculus, a tract connecting the limbic system with the medial prefrontal cortex areas. Reduced integrity of this tract has been a consistent finding in patients suffering from major depression disorder (Taylor et al., 2007; Cullen et al., 2010; Carballedo et al., 2012), suggesting that white matter integrity of this tract could partly underlie the development of depressive symptoms under influence of cortisol exposure.

On a more analytical note, the findings of this study provide a good example why it is important to perform a whole brain analysis supplementary to the more hypotheses driven region-of-interest analysis. If we had settled for the region-of-interest analysis, we would have confirmed our hypotheses about localization of the effects on white matter integrity, but would have missed the fact that the effects were widespread, suggesting more general white matter affecting properties of hypercortisolism instead of localized effects.

Resting-state functional connectivity

Resting-state functional connectivity between limbic areas and the medial prefrontal cortex appears to be very sensitive to stress (Urry et al., 2006; Kern et al., 2008; Henckens et al., 2010; Veer et al., 2012). In addition, aberrant connectivity patterns between these two areas have consequently been reported in stress-related disorders (Phillips et al., 2003; Drevets et al., 2008; Liberzon and Sripada, 2008; Veer et al., 2010), as well as in relation to childhood maltreatment (Herringa et al., 2013; Birn et al., 2014; Insana et al., 2015). Contrary to these findings, our results in Chapter 2 did not point at aberrant connectivity between the amygdala and the medial prefrontal cortex. An explanation could be that this pattern on functional connectivity reflects behavioral symptoms, whereas we controlled for the presence of psychopathology in our study. This also fits the model in which the medial prefrontal cortex plays an important modulatory role within the stress

system by inhibiting the amygdala (Liberzon et al., 2007). Failure to exert top-down inhibition on the amygdala can lead to sustained excessive amygdala activity, which is reflected in behavioral symptomatology.

Investigating seed-based resting-state functional connectivity from the amygdala in adults with a history of childhood maltreatment, we found decreased connectivity with bilateral precuneus and a cluster extending from the left insula to the hippocampus and putamen. Although we used another technique (probabilistic independent component analysis) to examine resting-state functional connectivity in the patients with remission of Cushing's disease, findings did not correspond. This suggests that the aberrant resting-state functional connectivity with the amygdala in adults with childhood emotional maltreatment was not modified under influence cortisol exposure.

Both the resting-state functional connectivity patterns we found in Chapter 5 and those in previous research conducted in stress-related disorders and stress exposure show patterns of aberrant connectivity between subcortical subregions of the limbic network (i.e., the amygdala and the hippocampus) and the medial prefrontal cortex. However, the direction of the findings is conflicting. Stress exposure and stress-related disorders are related to decreased connectivity between the areas, which also fits the model of top-down inhibition by the medial prefrontal cortex. However, we found increased connectivity between the limbic network and the subgenual anterior cingulate cortex. This could indicate that the human brain attempts to correct the initial suppression in functional connectivity under influence of hypercortisolism. Analogue to holding and releasing an air filled football underwater; it might be the case that once the hypercortisolism is successfully treated the suppression in functional connectivity will fade out, resulting in an overshoot of functional connectivity. Studies focusing on resting-state functional connectivity patterns of active hypercortisolism as well al more longitudinally designed studies should be able to provide more conclusive knowledge.

Future Perspectives

The results presented in the current thesis are in support of the hypothesis that individuals with a history of hypercortisolism show differences in the brain structure and function in the absence of tasks compared to a healthy control group. The next step would be to investigate the brain in directed action, using task-based fMRI. In doing so we can study brain function during tasks that are closely related to the behavioral symptoms displayed by the patients in long-term remission of Cushing's

disease. These studies give an indication about localization of affected brain function under influence of exposure to hypercortisolism. In fact, we already have taken a first step in this direction by investigating brain activity during processing of emotional stimuli (Bas-Hoogendam et al., 2015). In this study we found that patients with long-term remission of Cushing's disease showed less mPFC activation during the processing of emotional faces compared to the healthy control group.

Next, Cushing's disease should be studied in a longitudinal design to be able to draw causal conclusions about the effects of hypercortisolism on the brain. In addition, longitudinal studies could tell us something about the flexibility of the brain after correction of hypercortisolism. We already know that behavioral and cognitive functioning is improved after successfully curing the hypercortisolism. Longitudinal MRI studies will show us, which brain regions are associated with this restoration in functioning and which brain areas show more persistent changes under influence of hypercortisolism.

MRI is an instrument that allows us to investigate the human brain in vivo. However, MRI scans can only give us information about the brain on a macro level. Therefore, we still not know what happens to the brain of a living person under influence of hypercortisolism on a microbiological level. With regard to white matter integrity there is evidence from animal studies indicating that prolonged exposure to hypercortisolism affects oligodendrocyte-influenced remyelination (Alonso, 2000; Miyata et al., 2011). Animal studies on the effects of glucocorticoids on gray matter using stress-inducing paradigms found changes in hippocampal pyramidal cell morphology, and cell loss and suppression of neurogenesis in the hippocampus and parts of the medial prefrontal cortex (Uno et al., 1989; Sapolsky et al., 1990; Watanabe et al., 1992; Lambert et al., 1998; McEwen, 2008; Arnsten, 2009). Ideally, we would also want to measure these microbiological changes in humans. Progress in this area is being made by for instance the Allen Institute for Brain science. Combining information on neuroanatomy and genomics, the Allen Institute for Brain science has created gene expression maps for the human brain as well as the mouse brain. Using this information in combination with information from MRI studies like our study in Cushing's disease could give us more insight into which genes are influenced by cortisol excess and how they relate to changes in brain structure and function. The use of these Allen brain atlases could prove a pivotal in establishing an association between knowledge gained from MRI studies and localized gene expressions (Lein et al., 2007). In the studies with the patients with long-term remission of Cushing's disease, we focused on differences in brain

structure and function and subsequently attempted to explain persisting behavioral effects by examining brain characteristics. This was only possible through an intensive collaboration of various specialized departments, including psychiatry, endocrinology, and radiology. As science progresses it is insurmountable that, as we try to solve these complicated issues, collaboration between different specializations becomes more integrated in research structure.

Section II: Brain characteristics related to resilience to stress.
The main research question of this section is: What are brain characteristics of resilience to stress and how do they relate to brain characteristics associated with stress-related disorders?

Since neuroimaging studies on resilience are still very scarce (Chapter 6), it is very difficult to give a robust answer to the research question. Most studies examining resilience use knowledge gained from research into stress-related disorders as an underpinning to derive hypotheses on relevant networks in the brain (the most prominent regions are described in Chapter 6). Although this is a logical first approach, it assumes that on a neural level resilience is the opposite of having stress-related symptoms, which is not necessarily true. As a result, the majority of locations in the brain are ignored and potentially valuable information is lost. Based on the data that is currently available, it is still too early for building comprehensive models on the neural mechanisms of resilience to trauma. Due to the fact that resilience is such a dynamic and multidimensional construct, studies also vary on the operationalization they use to identify resilience. Some studies chose to define resilience as a trait, using personality characteristics and questionnaires to define resilience at a certain point in time (baseline) (Friborg et al., 2005; Campbell-Sills et al., 2006). Others define resilience as adequate or adaptive behavior during exposure to stressors, focusing on the ability to learn new adaptive coping techniques or speed of recovery (Masten and Coatsworth, 1998). Resilience is sometimes even interchanged with the concept of resistance to stress, the latter meaning that individuals show no dysregulation during exposure to a stressor at all. Lastly, some studies (including the ones presented in this thesis) define resilience by outcome, e.g., individuals who did not develop any psychiatric symptoms after the experience of a traumatic event (Gilbertson et al., 2002; Admon et al., 2013). These variations in definitions and time points of measurements complicate the integration of findings into a model for resilience.

Gray Matter

In Chapter 8 we hypothesized to find specific characteristics related to resilience in gray matter volume and shape of the hippocampus. This hypothesis was based on prior research indicating that increased hippocampal size is related to resilience (Gilbertson et al., 2002; Yehuda et al., 2007), and on the notion that the hippocampal structure is very susceptible to stress hormones (Starkman et al., 1992; Pryce, 2008). Contrary to our expectations we did not find increased hippocampal volumes in the resilient individuals. One explanation could be that the police force typically selects specific personality profiles and psychological abilities related to resilience, based on the extensive psychological testing that takes place before admittance. If these characteristics are also related to larger hippocampal volumes the selection criteria might inadvertently be biased towards selecting larger hippocampal volumes, thus taking away some of the variation that is common within the general population; a so called ceiling effect. To examine whether a ceiling effect is present in groups consisting of high-risk professionals, future designs should encompass a control group of individuals from the general population. Comparing this group to the high-risk professionals could clarify whether high-risk professionals already have a larger hippocampus compared to the general population as a result of the selection criteria.

Connectivity

The regions-of-interest we used in Chapter 8 consisted mainly of white matter tracts connecting medial prefrontal areas with subcortical areas. These areas are mainly implicated in emotion and behavioral regulation through risk and reward analysis as well as inhibitory control of prefrontal areas over the subcortical areas (Bechara et al., 2000; Roberts and Wallis, 2000; Hansel and von Kanel, 2008; Johnson et al., 2011). Proper structural connectivity between these areas is imperative for optimized functioning of these behavior and emotion regulating processes. This could also be deducted from studies showing decreased structural connectivity of these white matter tracts in stress-related disorders with accompanying deficits in emotion regulation (Taylor et al., 2007; Kawashima et al., 2009; Kim and Whalen, 2009; Phan et al., 2009; Baur et al., 2012; Zhang et al., 2012; Baur et al., 2013). The ceiling effect, due to the selection profile of our subjects, could also underpin the null-findings in white matter integrity in these a priori hypothesized regions. However, it did enable us to examine in which other regions connectivity differentiated the most resilient inside our already high-resilient group of police officers. To investigate these regions and to counter the risk of missing out potentially valuable information in other non-hypothesized areas, we used an explorative whole brain

analysis. We found that increased white matter integrity of the corticopontine tract was specific for the high-resilient group. The corticopontine tract is a white matter tract not otherwise implicated in stress-related disorders previously. Additionally, the structural connectivity differences in this area were accompanied by specific patterns of resting-state functional connectivity between a gray matter seed directly adjacent to the corticopontine effect (the putamen), and the posterior cingulate cortex and the precuneus. This pattern of findings suggests that resilience and stress-related disorders are not opposites on a neural level. Importantly, both the structural connectivity and functional connectivity findings were related to positive reappraisal strategies in resilience individuals. Positive reappraisal as a cognitive strategy to cope with stressful experiences refers to strategies that encompass giving positive meaning to experiences in terms of personal growth (Spirito et al., 1988; Carver et al., 1989; Garnefski et al., 2001). It is a higher-order cognitive process that can take place long after a stressful experience has ended, and is therefore remotely different from the more fast-paced emotion-regulation strategies that take place during stressful situations and implicate medial prefrontal and subcortical areas as well as their reciprocal connectivity. In addition, positive reappraisal can influence the image an individual has of oneself. Not surprisingly, we found cognitive reappraisal to be related to connectivity differences with the precuneus; an area involved in self-referential processing, self-consciousness, and autobiographic memory (Cavanna and Trimble, 2006; Cavanna, 2007).

The findings in Chapter 7 also support the notion that higher-order cognitive processes are important in resilience. We found increased resting-state functional connectivity between the salience network and an area encompassing the lingual gyrus and the occipital fusiform gyrus. This finding fits the dual representation theory of visual intrusions (Brewin et al., 1996; Brewin et al., 2010). Visual intrusions are a core symptom of PTSD, but are also present in depression (Kuyken and Brewin, 1994; Brewin et al., 1998; Reynolds and Brewin, 1998), panic disorder (Beck et al., 1974; Ottaviani and Beck, 1987), social anxiety (Hackmann et al., 1998; Hackmann et al., 2000), agoraphobia (Day et al., 2004), and obsessive-compulsive disorder (Speckens et al., 2007; Lipton et al., 2010). The dual representation theory explains visual intrusions in terms of memory encoding and retrieval in two memory systems: contextual memory and sensation-based memory. Integrative processing of both memory systems is necessary for normal encoding of traumatic events. When traumatic experiences are only processed in the sensation-based memory this leads to involuntary access of traumatic memories and accompanying autonomic responses, in other words: visual intrusions. According to the neural model of

memory and imagery the salience network, with its function of assessing relevance of internal and external stimuli, is part of the sensation-based memory system. The lingual gyrus and occipital fusiform gyrus, however, are involved in associating autobiographical knowledge to the encoding and retrieval of memories. (Burgess et al., 2001; Byrne et al., 2007; Brewin et al., 2010). Communication between these two areas is necessary for memories to be integrated in both the sensation-based memory system and the contextual memory system. Our results of increased functional connectivity between these areas related to resilience, indicate that an increase in connectivity between these two areas provide a protective mechanism for developing psychopathology after severe stressful experiences. Possibly this is achieved by an increased ability to successfully encode memories in both memory systems, resulting in decreased chances on experiencing intrusive images, which in turn could lead to other psychiatric symptoms and eventually psychopathology.

Future perspectives

We investigated characteristics of brain structure and resting-state functional connectivity related to resilience to trauma. Next, brain function during externally controlled tasks that elicit processes involved in resilience should be further investigated. For instance, it would be highly relevant to see how brain function in the resilient group differs from the other groups during emotion regulation, working memory performance during emotional distraction, and during (social) stress. Cortisol response to a stressor and the occurrence of certain mineralocorticoid receptor and glucocorticoid receptor influencing haplotypes should be studied in concert, since there is evidence that these haplotypes are related to resilience (Klok et al., 2011).

As explained in the previous Chapter, we suggest adding a healthy control group from the general population when studying resilience in high-risk occupations like police officers and military personnel. This would allow investigating whether some of our null-findings could be explained by a ceiling effect.

Finally, we highly recommend studying a complex construct like resilience in a longitudinal design, which allows for drawing causal conclusions. In addition, it will enable investigation of brain characteristics that predict resilient behavior in the face of trauma exposure, which may provide very valuable knowledge for establishing further selection criteria for high-risk occupations, as well as possible targets for prevention.

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