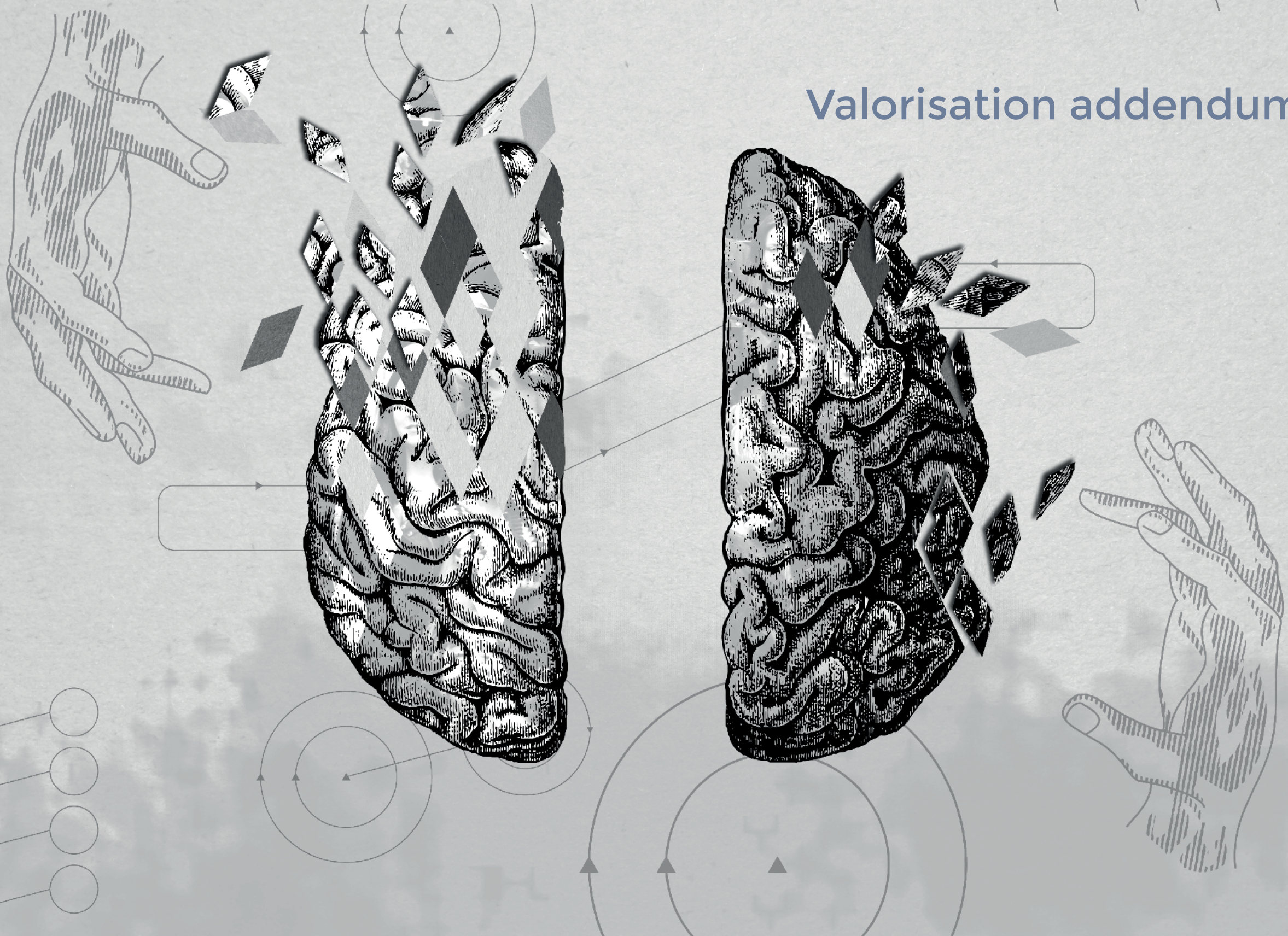
Stress resilience : learning from imaging the brain

Valorisation addendum



The work presented in this dissertation aimed to identify the changes in neural responding that underlie adaptability after exposure to acute stress, i.e., changes that are said to characterize stress resilience. The theoretical and practical implications of our findings were described in the various chapters throughout this thesis. Below, our findings are discussed in a broader societal context.

Societal relevance

We all know how it feels to be stressed. Our lives are filled with daily hassles such as rushing for an appointment for which you are already late, managing deadlines at work, taking an exam at school or giving a presentation in front of a large audience. Even planning a holiday or going to the dentist can be daunting to some of us. Besides, about half of all adults experiences at least one severe stressor in their life (e.g., violence, abuse, a life threatening accident). In all forms, prolonged exposure to stress has adverse effects on mental functions and makes us vulnerable for mental disorders. Mood and anxiety disorders are examples of a loss of resilience and are accompanied by social disabilities and high societal costs. Depression and post-traumatic stress disorder (PTSD) are characterized by changes in brain circuitry and function. These neural alternations probably result from both stress vulnerability and acute stressors that precipitate the disorder. Still, the exact changes in brain function leading to stress-related psychopathology are hitherto not well understood, hampering the development of novel therapeutic interventions. Moreover, the current psychological and pharmacological treatments are efficacious in only approximately half of the patients, thus leaving much room for improvement.

Learning why some individuals are better able to cope with stressful events than others is important to inform intervention and prevention programs targeting stress resilience. We therefore explored the possibility to modify cortical brain activity via neurofeedback to open a window of opportunity that may boost the efficacy of the other treatments. The development of prevention programs is particularly significant for professionals who have a heightened risk of exposure to stressful life events, such as emergency workers, police officers, and military personnel. Overall, the main aim of this thesis was to identify changes in the brain associated with acute stress. The next step is to understand how exactly these brain processes impact psychological functions and increase

the risk for mental disorders. This requires collaborative efforts from experimental psychology, neuroimaging and psychiatry.

Scientific perspectives and innovation

Abnormalities in the regulation of the neuroendocrine stress system have been linked to an increased susceptibility to psychopathology and disease after a stressful experience. There is substantial evidence of an altered functioning of the neuroendocrine system in depression (i.e., distorted basal cortisol levels) and PTSD (i.e., lowered basal cortisol levels). Therefore, empirical knowledge on how stress and stress hormones affect brain function can inform us about the aetiology and mechanisms in stress-related psychopathology. A first step in achieving this is reaching a better understanding of the dynamic acute stress-induced changes in processing in the brain that underlie adaptability after exposure to acute stress.

We investigated the reactivity of the stress system in a multidisciplinary way by addressing the interplay between psychophysiological markers (e.g., cortisol) and brain substrates underlying stress resilience. Using the definition of resilience as the ability to recover swiftly after a stressful life event, we investigated the contribution of different brain areas in post-stress regulation. To this end, we adapted a procedure used in experimental psychology during neuroimaging (i.e., the iMAST) that allows investigating the contribution of different brain areas during different phases in stress regulation. In particular, by looking at changes in amygdala connectivity, this work reveals a dynamic brain mechanism that is regulated by cortisol and involved in coping with acute stress. A particularly innovative aspect of this study is that it included repeated resting-state assessments enabling the investigation of post-stress brain activation changes during different phases after acute stress exposure.

Based on this innovative design, we were able to show that in the immediate stress phase, cortisol moderated the connectivity in the core areas of the salience network. Particularly, we found an enhanced amygdala - vmPFC connectivity in cortisol responders during immediate stress. This, together with the enhanced amygdala - vmPFC connectivity found in disorders marked by HPA-axis dysregulation like PTSD, suggests that the connectivity between the amygdala and vmPFC might characterize vulnerability *during a state of acute stress*. During the early recovery, a cortisol moderated time-dependent shift in the dorsal control network was found. Cortisol responders were characterized by reduced amygdala-left dlPFC connectivity during stress recovery. Combined with the findings that depressed patients show an impaired cortisol recovery pattern and display right-sided lateralized frontal brain activity, this points toward a cortisol mediated left dlPFC regulatory circuit involved in adaptive *recovery from stress*. An important objective for future research will be the use of longitudinal designs, to determine whether acute stress related functional connectivity is useful in predicting clinical outcomes.

Another hallmark feature of PTSD, besides dysregulation of the stress system are disturbances of memory. Therefore, basic knowledge about how stress hormones affect memory processes, might have implications for the understanding and treatment of anxiety disorders. We investigated the time-dependent cortisol effects on memory encoding and found that timing of stress exposure influenced the direction of the association between the cortisol response and the total number of remembered pictures 24 hours later. The number of correctly recognized neutral pictures was positively associated with cortisol responses in the immediate stress condition, whereas it was negatively associated within the 30-min pre-learning stress condition. Our results indicate that it is crucial to carefully take the time lag into account when considering cortisol as additional treatment during exposure techniques that are part of cognitive-behavioural therapies for PTSD.

In recent years, important insights into the putative functional role of oscillatory brain activity for cognitive processes and emotional states have been gained. For instance, it has been shown that frontal hemispheric asymmetry in the alpha band is linked to the processing of emotions. We demonstrated for the first time that brain asymmetry of the frontal cortex plays a functional role in acute stress processing (i.e., relative left frontal baseline activity resulted in a smaller task-induced cortisol response). This corresponds well with prior research showing that alternations in frontal asymmetry are associated with features of stress-related disorders, such as depression. Together, these findings suggest that frontal asymmetry is a potential target for interventions aimed at increasing resilience.

EEG neurofeedback is a method that could be used to modulate frontal asymmetry. EEG neurofeedback is based on real-time analysis of EEG signals. The use of real-time analysis of ongoing brain activity enables us to provide individuals with feedback information about their brain activity, which can then be used to directly train specific parameters of brain

activity and consequently change behavior. We aimed to validate and explore the potential of frontal alpha asymmetry neurofeedback and its behavioural usefulness. A particular strength of our study is that we compared two frontal asymmetry protocols with a placebo condition. Moreover, we extended prior studies by determining frontal asymmetry for each participant based on individual alpha peak frequency and by including two follow-up measurements (i.e., one week and one month later). Individual frontal alpha frequency neurofeedback resulted only in a change in relative frontal asymmetry at rest in participants who were trained to increase relative right-sided frontal alpha asymmetry. This change in relative frontal alpha asymmetry seemingly intensified subjective stress experiences. Importantly, our results indicate that there are marked individual differences in the ability to learn how to self-regulate frontal asymmetry. Ensuring reproducibility both on the individual level and over time is a key challenge in neurofeedback studies. Investigating the effectiveness of EEG neurofeedback using a placebo controlled designed and by comparing it with other therapies (i.e., psychotherapy, pharmacological treatment) is important before any translation to a more applied context is justified.

Translation and knowledge dissemination

This dissertation describes studies looking into the neural correlates of acute stress processing in the brain and may thus be of interest to members of the scientific community working in various fields, including affective neuroscience, emotion and memory. Given the stage of imaging in stress research and the fact that the current findings warrant replication, the main focus is on knowledge transfer within the scientific community. The findings of our studies have been communicated via publications in peer-reviewed journals. Moreover, the knowledge that was acquired while conducting the studies has been communicated via several presentations on international research conferences and meetings of the National Initiative Brain and Cognition (e.g., brain product day; explore your research day; meetings of the innovative programme resilience and vulnerability following stress). Additionally, several lectures (e.g., Maastricht University) and workshops were given about the application of neurofeedback (e.g., first meeting focus area Safety in Utrecht; 2nd Forensic Psychology Update in Maastricht). Furthermore, transfer of the practical skills that were acquired in the process of conducting the studies has taken place via teaching (i.e., practical; internships). Knowledge transfer outside the scientific community occurred via demonstrations on the university open day. Finally, communication of the findings of the studies in this thesis outside the scientific community will be done via a press release of NWO.