I GENERAL INTRODUCTION

Anxiety is one of the most fundamental sensations in humans and other mammals. Social contact is one of the most fundamental human needs. In social anxiety disorder (SAD), both aspects collide in a way that results in substantial suffering. That is, social interactions imply severe psychological stress for SAD patients. Despite this essential relation, little is known about the psychobiological mechanisms underlying SAD patients' social interaction behavior under stress. This includes one of its most basic aspects, the stress response in SAD. To date, the physiological stress reaction in patients with SAD is not completely understood. From neuroimaging studies, there is evidence that SAD patients exhibit elevated amygdala reactivity in response to social threat (Evans et al., 2008; Gentili et al., 2016; Straube, Mentzel, & Miltner, 2005; Yoon, Fitzgerald, Angstadt, McCarron, & Phan, 2007). As the amygdala plays a vital role in the detection of threat and the regulation of the subsequent endocrine and autonomous stress response (Forray & Gysling, 2004; Gray, 1993), an exaggerated response to stress in SAD might be expected. However, literature on the physiological stress response in SAD is ambiguous with findings of both elevated reactions (e.g. Condren, O'Neill, Ryan, Barrett, & Thakore, 2002; van West, Claes, Sulon, & Deboutte, 2008) and no differences to healthy controls (e.g. Klumbies, Braeuer, Hoyer, & Kirschbaum, 2014; Martel et al., 1999). A better understanding of the psychophysiological processes underlying the experience of stress in SAD may extend our knowledge of this disorder and help develop adapted treatments. Thus, one aim of this thesis was to investigate the stress response in patients with SAD and matched healthy controls in both major stress pathways, i.e. the hypothalamus-pituitary adrenal (HPA) axis and the sympatho-adrenal medullary (SAM) system, as well as on the subjective stress level. Acute psychosocial stress was induced through a standardized and well-established method, the *Trier Social Stress Test for Groups* (TSST-G; von Dawans, Kirschbaum, & Heinrichs, 2011).

As stress is an everyday phenomenon in our lives, we need reliable ways of regulating its psychological and physiological consequences in order to prevent health hazards, such as hypertension, type-2 diabetes mellitus or psychiatric

disorders (Chrousos, 2009; McEwen & Stellar, 1993). Humans have a general need to affiliate with others and form stable relationships (Baumeister & Leary, 1995; Caporael, 1997). Belongingness and being in close relationships has a positive impact on health and well-being (Cacioppo, Cacioppo, Capitanio, & Cole, 2015; Holt-Lunstad, Smith, & Layton, 2010). Accordingly, a vital source of coping is social support (Ditzen & Heinrichs, 2014). While the classical view of the behavioral stress reaction in humans is the *fight-or-flight* response (W. B. Cannon, 1915), which describes aggressive or escaping behavior in response to stress, this view has been broadened by a concept that takes into account the social dimension of human stress. In their *tend-and-befriend* model, Taylor and colleagues (Taylor, 2006; Taylor et al., 2000) suggest that acute stress promotes affiliation to others, which in turn leads to stress reduction, resulting from social support through positive social contacts. This entails difficulties for people suffering from SAD, as key symptoms of this disorder are insecurity and uneasiness regarding social encounters and avoidance of social situations (e.g. Rapee & Heimberg, 1997). While there is accumulating empirical evidence for a *tend-and-befriend* response to stress in healthy individuals (Berger, Heinrichs, von Dawans, Way, & Chen, 2015; Buchanan & Preston, 2014; Takahashi, Ikeda, & Hasegawa, 2007; von Dawans, Fischbacher, Kirschbaum, Fehr, & Heinrichs, 2012), it is unclear whether this mechanism exists in SAD.

Moreover, social cognitive abilities, such as inferring the other's mind, form an important prerequisite for successful social contacts. Deficiencies in these abilities lead to miscommunication and impaired social functioning (Fett et al., 2011; Shanafelt et al., 2005). Taking into account these basic requirements and how they might influence patients' social response to stress enables us to derive conclusions about the social behavioral consequences of acute stress in SAD and its possible underlying mechanisms. Thus, to shed further light on the interactional consequences of stress in SAD, the second aim of this thesis was to examine the effects of stress on social interaction behavior in patients with SAD, taking into consideration the individual empathic abilities. This approach is in accord with the Research Domain Criteria project ("NIMH » Research Domain Criteria (RDoC)," n.d.), an initiative to promote psychopathology research that focuses on dimensional constructs rather than solely on hypothetical diagnosis categories.

The present thesis is based on two empirical chapters from an experimental study on stress reactivity and social interaction behavior after stress in SAD. The empirical section is preceded by a theoretical section that addresses principal characteristics of the stress system (chapter 1), social behavior (chapter 2), social behavior in light of stress (chapter 3) and social anxiety disorder with its psychopathology, etiology, and treatment (chapter 4). It is followed by an enclosing discussion (section IV), which summarizes the key findings and discusses methodological considerations and limitations. Finally, an integrative model of the effects of stress on social behavior in health and psychopathology is presented and clinical implications as well as new directions for fruitful future research are highlighted.

II   THEORETICAL BACKGROUND

1   Basic Knowledge on the Human Stress Response

Stress. We are constantly confronted with it throughout our lives, whether we experience it running to catch a bus, clashing with friends or colleagues, or from more severe, traumatic events.

As one of the pioneers of stress research, Walter Bradford Cannon developed the concept of 'fight or flight' to describe an organism's response to threat (W. B. Cannon, 1915). He found that in confrontation with a stressor, the sympathetic branch of the autonomous nerve system activates the secretion of catecholamines in the adrenal medulla ("sympathoadrenal" system), mobilizing the organism's reaction. Drawing on the idea of a 'milieu intérieur' by Bernard (1878), he later coined the expression *homeostasis* (1929) to describe the physiological adaptations of the organism to maintain a stable internal environment. In the title of his summarizing work "The Wisdom of the Body" (1932), Cannon already acknowledged that the stress reaction forms a vitally important mechanism.

Another pioneer in this area, Hans Selye, extended the work by Cannon by emphasizing the activation of the hypothalamic-pituitary-adrenal (HPA) axis and associated secretion of glucocorticoids (1936). He suggested that this response pattern to stress was nonspecific. That is, independent from the nature of the stressor, the body would react with specific changes such as secretion of cortisol and catecholamines. In his concept of a *general-adaption-syndrome,* he proposed that the organism reacts in a profile with three phases: an "alarm state", analogous to Cannon's fight-or-flight reaction, an "adaption state", associated with resistance, and eventually an "exhaustion state" (1950).

Selye's concept was later extended by Mason (1971), arguing that the concept of non-specificity is lacking psychological processes. He claimed that the psychological evaluation of the stressor initiated the stress response, thus framing the concept of stress as not primarily physiological, *"[…] but rather as a behavioral concept"* (Mason, 1971, p. 331).

McEwen (1998b) integrated physiological aspects of the stress reaction and the individual perception of the stressor into his model of allostatic load. The model differentiates between a regular, moderate reaction to a stressor, and an aberrant reactivity. Normally, the physiological stress response is initiated, sustained for an appropriate time and then terminated, thus providing the organism with a flexible and advantageous reaction to the environment. However, due to multiple stressors or a lack of adaptation, for example, the stress response remains on a high level, resulting in 'allostatic load'. This state in turn results in adverse consequences for the organism. The model thereby underlines the dissociation of the physiological stress response, both as an important mechanism for the organism's survival, and as a potential health risk when endured chronically or when the system is unable to adapt sufficiently.

1.1 The physiological stress reaction

On the biological level, stress can be described as a state of imbalance, with the stress reaction attempting to regain balance and to "maintain physiologic integrity" (Ulrich-Lai & Herman, 2009, p. 397). Two distinct but interconnected systems are responsible for the execution of those adaptations: the sympathetic-adrenal-medullary system (SAM) and the hypothalamus-pituitary-adrenal axis (HPA-axis) (**Fig. 1.1**). A prompt response to the stressor is realized by the autonomic nervous system (ANS), more precisely via the SAM. Under resting conditions, the sympathetic and the parasympathetic parts of the ANS act in synergy; under stress, the activity of the sympathetic branch predominates and the influence of the parasympathetic branch is reduced. Due to their antagonistic functioning, an attenuation of the parasympathetic part can result in effects analogous to those of the sympathetic branch (Chrousos & Gold, 1992). That is, under stress, the hypothalamus addresses nuclei in the brainstem, which transmit the signal to the preganglionic sympathetic neurons of the spinal cord. These, in turn, project via pre- or paravertebral ganglia to the adrenal medulla. By this, secretion of epinephrine (esp. in the adrenal medulla) and norepinephrine (esp. in the postsynaptic sympathetic neurons) is triggered (Ulrich-Lai & Herman, 2009). This cascade results in immediate physiologic changes, such as accelerated heart rate, elevated blood pressure, and

vasodilatation in muscles, preparing the body for action by ensuring blood sup-supply to the relevant structures. Moreover, glycogenolysis in the liver provides energy through increased glucose levels (Gunnar & Quevedo, 2007) and on the brain level, norepinephrine is released in the locus coeruleus in the brainstem, resulting in enhanced vigilance and arousal (Gunnar & Quevedo, 2007). These physiologic changes can be assessed as markers of ANS activity. In psychological research, one of the most prominent peripheral physiologic markers is the detection of heart rate (Birbaumer & Schmidt, 2002; Freeman, 2006) Alternatively, endocrine changes can be measured as direct products of ANS activity, such as level of catecholamines epinephrine or norepinephrine in blood or saliva (B. Kennedy, Dillon, Mills, & Ziegler, 2001; Okumura, Nakajima, Matsuoka, & Takamatsu, 1997).

The HPA axis is the slower of the two systems (de Kloet, Rots, & Cools, 1996). This is mainly due to the respectively faster and slower mechanisms of neural versus humoral information processing and synthesis of the end-effector glucocorticoids in the HPA system, which involves gene transcription (Gunnar & Quevedo, 2007; R. M. Sapolsky, Romero, & Munck, 2000). In the parvocellular division of the paraventricular nucleus (PVN) of the hypothalamus, corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) are secreted (Chrousos, 1992). Under circumstances of stress, CRH is released into hypophysial portal vessels and activates cyclic adenosine monophosphate (cAMP), which stimulates the release of adrenocorticotropic hormone (ACTH) in the anterior pituitary. The neuropeptide AVP potentiates these effects of CRH on ACTH release (Rivier & Vale, 1983). ACTH, in turn, binds on receptors in the adrenal cortex, where glucocorticoids (in humans esp. cortisol) are synthesized and released into the bloodstream. From here, they bind to receptors throughout body and brain (Charmandari, Tsigos, & Chrousos, 2005; S. M. Smith & Vale, 2006). The name *glucocorticoid* indicates its involvement in the glucose metabolism, its synthesis in the adrenal cortex, and its steroid structure. The initiated metabolic effects include glycogenolysis, gluconeogenesis, the allocation of lipids and amino acids through lipolysis in fat cells, and the inhibition of protein synthesis in muscle cells (Sapolsky et al., 2000). This results in increased blood glucose levels and modifies fat and

protein metabolism (Stephens & Wand, 2012). Further, glucocorticoids have immunosuppressive and anti-inflammatory effects, namely through changes in leukocyte traffic and decreased cytokine production (Chrousos, 1995). Moreover, glucocorticoids are crucial for the termination of HPA axis activity, forming a negative feedback loop by inhibiting CRH and ACTH production in extrahypothalamic centers, in the hypothalamus and in the pituitary gland (Miller et al., 1992; S. M. Smith & Vale, 2006). Hence, the stress response constitutes a pivotal mechanism that allows the organism to adapt to challenging situations. On the downside, if stress has to be endured chronically, it is associated with structural changes in the brain (Arnsten, 2009) and impairs learning by inhibiting long-term-potentiation (de Kloet, Oitzl, & Joëls, 1999). Moreover, stress-related immunosuppression means that stress is one of the most significant risk factors for diseases associated with insufficient immune response, such as tuberculosis or certain kinds of tumors (Elenkov & Chrousos, 1999). On top of that, chronic stress is associated with increased risk for heart attack, and with mental diseases like depression and anxiety disorders (for reviews, see Chrousos, 2009; Kalia, 2002).

Regarding the investigation of stress-related HPA-axis activity, cortisol has been considered the best characterized marker (Foley & Kirschbaum, 2010). Only a small proportion (2-15%) of cortisol remains unbound and "free". However, it is this unbound cortisol that yields the glucocorticoid effects in tissue and brain. Due to its small size and lipid-soluble structure, unbound cortisol can easily pass cell membranes and thus occurs in all body fluids, including blood and saliva. In blood, both bound and unbound cortisol is measurable. Assessment of saliva does not imply an additional stressor for participants the way that venipuncture for blood sampling does. Thus, salivary cortisol depicts a valid and useful measure of HPA-axis activity (Kirschbaum & Hellhammer, 1989).