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Table of content

List of abbreviations

ACTH adrenocorticotrophic hormone

BeCOME Biological classification of mental disorders study

BDI Becks depression inventory

CIDI Composite International Diagnostic Interview

DMN Default mode network

FC Functional connectivity

fMRI functional magnetic resonance imaging

HPA hypothalamus pitutiary axis

MDD major depressive disorder

RDoC research domain criteria

SAD social anxiety disorder

SAM sympathetic adrenal medullary

TAI trait anxiety inventory

TSST Trier social stress task

List of publications

Peer-reviewed articles

Müller, F. K., Teckentrup, V., **Kühnel, A.**, Ferstl, M., & Kroemer, N. B. (2022). Acute vagus nerve stimulation does not affect liking or wanting ratings of food in healthy participants. *Appetite*, *169*, 105813.

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1. Introductory Summary

Stressful events—small and big—are an integral part of everyday life. In most cases, the experience of stress leads to an adaptive response that helps us overcome a challenging situation. For example, the heightened arousal, indexed by an increased hear rate, before an oral exam might help us be more alert so that we can perform better (Degroote et al., 2020; Sandi, 2013). This adaptive response is orchestrated by activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis (McEwen, 1998; Selye, 1956). More specifically, activation of the SAM axis induces a release of noradrenaline and a subsequent increase in heart rate. On the endocrine level, activation of the HPA axis leads to release of cortisol (Figure 1). Crucially, in a healthy organism, the acute response is quickly downregulated after stress and the organism returns to its baseline state (Kim et al., 2015; McEwen, 1998) highlighting the importance of the precise dynamics of the response from anticipation to recovery. However, especially when stressful events occur very frequently or for a longer time, the necessary recovery of the system might be impaired. An incomplete stress recovery then may lead to dysregulated dynamics of the stress system in response to subsequent stress hits. For example the stress system might sensitize over repeated stress hits which in the end might induce negative long-term health consequences (McEwen, 1998; Ursin & Eriksen, 2004). Stress, especially chronic stress, is a risk factor for poor physical health, including disorders such as obesity (Jackson et al., 2017; van Rossum, 2017), cardiovascular disease (Känel, 2012; Steptoe & Kivimäki, 2012), and other physical health problems (Guidi et al., 2021). Likewise, stress plays an important role in the etiology and maintenance of mental disorders (Marin et al., 2011; Nolen-Hoeksema et al., 2008). Notably, stress consequences such as mood and anxiety disorders are some of the most common diseases across the world, with lifetime incidence of depression of up to 20% and even 33 % for anxiety disorders (Bandelow & Michaelis, 2015; Kessler, 2012). Considering the high burden of these often chronic disorders (Vos et al., 2015) and their relationship with the repeated occurrence of stress, it is of high importance to determine characteristics of an acute stress responses and their dynamics (i.e., anticipation and recovery as well as adaptation to repeated stress hits) already indicating maladaptive consequences. Ultimately, acute stress response dynamics might already show specific physiological or psychological signatures that indicate a higher risk for developing long-term maladaptive consequences. Therefore, this dissertation will explore how neural stress response dynamics are reflected in mood and anxiety disorders.

1.1 Stressed or not: Inter- and intraindividual factors influencing stress consequences

To identify acute responses that potentially predict long-term negative consequences, it is first essential to understand which factors determine whether the physiological response to a

stressful event leads to adaptive or maladaptive consequences (Roth et al., 2012; Ursin & Eriksen, 2004). Of course, characteristics of the stressor itself such as the magnitude, duration, and frequency are important (McEwen, 2003, 2004). Importantly, maladaptive consequences might be indicated by specific response dynamics, such as sensitization or a lack of recovery of the system. Likewise, more qualitative differences in stressor type might also contribute to risk, as situations described as uncontrollable and unsolvable are more frequently associated with maladaptive stress responses that might later translate into mental health problems (Ursin & Eriksen, 2004).

Nonetheless, there are important interindividual differences that influence whether the experience of a stressor leads to negative long-term consequences or not, differentiating susceptible or at-risk individuals from resilient individuals. This is strikingly illustrated by the observation that even the experience of very strong stressors such as war or natural catastrophes do not lead to the development of mental disorders in all affected individuals (Dunn et al., 2014; Murthy & Lakshminarayana, 2006). On a biological level, differences in the genetic disposition have been proposed as moderators determining who is susceptible or resilient in response to stress. Moreover, genetic dispositions might interact with the cumulative stress exposure of an individual (Elbau et al., 2019).

On a psychological level, personality traits or trait-like characteristics that are relatively stable such as habitual coping strategies in response to stress might also play a role. Therefore, the cognitive activation theory of stress postulates that the cognitive appraisal of the stressor and the outcome determine the adaptiveness of the response (Folkman et al., 1986; Ursin & Eriksen, 2004). For instance, neuroticism or dispositional negative affectivity describe trait-like tendencies to react more negatively to stressful life events. Consequently, they are risk factors for the development of mood and anxiety disorders (Böhnke et al., 2014; Eaton & Bradley, 2008; Gulley et al., 2016; Hur et al., 2019; Zellars et al., 2009). In line with the diathesis-stress model only a vulnerable individual, for example with high trait-like negative affectivity, might then develop depression in response to a meaningful stressor (Zuckerman, 1999). Notably, a trait-like characteristic such as the tendency to ruminate in response to stress might be a risk-factor in the beginning. In high-risk individuals t, a stressful situation might then not just trigger a transient increase in arousal but instead lead to increased rumination and negative thoughts or even lasting anxiety (Brosschot et al., 2006) that may ultimately result in increased avoidance of everyday stressors (Spinhoven et al., 2017). Thereby, risk-traits might be exacerbated over time and thus contribute to the maintenance and worsening of symptoms (Nolen-Hoeksema et al., 2008) or even become a symptom of a mental disorder itself, such as excessive worrying in generalized anxiety disorder or avoidance in phobias. Consequently, mental disorders, such as mood and anxiety disorders, but also posttraumatic stress disorder are often characterized by maladaptive responses to stress (Aldao et al., 2010; Joormann & Gotlib, 2010). Thus, mechanistic links between acute stress response dynamics and relevant risk factors for mood and anxiety disorders are critical in understanding and preventing the development of mental disorders.

1.2 Stress in the lab: Measuring the stress response

Stress occurs nearly every day in naturalistic settings. However, investigating stress reactivity in a lab setting is a more challenging endeavor as what is experienced as stressful varies considerably between individuals. There are different approaches to induce stress in a laboratory setting. Broadly, stress tasks can be divided in tasks using either physiological (e.g., physical activity or pain) or psychological (e.g., social threat) stressors. In general, all tasks induce a negative emotional response (Bali & Jaggi, 2015; Skoluda et al., 2015). However, tasks relying on a physiological stressor such as the cold pressor task or an ergometer test predominantly induce a cardiovascular response while the HPA axis response is less reliable (Schwabe et al., 2008; Skoluda et al., 2015). In contrast, tasks relying on a psychological stressor such as a cognitive demanding task (e.g., Stroop) or negative emotion induction (e.g., aversive pictures or movies, Noack et al., 2019) more robustly induce an HPA axis response (Skoluda et al., 2015). Still, not all psychological stressor are comparably successful in inducing an HPA axis response (Dickerson & Kemeny, 2004). While passive negative mood induction only sometimes induces an HPA axis response, the combination of a cognitive task with social-evaluative threat led to a more robust response (Dickerson & Kemeny, 2004). Therefore, the Trier social stress task (TSST, Kirschbaum et al., 1993) that relies on social-evaluative threat of the situation as well as the uncontrollability of success to induce stress is one of the most used and best validated stress induction paradigms (Allen et al., 2014). In the TSST, stress is induced by a psychosocial manipulation where participants prepare and then give a speech in front of a committee followed by performing math (i.e., consecutively subtracting 13 from a high number). Moreover, adapted version of the TSST that still incorporate the critical components of social-evaluative threat but can be used in functional magnetic resonance imaging have been developed (fMRI, Dedovic et al., 2005; Shilton et al., 2017).

The TSST has been frequently used throughout the last 30 years and a multitude of factors influencing the (HPA axis) stress response have been determined (Allen et al., 2014; Dickerson & Kemeny, 2004; Seddon et al., 2020). While the task itself often follows a standardized protocol and initiatives have recently called for even further standardization (Laufer et al., 2022; Narvaez Linares et al., 2020), there are many slight variations in the procedure that still impact the stress response. For example, time of day of the measurement (Kudielka et al., 2004), the measurement protocol (i.e., saliva or serum samples and sampling timepoints, Dickerson & Kemeny, 2004; Goodman et al., 2017; Liu et al., 2017), the compositions of the feedback panel (male vs. female, Duchesne et al., 2012), the feedback type (neutral vs. negative, Allen et al., 2014), the setting (group vs. individual, Allen et al., 2014; Childs et al., 2006), and events changing baseline cortisol levels such as a preceding stressor (e.g., fMRI environment, Gossett et al., 2018) or physical activity (Zschucke et al., 2015) affect stress responses. Likewise, the stress response differs across age (Otte et al., 2005), between males and females (Liu et al., 2017), and even depending on the menstrual cycle (Kirschbaum et al., 1999). Nonetheless, the tasks are regularly used to investigate alterations in stress responses across many mental disorders including mood and anxiety disorders with inconsistent evidence (Zorn et al., 2017). These inconsistencies could partly be explained by variation in measurement

protocols. Therefore, it is critical to include not only measurements of the acute stress response but also of the baseline state, stress recovery (i.e., at least 30 minutes after the end of the task), and changes elicited by the procedure to determine different sources of variation in the stress response.

Sampling stress reactivity throughout the task is imperative to assess potential confounding factors. However, it is even also necessary to quantify the complete stress response (Brosschot et al., 2005; Kim et al., 2015; McEwen, 1998). A stress response is not only characterized by the peak response to stressor but also includes the anticipation before (Gaab et al., 2005) and the recovery after the stressor (Brosschot et al., 2005). Notably, those phases are apparent across different stress read outs, including the psychological experience (Gaab et al., 2005; Nolen-Hoeksema et al., 2008), cardiovascular changes (Schwartz et al., 2003; Waugh et al., 2010; Weber et al., 2010), and the HPA axis response (Engert et al., 2013; Stewart et al., 2013), albeit with different timing (Allen et al., 2014).Critically, mood and anxiety disorders are characterized by altered stress responses across all phases in addition to a dysregulated acute response magnitude (de Kloet & Joëls, 2020). For instance, it is conceivable that in anxiety disorders there is heightened arousal already in anticipation of a stressor (Dieleman et al., 2015; Shin & Liberzon, 2010), while rumination (a symptom of mood and anxiety disorders) might be associated with a slower recovery from the stressor (Nolen-Hoeksema et al., 2008). Thus, assessing the complete stress response and its dynamics might yield insights into specific stress response trajectories that are associated with symptoms of mood and anxiety disorders.

1.3 Stress responses of body and mind

The stress response can be measured across different levels corresponding to different stress response systems. Of course, the subjective experience of a stressful event is critical in evaluating how aversive the experience is. At the same time, the underlying physiological activation of the SAM axis reflected in the cardiovascular response and of the HPA axis reflected in the cortisol response are important markers of an individuals' stress response system. Consequently, individuals with a mood or anxiety disorder or relevant risk-factors might show specific dysregulations on any of the stress response levels. The following sections will characterize adaptive stress responses on the subjective, cardiovascular, and endocrine level and highlight confounding factors and methodological considerations that are essential to assess stress responses. Additionally, for each stress response level, evidence for dysregulated stress reactivity in mood and anxiety disorders is presented. To conclude, key considerations in investigating stress reactivity in mood and anxiety disorders are summarized.

1.3.1 The stressed mind: The subjective stress response

In anticipation of a stressful situation and even more during the stressor itself, when the general arousal increases, our mood frequently worsens (Capobianco et al., 2018; Seddon et al., 2020). This includes increases in self-reported stress (Buske-Kirschbaum, Gierens, Höllig,

& Hellhammer, 2002), anxiety (Jezova et al., 2004; Rimmele et al., 2007), and general negative affect (Childs et al., 2006; Rimmele et al., 2007; Yim et al., 2010), but also anger (Moons et al., 2010). However, whether an increase in arousal (i.e., the generally adaptive response to a surprising or stressful situation) is associated with a negative emotional response, depends on the cognitive appraisal of the situation and the resulting physiological response as potentially harmful (Folkman et al., 1986; Ursin & Eriksen, 2004). More specifically, a situation that is experienced as hopeless and with uncertain outcome expectations leads to feelings of helplessness and anxiety which in turn lead to a negative emotional experiences (Folkman et al., 1986; Ursin & Eriksen, 2004). This is exacerbated when coping resources are appraised as insufficient (Folkman et al., 1986; Ursin & Eriksen, 2004). Expectations and appraisals of the stressful situation influence the acute emotional stress response during exposure. Critically, expectations and employed coping strategies also shape the anticipatory experience (Gaab et al., 2005; Jamieson et al., 2018). Likewise, in the aftermath of a stressful situation, the strategies used to regulate emotions and how we appraise the outcome, influences psychological and physiological stress recovery (LeMoult et al., 2013). Importantly, it also impacts how we react to the next challenge (Roth et al., 2012). Notably, subjective stress responses and physiological responses are thought to affect each other, highlighting the importance of investigating the stress response across physiological and subjective levels.

How a stressful situation is experienced is not only relevant for the emotional response in this instance, but may have lasting consequences, since repeatedly unsuccessfully coping with stress increases the risk of mental disorders (McEwen, 2003). Prominent theories of cognitive stress reactivity in depression postulate that a core maladaptive process in depression is how stressful events are processed (i.e., negativity bias) and how resultant emotions are regulated (LeMoult, 2020). Therefore, stress responses might be dysregulated in mood and anxiety disorders, for example reflected in lasting negative affect after stressful situations (Nolen-Hoeksema et al., 2008; Ottaviani et al., 2016) or increased anxiety in anticipation of a psychosocial stressor (Helbig-Lang et al., 2015). Moreover, the magnitude of the acute subjective stress response is higher across depression and anxiety (de Rooij et al., 2010). Transdiagnostic risk factors such as maladaptive coping strategies also increase stress-induced negative affect (Krkovic et al., 2018). Similarly, recovery is slower when participants are asked questions inducing worrying after a stress task (Capobianco et al., 2018). Taken together, the emotional stress experience is critical to differentiate between adaptive or maladaptive experiences of physiological arousal. Furthermore, interindividual differences in dimensional symptoms across mental disorders such as rumination or avoidant coping might affect how stress is experienced.

1.3.2 The stressed heart: The cardiovascular stress response

The sympathetic nervous system controls the fast, initial physiological response to a stressor that increases arousal and prepares the organism to quickly react to the stressor. Briefly, physical (but also psychogenic) stressors activate the SAM axis, for example, via direct inputs from peripheral organs mediated by the autonomic nervous system (Sharpley, 2009).

Subsequently, activation of the SAM axis leads to an increase in heart rate, a corresponding decrease in heart rate variability, and an increase in blood pressure (Sharpley, 2009). At the same time, the adrenal medulla is activated and secrets (nor)adrenaline. Adrenaline is a hormone with systemic effects that ensures the physical ability to react to the stressor, for instance, by affecting blood vessel dilation and thereby increasing heart rate (Sharpley, 2009). Moreover, it orchestrates the systemic stress response in the locus coeruleus (Goddard et al., 2010; Pacák & Palkovits, 2001). Thus, psychosocial stress tasks elicit increases in adrenaline, noradrenaline, alpha amylase, and heart rate, as well as decreases in heart rate variability (Allen et al., 2014; Gold et al., 2004; Jezova et al., 2004). Mirroring findings regarding the psychological stress response, not only the magnitude of acute response to the stressor itself is relevant, but heightened anticipation as well as how dynamics of the recovery contain important information (Brosschot et al., 2005; McEwen, 1998). Highlighting the importance of the anticipatory state of the system, baseline levels of autonomous activity such as heart rate or heart rate variability have been shown to influence the stress response on all levels (i.e., cardiovascular, endocrine, or psychological, Weber et al., 2010). On the other hand emphasizing the role of cardiovascular recovery, slower recovery might predict long-term negative health consequences of chronic stress such as higher blood pressure (Steptoe & Marmot, 2006). Comparably, recovery of the heart rate is also associated with symptoms of mental disorders such as excessive rumination (Ottaviani et al., 2016). To conclude, cardiovascular stress responses are an important measure quantifying stress reactivity and recovery.

In addition to the psychological consequences (B. E. Cohen et al., 2015) of chronic stress it also increases the risk for cardiovascular disease (S. Cohen et al., 2007; Kessler, 1997; Sparrenberger et al., 2009). Therefore, it is hypothesized that altered autonomic responses to acute stress could be a common risk factor or biomarker for depression. In a review, Schiweck and colleagues (2019) discussed the potential of cardiac responses to stress as biomarker or early indicator for depression. They showed that clinical groups with depression had a higher resting heart rate and lower increase in heart rate in response to stress compared to healthy controls. Critically, nearly half of the study populations reporting depression had comorbid anxiety symptoms and in general stress response profiles for depression and anxiety disorders could not be differentiated. Likewise, similar patterns of reduced autonomous reactivity and increased resting cardiovascular activity were reported in anxiety disorders (Chalmers et al., 2014; Lang & McTeague, 2009). Taken together, this indicates that in the same way symptoms of a dysregulated subjective stress response occur transdiagnostically, altered cardiovascular stress reactivity might be a biological symptom that is shared across different mood and anxiety disorders.

1.3.3 The stress hormone system: The cortisol stress response

In response to an acute stressor, sensory inputs relaying homeostatic imbalances (e.g., via the nucleus of the solitary tract) excite the paraventricular nucleus of the hypothalamus (Ulrich-Lai & Herman, 2009). The hypothalamus then releases corticotrophin-releasing hormone which in turn triggers the secretion of adrenocorticotrophic hormone (ACTH) from the

pituitary. Subsequently, ACTH leads to the release of the glucocorticoid cortisol from the adrenal cortex, increasing cortisol concentration in peripheral blood (Antoni, 1986). In the end, the HPA axis (Figure 1) response is downregulated via a negative feedback loop where cortisol binds to glucocorticoid and mineralocorticoid receptors in the brain and the anterior pituitary (Gjerstad et al., 2018; Herman et al., 2016; Myers et al., 2012). Across the body, cortisol increases in peripheral blood also affect cortisol levels in saliva and urine (Turpeinen & Hämäläinen, 2013). Both salivary and urine cortisol captures approximately real-time cortisol output, although urine cortisol is frequently used to assess cortisol output across 24-48 hours (Russell et al., 2012). In contrast, longer timescales of chronic stress-induced cortisol responses are observable in hair cortisol levels (Russell et al., 2012). Therefore, acute HPA axis responses to acute stress are assessed using blood, saliva, or urine sampling (Allen et al., 2014; Russell et al., 2012), whereas cortisol levels of hair can be used to capture a cumulative history of stress responses in the last months (Russell et al., 2012; Stalder et al., 2017).

Because saliva sampling and analysis is relatively cheap, easy, and less invasive compared to blood sampling, salivary cortisol is one of the main biomarkers assessing HPA-axis reactivity in stress research (Hellhammer et al., 2009). The main read out often is exclusively the magnitude of the acute response (Gjerstad et al., 2018; McEwen, 1998), which shows a robust cortisol increase at the group level in standardized stress tasks (Jezova et al., 2004; Kirschbaum et al., 1999). Still, individual cortisol reactivity is highly variable, and frequently only around 50% of a sample show a significant cortisol response (Miller et al., 2013). There are multiple factors influencing the magnitude of the stress response including individual characteristics such as age, sex, and menstrual cycle phase (for a review: Allen et al., 2014). As previously described for the subjective and cardiovascular stress response, the baseline state of the organism is again essential as baseline cortisol levels have been shown to affect subsequent cortisol reactivity (Engert et al., 2013; Het & Wolf, 2007). Therefore, potentially stress-inducing parts of the procedure, for example when the task is performed in an fMRI scanner (Gossett et al., 2018; Muehlhan et al., 2011), or a preceding physical activity (Zschucke et al., 2015), could induce a pre-task cortisol response that influences the subsequent stress experience. While there is evidence at the group level that higher baseline cortisol or a preceding cortisol response is associated with a reduced response to the stressor itself (Het & Wolf, 2007), anticipatory cortisol responses have also been associated with an increased task reactivity (Engert et al., 2013). Nonetheless, many study designs implicitly assume that multiple stress hits in a short time window have independent and additive affects (Goodman et al., 2017). However, there is little experimental evidence whether a preceding cortisol response sensitizes or habituates the stress system and whether potential habituation or sensitization affects the subsequent stress response across endocrine, cardiovascular, and psychological levels. Importantly, interindividual differences in habituation or sensitization of the HPA axis to repeated stressors might differentiate susceptible from resilient individuals (Grillon et al., 1996; McLaughlin et al., 2010). Therefore, it is essential to characterize dynamics of stress responses even including multiple stress hits (Rohleder, 2019).

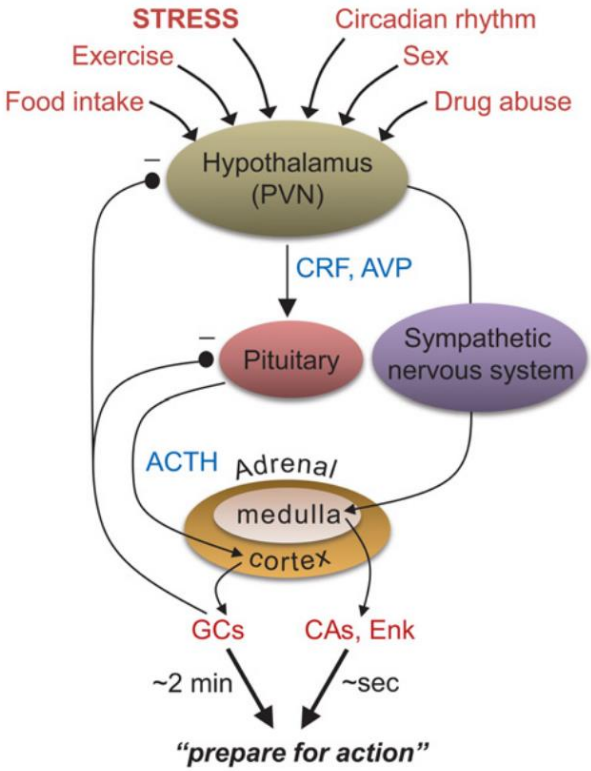

Figure 1: The hypothalamic-pituitary-adrenal (HPA) axis is the main stress response system orchestrating the endocrine (cortisol) stress response. Downregulation is achieved via a negative feedback loop mediated by glucocorticoid receptors in hypothalamus. Figure reprinted under Creative Commons License from Kim et al. (2015)

Negative consequences of chronic stress such as an increased risk for mood and anxiety disorders are not only reflected in the previously described dysregulated psychological and cardiovascular stress responses. In addition, chronic stress might elicit a long-term dysregulation of the endocrine stress system (Marin et al., 2011) which incurs a risk to develop a mood and anxiety disorder (Mizoguchi et al., 2008; Watson & Mackin, 2006). Similar negative consequences arise when experiencing stress during a sensitive period such as childhood or adolescence (Albott et al., 2018; Daskalakis et al., 2013; Wright et al., 2008) It is still not conclusively resolved which factors determine whether experiencing stress leads to the development of a stress-related disorder or not (Franklin et al., 2012). One potential factor contributing to individual risk are gene-environment interactions (N. Alexander et al., 2009; Elbau et al., 2019). Congruently, the genetic variants that are associated with the transcriptomic response to glucocorticoids also predict the endocrine stress response and a higher risk for depression (Arloth et al., 2015; Elbau et al., 2019).

To better understand the link between chronic stress, a dysregulated stress system, and mood and anxiety disorders, the acute endocrine stress response has been a long-standing target as biomarker for stress-related disorders (Zorn et al., 2017). Correspondingly, clinical tests assessing cortisol reactivity have been developed to aid diagnoses as early as 50 years ago (Carroll et al., 1968; Ising et al., 2007; Leistner & Menke, 2018). Although there is meta-

analytic evidence that the cortisol response is blunted in depression (Zorn et al., 2017), the evidence across studies is highly heterogeneous including effects in the opposite direction (Lupien et al., 2017). One factor that might explain contradictory results is sex, as the meta-analysis revealed a blunted response for females and a higher response for males with depression. Furthermore, the experience of early trauma might differentiate subgroups of patients with opposing changes in the stress system (Heim et al., 2004). Additionally, blunted cortisol responses are also apparent in anxiety disorders and schizophrenia (Zorn et al., 2017) which is analogous to the unspecific alterations of the cardiovascular stress response and precludes the use of the cortisol response as biomarker for major depressive disorder (MDD). Congruently, interindividual differences in transdiagnostic characteristics of altered behavioral stress reactivity affect the cortisol response in comparable ways to the diagnoses themselves. Importantly and echoing the results on the psychological and cardiovascular level, dysregulation associated with traits incurring a higher risk for mood and anxiety disorders can occur across all phases of the stress response. Thus, there is evidence for dysregulation during anticipation (negative affectivity and cognitive reappraisal coping (Morris et al., 2012, 2017; Schlotz et al., 2011)), the acute response (negative affectivity: Quirin et al., 2009; Zellars et al., 2009), and stress recovery (rumination (Quinn et al., 2018; Stewart et al., 2013) vs. distraction (Janson & Rohleder, 2017; Salzmann et al., 2018) vs. cognitive reappraisal (Cheetham-Blake et al., 2019); and anxiety symptoms: (Fiksdal et al., 2019)). To conclude, comparable to the results described for the other stress response levels, dysregulated endocrine stress reactivity can occur across the complete stress response and might be related to transdiagnostic alterations in coping and cognitive stress reactivity.

1.3.4 When stress goes wrong: Maladaptive stress responses in mental disorders

To summarize, across stress response levels, psychosocial stress leads to robust increases in heart rate, negative affect, and cortisol levels. Critically, across all levels (i.e., endocrine, cardiovascular, and psychological) an adaptive stress response is characterized by specific dynamics from anticipation through recovery. An acute stress response is influenced by intra- and interindividual factors. Intraindividually, dynamics extending from the one acute stress response and including, for example, an altered baseline HPA axis state because of a previous stress response that is not yet recovered, might affect subsequent acute stress responses. Thus, assessing dynamics of the stress is crucial to derive individual stress signatures. Interindividually, stress reactivity across levels might be altered in mood and anxiety disorders and importantly all phases of the response have been shown to be dysregulated in mental disorders. This again highlights the importance of dynamic stress signatures as potentially indicative of maladaptive processes.

However, comparing participants with vs. without mood and anxiety disorders on a group-level, shows high heterogeneity in results across studies. Moreover, effects are not specific for a categorical mental disorder that often co-occur and thus hinder the use of acute stress responses as biomarkers for specific, currently defined diagnostic categories. A key reason

for this phenomenon of relatively small and unspecific alterations in stress reactivity might be the heterogeneity and low discriminability of specific psychiatric conditions (Lupien et al., 2017; Menke, 2019). Instead, dysregulated stress responses on all stress response levels are shared across mental disorders as suggested by the meta-analyses showing blunted cardiovascular and cortisol responses in MDD, anxiety disorders, and schizophrenia (Lupien et al., 2017; Schiweck et al., 2019; Zorn et al., 2017). Additionally, cardiovascular, endocrine, and subjective stress responses are associated with transdiagnostic factors capturing trait-like behavioral stress reactivity such as typical coping strategy (Janson & Rohleder, 2017; Raymond et al., 2019) or trait anxiety (Gecaite et al., 2019; Jezova et al., 2004) as well as more acute symptoms of mood and anxiety (Brugnera et al., 2019; Fiksdal et al., 2019) disorders such as excessive rumination (Capobianco et al., 2018; LeMoult et al., 2013; Stewart et al., 2013). Taken together, this highlights the transdiagnostic nature of altered stress reactivity.

The idea of describing mental disorders along symptom dimensions has been further developed by initiatives such as RDoC (Insel, 2014) or the hierarchical taxonomy of psychopathology (HiTOP, Kotov et al., 2017). For example, RDoC proposes to quantify individual symptom profiles across different predefined domains (e.g., negative valence or positive valence) that map onto specific neurobiological systems across the self-report, behavioral, network, molecular, and even genetic level (Brückl et al., 2020). Intuitively, stress reactivity seems like a promising target for such a dimensional approach, as it can be measured across many of these levels from genes and molecular responses to brain-wide network reconfigurations. Similarly, trait-like or acute maladaptive stress responsivity on the behavioral level can be measured by using questionnaires. For instance, the extent to which usual coping strategies such as avoidance or rumination are used is indicative of adaptive or maladaptive responses to stress across mood and anxiety disorders (Cantave et al., 2019; Höhne et al., 2014; Stewart et al., 2013). Another promising target for dimensional approaches is negative affectivity, closely related to neuroticism, a risk factor or characteristic trait in many patients with mood and anxiety disorders (Böhnke et al., 2014; Gulley et al., 2016; Muris et al., 2005; Weinstock & Whisman, 2006; Williams et al., 2021). It describes a generally heightened sensitivity to stress and stress-induced negative emotional responsivity (Eaton & Bradley, 2008; Jacobs et al., 2006). Negative affectivity is closely related to trait anxiety, specifically the depression dimension of trait anxiety (Balsamo et al., 2013; Knowles & Olatunji, 2020), with both having a shared genetic signature (Thorp et al., 2021) and affecting stress responses (Gecaite et al., 2019; Zellars et al., 2009).

To conclude, for a characterization of adaptive and maladaptive stress responses in mood and anxiety disorders, it is essential to investigate not just acute stress response magnitudes but consider dynamics of stress responses within one response and across multiple hits or depending on the baseline state. Moreover, transdiagnostic approaches focused on symptoms affecting specific domains seem more promising to link acute stress responses to behavioral risk-factors.

1.4 The stressed brain: networks regulating stress responses

To understand acute adaptive and maladaptive stress responses across all levels from genes to systems, it is necessary to also characterize the neural stress response. However, whereas the physiological stress responses of the SAM and HPA axes have been extensively studied and are comparatively well understood, identifying robust changes in brain responses including activation and functional connectivity (FC) has proven more challenging (Noack et al., 2019). The following sections will first review the current literature on neural stress responses in healthy participants and individuals with mood and anxiety disorders. The last section will then provide a detailed overview on open questions and methodological improvements that are essential to advance our understanding of dynamic neural stress signatures in healthy individuals and individuals with mood and anxiety disorders.

1.4.1 Adaptive neural stress responses

Between 2005 and 2008, first studies using psychosocial stress tasks comparable to the TSST in an fMRI setting revealed stress-induced deactivations in the ventromedial prefrontal cortex (vmPFC) and other regions of the default mode network (DMN). In contrast, regions of the salience network including the insula and anterior cingulate cortex showed stress-induced activations (Pruessner et al., 2008; Wang et al., 2005). Moreover, other generally task positive regions such as the angular gyrus/intraparietal sulcus, supplementary motor area or the visual cortex are often activated during stress. Those activations are predominantly observed in paradigms relying on cognitive stressors such as TSST adaptions and are presumably related to the increased load in the stress conditions (Dedovic et al., 2005; Dedovic, D'Aguiar, et al., 2009; Elbau et al., 2018; Pruessner et al., 2008). The hippocampus has been proposed as a main mediator of the HPA axis stress response since stress-induced activity of this brain region correlated with the cortisol response (Dedovic, Duchesne, et al., 2009; Elbau et al., 2018; Pruessner et al., 2008). Furthermore, stress-induced hippocampus activation also correlated interindividual differences in genetic variants regulating the transcriptomic response to glucocorticoids (Elbau et al., 2018). More recently, however, systematic reviews (Noack et al., 2019) and meta-analyses comparing psychosocial stress to physiological stressors (Kogler et al., 2015) or comparing different psychosocial stress paradigms (Berretz et al., 2021) have highlighted the substantial heterogeneity of activation maps across studies. In contrast to earlier work, only the insula showed a robust stress-induced activation and the parahippocampal gyrus stress-induced deactivations (Figure 2). To summarize, there are only very few regions showing a robust change in activation (i.e., blood-oxygen-level-dependent (BOLD) response) in response to psychosocial stress, raising the question whether neural responses are best captured by average whole-brain changes in activation.

If stress does not predominantly change activation in specific brain regions, it may instead elicit large scale reconfigurations of network interactions as indicated in preclinical work (Hultman et al., 2016). In line with this idea, seminal work by Hermans and colleagues (Hermans et al., 2011) has shown that an adaptive stress response to watching threat-related movies

elicits widespread changes in FC across the salience network and fronto-parietal network. More specifically, the salience network is thought to support vigilant processing and orientation of the system towards salient stimuli (van Oort et al., 2017). In contrast, the fronto-parietal or central executive network supports higher-order executive functioning that are necessary for complex tasks (Hermans et al., 2014). In addition to stress-induced changes in salience and fronto-parietal network connectivity, changes in DMN connectivity supporting self-referential processing have also been reported (van Oort et al., 2017). Comparable changes in FC across those networks have been reported when using threat related images (Goldfarb et al., 2020; Sinha et al., 2016) or movies (Oort et al., 2020) to induce stress. However, stress-induced FC changes have rarely been investigated during a psychosocial stress task (Corr et al., 2022; Wheelock et al., 2018) but mostly by comparing resting state FC before and after a stress task (Dimitrov et al., 2018; Vaisvaser et al., 2013; van Marle et al., 2010; Veer et al., 2011; Zhang et al., 2019, 2020, 2021). Remarkably, however, even when changes in FC instead of activation are investigated temporal dynamics of the response through anticipation and recovery are mostly disregarded. Considering the importance of stress response dynamics on the endocrine, cardiovascular, and subjective level for defining an adaptive stress response, this approach might miss important mechanistic insights. To conclude, an in-depth characterization of dynamic trajectories of brain responses and FC changes during a stress task across anticipation, the acute response, and recovery is still an open question. Nonetheless, such an in-depth characterization might provide crucial new insights linking neural traces of stress with similar trajectories on the endocrine or cardiovascular level.

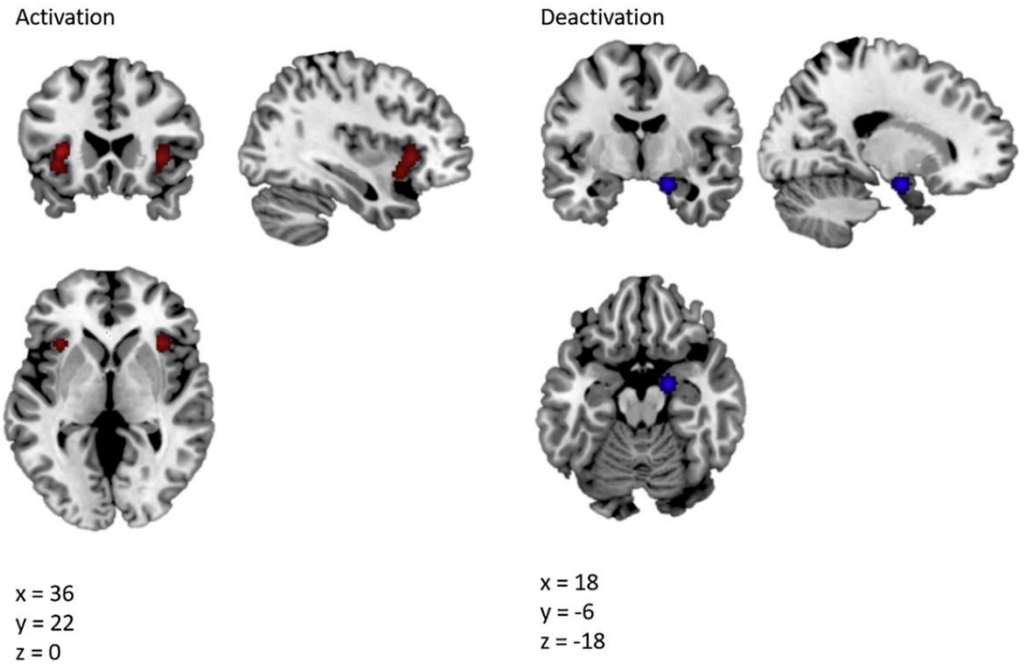

Figure 2: Meta-analytic whole-brain activation maps showing clusters that are activated (red) or deactivated (blue) during different stress paradigms. Reprinted with permission from (Berretz et al., 2021)

1.4.2 Neural stress responses in mood and anxiety disorders

Building on the insights regarding the neural stress response uncovering underlying alterations in the neural stress response has been an important goal in recent years (Allen et al., 2014). Still, findings to date have been inconclusive. On the one hand, MDD has been associated with increased stress-induced activations in striatal regions (Admon et al., 2015) but also decreased activation in the central autonomous network including the pallidum (Villarreal et al., 2021). On the other hand, the role of the DMN has been highlighted. For example, Waugh and colleagues (2012) reported increased stress-induced responses in DMN-related midline structures in MDD with and without comorbid social anxiety disorder (SAD). Further supporting the increased activation in DMN-related midline structures, van Oort and colleagues (2020) showed decreased downregulation of DMN FC in response to stress across different mental disorders including stress-related disorders and/or attention deficit disorders. Furthermore, the insula was implicated across studies with stress-induced activations either decreased (Villarreal et al., 2021) or increased (Waugh et al., 2012) in MDD. At the same time insula activation was attenuated during stress recovery in SAD (Waugh et al., 2012), emphasizing the importance of downregulation of the stress response also at the neural level. Crucially, the high overlap of stress-induced alterations across different diagnoses within the studies including MDD, SAD, and bipolar disorder again highlights that dysregulated stress reactivity might be better conceptualized as transdiagnostic symptom on the behavioral as well as neurobiological level (Oort et al., 2020).

Correspondingly, there is preliminary evidence that trait anxiety, either assessed in a healthy sample (Wheelock et al., 2016) or in a sample of adolescents with a broad range of stress-related disorders (Corr et al., 2020) is associated with stress-induced brain responses in the dorsomedial prefrontal cortex, PCC, and insula or ventral striatum, hippocampus, and putamen, respectively. Furthermore, Corr and colleagues (2022) showed a decrease in DMN FC to the insula in adolescents reporting poly-victimization, like childhood trauma a risk factor for stress-related disorders (Hickman et al., 2013). To summarize, several studies have attempted to uncover the neural basis of dysregulated stress responses in mood and anxiety disorders. However, neither the studies comparing different diagnostic groups nor the studies using transdiagnostic dimensional approaches have yet yielded converging results regarding alterations of the neural stress response. Still, considering the high overlap in behavioral symptoms of mood and anxiety disorders, transdiagnostic approaches are likely more promising.

1.4.3 Methodological challenges

While there is some preliminary evidence regarding dysregulation of the brain's stress response in mood and anxiety disorders, the number of studies is still limited. Moreover, there is little convergence across studies although alterations in stress-induced brain responses of the DMN, insula, and striatum have been reported multiple times. Importantly, a similar lack of convergence of results is apparent in studies characterizing adaptive brain responses to

stress in healthy samples (Noack et al., 2019), indicating that more methodological work is necessary, to first robustly measure the brain's stress response. There are several methodological considerations that might help explain the lack of convergence across studies. In turn tackling those limitations is essential to uncover mechanistic links between acute stress and psychopathology.

1.4.3.1 Study design

A lack of replicability of neuroimaging results regarding alterations in mood and anxiety disorder has been identified as a core issue impeding the identification of pathomechanisms (Saggar & Uddin, 2019). This is also true in studies investigating neural stress responses in mood and anxiety disorders. One issue is the generally low sample size, even for the characterization of the stress response in healthy samples (often N~30; Berretz et al., 2021). More importantly, the sample sizes are comparably low in studies comparing healthy populations with participants with mental disorders where most studies include between 20 and 30 participants per group (Corr et al., 2020; Villarreal et al., 2021; Waugh et al., 2012). This might explain the variability in results, considering that on the endocrine level there is substantial interindividual variability whether a stress response is elicited at all even within healthy populations (Miller et al., 2013). Likewise, sampling variance in small studies might explain inconsistent results even in opposite directions taking into account the expected effect sizes (Cremers et al., 2017; Schönbrodt & Perugini, 2013). Therefore, much larger samples are necessary to discover reproducible whole-brain associations with mood or anxiety disorders (Anderson & Maxwell, 2017; Marek et al., 2022).

Nonetheless, even when sample sizes are sufficient, there are other sources of variability that contribute to diverging results across studies. As described for studies assessing the endocrine stress response, the variability in study protocols might be an important confounding factor (Foley & Kirschbaum, 2010; Goodman et al., 2017; Narvaez Linares et al., 2020) and it is higher compared to the more standardized TSST without imaging (Allen et al., 2014). An important factor is the type of stressor since all induce psychological stress response, but the endocrine stress response is more heterogenous (Dickerson & Kemeny, 2004). In line with this distinction, the neural stress response also differs between induction methods (Berretz et al., 2021; Kogler et al., 2015) which might explain conflicting results regarding the dysregulation in mood and anxiety disorders. Another prominent confounding factor in laboratory studies is the baseline state of stress system. For example, parts of the procedure, such as the MRI environment (Muehlhan et al., 2011) or a blood draw might elicit a stress response affecting stress system dynamics to the task (Goodman et al., 2017). Even on the endocrine level, it is not yet conclusively resolved whether a preceding response is independent and additive or leads to habituation or sensitization. However, effects on other stress response levels such as the neural stress response are even less well understood. Therefore, an unintended and unaccounted preceding response might confound individual neural stress signatures. Notably, stress response dynamics across multiple stress hits might also be altered in mood and anxi-

ety disorders (McEwen, 1998), emphasizing the importance of accounting for complete dynamics of the stress system when investigating pathomechanisms in mood and anxiety disorders.

1.4.3.2 Characterizing mood and anxiety disorders

As described across the endocrine, subjective, and cardiovascular level, case-control studies might miss important variability and thus hamper identification of underlying pathomechanisms. On the one hand, there is high heterogeneity within one diagnosis category (i.e., non-ergodicity, Adolf & Fried, 2019) so that only a subgroup of participants might be characterized by symptoms of altered stress reactivity on the behavioral or physiological level. Thus, symptom specific alterations might be masked in case-control studies. On the other hand, many symptoms of mental disorders lack specificity across diagnoses (i.e., the same symptom is observed in many disorders, Clark et al., 2017) which prevents distinguishing different diagnoses based on underlying neurobiological mechanisms. Therefore, transdiagnostic approaches of maladaptive stress responsivity dimensions as described in the RDoC approach are key to uncover symptom specific alterations in dynamic (neural) signatures in response to acute stress.

1.4.3.3 Modeling the neural stress response

Substantial potential for innovative approaches might be in the analysis method chosen to operationalize the brain's stress response as whole-brain average responses might not ideally match the nature of an adaptive stress response. First, most studies have focused on changes in activation in response to stress and not modeled changes in network communication (i.e., FC). Considerable evidence for FC changes in response to stress comes from animal (L. Alexander et al., 2020; Hultman et al., 2016) and human (Grueschow et al., 2021; Hermans et al., 2014; van Oort et al., 2017) studies suggesting that stress is characterized by widespread reconfigurations of network communication. Interestingly, the networks that show FC changes in response to stress (e.g., DMN and salience network) are also implicated in mood and anxiety disorders. Moreover, mood and anxiety disorders are increasingly conceptualized as 'network disorders' characterized by alterations in network communication (Fornito et al., 2015; Hamilton et al., 2011; McTeague et al., 2020). Therefore, changes in FC might provide a more suitable link between acute stress reactivity and consequences of chronic stress.

In addition to the neurobiological plausibility of focusing of stress-induced FC changes, using task-based changes in FC have yielded stronger results when predicting relevant behavioral phenotypes (e.g., intelligence in challenging tasks) based on FC measures compared to rest (Finn & Todd Constable, 2016; Greene et al., 2020). Furthermore, task-induced FC changes also add predictive value beyond task-induced changes in activation that only performed well for behavior derived from the task performed in the scanner (Greene et al., 2020). This suggests that combining FC and activation changes explains task-induced network organization changes best. Thus, FC and activation signatures from behaviorally relevant stress

tasks are promising features for prediction of stress-related, transdiagnostic, trait-like factors on an individual level.

Considering the importance of the dynamics to distinguish adaptive from maladaptive responses on the endocrine, cardiovascular, and subjective level, it is perhaps surprising that neural responses are seldomly resolved at this temporal resolution. As a first indication of the potential of modeling response dynamics, dynamic stress-induced signatures have also been described in animal research (Hultman et al., 2016, 2018). Moreover, the power of neural dynamics in understanding mental disorders is emphasized by studies showing alterations in FC dynamics although at rest (Braun et al., 2016, 2018). To derive dynamic signatures of stress, first, the task has to be designed to differentiate anticipation from the acute response and recovery, which is often not the case as control and stress conditions are presented alternately. Another obstacle to measuring dynamic neural stress-response signatures is the need for sufficient data points to reliably estimate FC and for any given state or task block (Gordon et al., 2017). This is important, as estimates need to be sufficiently reliable to associate them with interindividual differences in transdiagnostic stress reactivity dimensions or compare participants with and without mood and anxiety disorders (Elliott et al., 2021). A promising solution for those issues is provided by implementing hierarchical models that simultaneously estimate changes in FC and activation for any given network connection between two regions. Those models, a hierarchical extension of generalized psychophysiological interaction analyses (McLaren et al., 2012), provide some regularization of individual activation and FC estimates and thereby improve reliability, generalizability, and predictive value (Farahibozorg et al., 2021; Katahira, 2016; Mejia et al., 2018). Still, especially in bigger samples, estimating such models is computationally expensive and has only become feasible with the availability of high-performance computer clusters. Therefore, characterizing dynamic neural stress signatures is an important next step in understanding stress responses. To conclude, resolving stress-induced changes in brain activation and FC across all parts of the stress response might help to link it to specific symptoms of mood and anxiety disorders such as increased rumination (e.g., slower stress recovery) or increased anxiety (e.g., heightened anticipatory response).

In summary, while many studies have investigated stress response dynamics in mood and anxiety disorders at the endocrine or cardiovascular level, underlying dynamical neural signatures are not yet well characterized. The studies presented in this thesis aim to advance the understanding of (mal)adaptive stress response dynamics from anticipation through recovery. To this end, in the first chapter, I evaluate the effect of a preceding cortisol response induced by a protocol variation (i.e., blood draw) on the multilevel stress response to the subsequent stress task. Quantifying the dynamics including an effect of a first ‘hit’ during anticipation on the stress response and recovery is essential to understand whether stress responses normally habituate or sensitize. Subsequently, it is possible to account for interindividual differences in the baseline state of stress system that might have been induced by the preceding hit. In the second part of the thesis, focusing on the neural dynamics of a single stress re-

sponse, dynamic FC and activation stress signatures will be derived across the complete response. Last, the trajectories will be associated with transdiagnostic dimensions capturing behavioral symptoms of stress responsivity also evaluating which stress phases are altered across dimensions. Ultimately, the work will provide important insights how dynamic signatures of acute stress are linked with risk-factors for mood and anxiety disorders by answering the following questions:

Key questions of the thesis

- Are stress responses across levels (i.e., endocrine, subjective, cardiovascular, and neural) affected by a preceding stress hit (Chapter 1)?
- Is the state of the stress system before stress onset associated with how the psychosocial stress task is experienced on the subjective, cardiovascular, endocrine, and neural level (Chapter 1&2)?
- Which phases of the stress response show altered dynamic signatures in mood and anxiety disorders (Chapter 2)?

1.5 Aims and results

In this thesis, I provide novel insights into dynamic trajectories of the stress response, particularly on the level of network reconfigurations, and how they relate to transdiagnostic, maladaptive, behavioral stress phenotypes. To this end, the first study lays the groundwork by characterizing the stress response across the psychological, autonomous, endocrine, and neural level in a self-reported mentally healthy subsample of the BeCOME study (Brückl et al., 2020). In this sample our study procedure included a 'multiple hit' scenario which enabled to test whether the (endocrine) stress system is sensitized or habituates after a preceding cortisol response. Specifically, the placement of an intravenous catheter (IVP) for repeated serum cortisol measurement approximately 60 minutes before the stress task was a stressor itself and induced a significant cortisol response in 35% of the sample. In line with the habituation theory, the endocrine stress response was lower in participants that showed a pre-task response to the IVP, although on the group level cortisol levels directly before the task had recovered back to baseline. Importantly, the habituation of the endocrine response was mirrored on the subjective, autonomous, and even neural level although effects were more pronounced in the stress recovery phase. Taken together, the study emphasizes the importance of standardized stress protocols, as even slight changes that seem uncritical at the group-level might induce interindividual variation in stress reactivity. Moreover, the results again emphasize that it is key to assess the complete trajectory of a stress response when investigating potential biomarkers of stress reactivity as interindividual differences in response to parts of the procedure may confound quantification of the 'true' stress response. Thus, the existence of a pre-task stress response was included in future work to account for this source of variability.

In the second study, the focus was on identifying dynamic trajectories of network configurations in response to stress and exploring corresponding transdiagnostic differences in mood anxiety disorders. The study included an extended sample of the BeCOME study with healthy participants as well as patients with mood and anxiety disorders that all completed the stress task. First, I identified four subnetworks that showed distinct changes in FC across the stress task. Specifically, DMN connectivity decreased, salience network connectivity increased, and cross network FC sharply decreased at stress onset and then gradually recovered back to baseline throughout the recovery phase. Importantly, individual FC trajectories across the four subnetworks but not changes in activation predicted the current stress state and corresponding changes in heart rate using support vector machines. Next, I derived five dimensions capturing self-reported stress responsivity and symptoms of depression. Two dimensions reflected different stress coping strategies and one dimension reflected negative affectivity and high trait anxiety. Last, I successfully used individual FC and activation trajectories to predict interindividual differences in negative affectivity using machine learning. Across analyses salience network connectivity and insula, a core hub of the salience network, activation contributed most to the prediction of stress states as well as negative affectivity underlining the integral role of the insula in regulating threat responses. Taken together, the results underline the potential of innovative approaches to quantify dynamic FC changes to identify alterations of stress reactivity in mood and anxiety disorders and thereby potentially provide an endophenotype for future translational and interventional studies.

1.6 Habituation of the stress system

We are frequently confronted with multiple stressful events within a short time window, and at the same time chronic stress is one of the main risk factors in the development of mental disorders (McEwen, 2004). A prominent concept in this context proposes that the repeated experience of stress is associated with increased arousal and cortisol levels which elicits lasting changes in the stress system also called ‘allostatic load’ that alter the set point of the organism (McEwen, 2003, 2004; Ursin & Eriksen, 2004). Hence, the recovery of the system to the baseline state is critical in preventing negative health consequences (Kim et al., 2015; Sluiter et al., 2003). To better understand how acute stress responses translate into lasting negative health consequences, it is therefore necessary to determine whether a stress response induces habituation or sensitization of the stress system (Rohleder, 2019). Extending reports indicating habituation of the endocrine stress response either when repeatedly experiencing the same stressor (Höhne et al., 2014) or when experiencing a physical stressor before a stress task (Zschucke et al., 2015), the results of the thesis show that the stress response across all levels habituates following a preceding cortisol response. On a neurobiological level, the habituation of the endocrine response might be explained by the negative feedback loop downregulating HPA axis activity after a stressor via GR-receptors in the hypothalamus and pituitary (Herman et al., 2005; Ulrich-Lai & Herman, 2009). The attenuated cortisol response to the stress task would then in turn translate to attenuated cardiovascular and subjective responses, since both heart rate (Adlan et al., 2018; Dodt et al., 2000) and the

psychological stress response (Het & Wolf, 2007) are affected by exogenous steroid administration. Likewise, activity in hippocampus, a region critically involved in regulating the stress response (Herman et al., 2005; Jacobson & Sapolsky, 1991; Knigge & Hays, 1963) was changed after hydrocortisone administration (Symonds et al., 2012). Of note, habituation effects were still apparent or even stronger during stress recovery, although acute stress effects and changes during stress recovery were highly correlated. This mirrors previous studies showing that pre-task exercise induced cortisol responses only showed a stress buffering effect during the recovery of the cardiovascular stress response (Hamer et al., 2006; Soravia et al., 2006). Generally, this indicates that the post stress recovery phase might be more sensitive in capturing interindividual differences either regarding the current state (e.g., current arousal level) or regarding trait-like differences (e.g., trait anxiety). One reason for this sensitivity might be that during recovery more higher-level top-down input regulating the stress response including various coping strategies is integrated (e.g., rumination or cognitive reappraisal, Brosschot et al., 2005; Gaab et al., 2005; Lü et al., 2016). To conclude, initial cortisol responses may have stress buffering effects in subsequent stressful situations independent of the nature of the initial response (i.e., aversive vs. positive Zschucke et al., 2015). Therefore, one could speculate that habituation or desensitization of the stress system, possibly mediated by negative feedback from the HPA axis, prevents the system from accumulating to much strain within a short timeframe and is therefore critical to maintain adaptive stress reactivity. As a next step it should be evaluated whether and how habituation of the stress system is altered in populations with chronic or repeated stress experiences, as chronic stress might change the setpoint of the stress system and thereby affect habituation or sensitization dynamics (McEwen, 1998). In addition, subgroups of mood and anxiety disorders or associated traits incurring a higher risk for future psychopathology might also be characterized by altered stress response dynamics across multiple stress hits (Rohleder, 2019).

1.7 Dynamic stress signatures

Whereas the importance of individual dynamics in stress reactivity across all phases is well documented on the endocrine (Daskalakis et al., 2022), cardiovascular (Ottaviani et al., 2016), and subjective level, many studies investigating underlying changes in brain responses still focus on the average acute response. Moreover, the focus has predominantly been on average whole-brain changes in activation, although results show substantial heterogeneity (Kogler et al., 2015) especially across stress-induction paradigms (Berretz et al., 2021). Comparably, neural habituation effects in the first part of the thesis were not apparent for specific regions but only when using representational similarity analysis that captures stress-induced changes independent of individual differences in specific location or direction of effects (Finn et al., 2015). The results of the second study of the thesis substantially expand on the current understanding of the neural stress response by characterizing changes in FC as well as activation within a predefined network of regions previously associated with stress reactivity (Hermans et al., 2014). The dynamics of the response were assessed from resting state across the complete stress task including recovery and concluding with another resting state. Only

trajectories of FC changes were able to recover the current stress state and corresponding heart changes of an individual, whereas this was not the case for changes in activation. Thus, stress predominantly reconfigures how different networks interact within and between each other.

More specifically, stress onset led to a pronounced decrease in cross network communication for example between DMN and salience network regions, possibly indicating an acute shift to exteroceptive processing whereas interoceptive replay may only become relevant with a delay (Craig, 2009; Kuehn et al., 2016). This hypothesis is further supported by increasing FC of the salience network throughout the complete task accompanied by decreasing FC of the DMN. The salience network, including the anterior insula, dorsal anterior cingulate cortex, hypothalamus, and amygdala (Seeley, 2019) is primarily coordinating the response to salient internal or external stimuli by orienting the attention towards them (Buckner et al., 2008; Menon, 2011). In that way, the salience network might support threat detection during stress (van Marle et al., 2010) and integrate as well as arbitrate between sensory and affective information by switching between the interoceptive DMN and top-down regulation from the central executive network in real time (Goulden et al., 2014; van Oort et al., 2017). The increase in salience network connectivity is in line with previously reported effects of stress (Hermans et al., 2011, 2014; van Oort et al., 2017) and might indicate an increase in arousal and threat monitoring (van Marle et al., 2010). Congruently, the decrease in DMN connectivity is also in line with previous studies (van Oort et al., 2017; Zhang et al., 2019) and suggests reduced introspective self-related processing (Sheline et al., 2009). Nonetheless, FC trajectories of the salience network dominated cluster were most predictive of the current stress state and heart rate changes. This mirrors and extends findings in mice, that the anterior insula, a core hub of the salience network as well as of the central autonomous network (Benarroch, 2012), shapes the bodily response to threat (Klein et al., 2021). Congruent with findings in resting state FC up to 60 minutes after the task (Dimitrov et al., 2018; Vaisvaser et al., 2013), both the decrease in DMN FC and increase in salience network FC persisted throughout the stress recovery phase of the task. One could speculate that amygdalar FC supporting threat detection might still be enhanced after the offset of the stressor and thereby facilitate the slow decline of vigilance in case the stressor reappears.

To summarize, at the neural level stress is characterized by dynamic network reconfigurations orchestrated by the salience network, particularly the insula. Increased salience network FC presumably supports orientation of attention towards the salient stressful stimulus and regulates the autonomous stress response while reducing the influence of self-referential thinking. However, as the analysis in the thesis focused on networks primarily affected in mood and anxiety disorders (i.e., DMN and salience network, Hamilton et al., 2011; McTeague et al., 2020), dynamic stress-induced changes in the central executive network supporting the cognitive component of the task response still need to be incorporated within this framework (Corr et al., 2022; Hermans et al., 2014). Thus, characterizing dynamic FC changes in response to stress across the whole brain would provide an even more extensive understanding of the neural stress response in the future.

1.8 Maladaptive stress signatures

After a comprehensive characterization of the stress response including dynamic trajectories of FC and activation changes, the natural next question is, whether those trajectories are altered in mood or anxiety disorders. Alternatively, specific symptoms reflecting either maladaptive stress reactivity or a higher risk to develop mood or anxiety disorders might be associated with altered dynamic FC trajectories. From the five dimensions capturing behavioral components indicative of (mal)adaptive stress reactivity, negative affectivity, a trait-like tendency to react more strongly to stress (Gulley et al., 2016; Hur et al., 2019), was predicted by combined FC and activation trajectories. In contrast, the presence of a mood or anxiety disorder did not differentiate the dynamic neural stress signatures. A similar distinction of trait-like susceptibility for depression and acute presentation of depressive symptoms has been shown in spatio-temporal signatures of threat in mice (Hultman et al., 2018) emphasizing that transdiagnostic markers of susceptibility might be more closely aligned to underlying dysregulation of the stress system.

On the network level, again, activation in the right and left insula together with FC changes in salience network FC contributed most to the prediction of negative affectivity which strengthens previous studies suggesting that stress-induced activity in the insula is associated with trait anxiety (Corr et al., 2020). Moreover, both salience network FC and insula activation are altered in mood and anxiety disorders (Sikora et al., 2016; Sripada et al., 2012; Whitton et al., 2019). Furthermore, the predictive value of stress-induced changes in salience network FC has been shown in natural settings as they successfully predicted the development of perceived stress levels and posttraumatic stress disorder symptoms in the future (Zhang et al., 2021).

Mechanistically, the results suggests that vigilance and threat monitoring might be altered in participants with high levels of negative affectivity (van Marle et al., 2010; van Oort et al., 2017). Likewise, the bodily response might be affected considering the role of the insula in regulating the physiological response to stress (Klein et al., 2021). Pinpointing the relevant phases of the stress response, salience network FC and activation changes during the anticipation phase contributed to the prediction which could indicate either a negative expectation in light of the impeding stress (Stegen et al., 2000) or an earlier identification of threat in the non-stress condition. A comparable time pattern can be observed for DMN connectivity, where anticipatory downregulation of DMN FC was associated with negative affectivity, although acute stress-induced changes in hippocampal activation also contributed. Dysregulated DMN connectivity in response to stress has been reported across disorders (Oort et al., 2020) and both resting DMN FC and hippocampal volume have been associated with MDD (Hamilton et al., 2011; Sheline et al., 2019). Furthermore, anticipatory activity in the putamen accompanied by acute FC changes in predominantly limbic connections were part of the most relevant predictors for negative affectivity. This is in agreement with previous studies highlighting the role of the striatum across mood and anxiety disorders at rest (Helm et al., 2018; Mulders et al., 2015; Pan et al., 2017) as well as in response to stress (Corr et al., 2020). Taken together the

results emphasize the role of aberrant salience network processing with a particular focus on the anterior insula in response to stress across mood and anxiety disorders. Together with preclinical findings showing the importance of the same networks in threat reactivity (Klein et al., 2021) and spatio-temporal trajectories differentiating stress-susceptibility from acute MDD-like symptoms (Hultman et al., 2018), the derived spatio-temporal networks trajectories might provide a promising target for translational research uncovering mechanistic links between acute stress reactivity and mood and anxiety disorders. Likewise, altered salience network processing might provide a potential target for treatments including non-invasive brain stimulation that targets the corresponding networks such as transcranial magnetic stimulation (Philip et al., 2018). Likewise, vagus nerve stimulation that has been shown to affect insula-dependent regulation of threat responses (Klein et al., 2021).

1.9 Modeling neural stress responses in mood and anxiety disorders

While the results add to our neurobiological understanding of adaptive and dysregulated brain responses to stress, they also provide methodological insights that should be considered in future studies. First, the psychosocial stress paradigm induced robust whole-brain activation changes. Nonetheless, stress-induced whole-brain changes in activation did not differed between participants with or without a current mood or anxiety disorder or depending on transdiagnostic dimensions of (mal)adaptive stress reactivity. Although, previous studies have reported such case-control differences (Villarreal et al., 2021; Waugh et al., 2012) or associations with trait anxiety (Corr et al., 2020; Wheelock et al., 2016), sample sizes were significantly smaller (~ 30/group) compared to the 217 participants included in the second part of the thesis and might not be replicable.

In contrast, applying hierarchical models covering complete temporal trajectories as well as activation and FC changes, uncovered interindividual differences relating to trait-like negative affectivity. These hierarchical models combine a number of advantages. The hierarchical estimation provides a certain degree of regularization increasing the reliability and predictive power of individual estimates (Farahibozorg et al., 2021; Katahira, 2016). Likewise, combining FC and activation changes in the model might more realistically reflect underlying mechanistic processes (L. Alexander et al., 2020; Grueschow et al., 2021). Moreover, previous work has shown that relevant task-induced changes in FC provide higher predictive power for associated phenotypes compared to rest and activation alone (Cole et al., 2014, 2016; Finn et al., 2017; Greene et al., 2020).

Second, (mal)adaptive behavioral stress reactivity was also characterized more in-depth by deriving transdiagnostic factors capturing different stress reactivity patterns and also including depressive symptoms and trait anxiety. Critically, only transdiagnostic dimensions such as general negative affectivity were related to spatio-temporal stress signatures. In contrast, signatures did not differ between participants with vs. without a mood or anxiety disorder. The transdiagnostic nature of alterations in neural stress reactivity were recently reported in a

relatively large sample including mood and anxiety disorders, autism, and attention deficit disorder (Oort et al., 2020). Likewise, alterations in brain activation across different paradigms were shared across major mental disorders (McTeague et al., 2020). More broadly, this again emphasizes the difficulties in dividing mental disorders into distinct groups as the heterogeneity in symptom profiles within groups is substantial while many symptoms are shared across diagnoses (Adolf & Fried, 2019). Approaches such as RDoC might therefore be more suitable to determine neurobehavioral phenotypes that have underlying mechanistic dysregulations and reflect symptoms across multiple mental disorders (Insel, 2014). Ultimately, endophenotypes such as a dysregulated stress response might provide targets for personalized treatments depending on the individual symptom profile (Brückl et al., 2020).

1.10 Limitations and outlook

The results presented in this thesis provide proof of principle evidence for neural spatio-temporal signatures of acute stress that are related to trait-like negative affectivity. The results are promising regarding their potential to uncover mechanistic links between acute stress reactivity and maladaptive stress response traits and may ultimately provide endophenotypes or treatment targets. Still, there are a few open questions and limitations that have to be addressed.

First while the thesis enhances our mechanistic understanding of the stress response on the neural circuit level, there is large potential in translational approaches combining insights from human fMRI with genetic, molecular, or preclinical work (e.g., Meijer et al., 2021). In addition to the link with preclinical work (Hultman et al., 2018; Klein et al., 2021), another avenue would be to identify genetic factors that are associated with an altered molecular stress response (Daskalakis et al., 2022), for example, FKBP5 (Matosin et al., 2018; Menke et al., 2013) genotypes or polygenic scores capturing transcriptomic responses to glucocorticoids (Arloth et al., 2015; Penner-Goeke et al., 2022). Subsequently, genetic factors can be related to the dynamic stress signatures and provide further insights into mechanisms liking acute stress reactivity with individual risk factors for mood and anxiety disorders.

Second, to determine the clinical utility of the proposed spatio-temporal trajectories, more validation work is necessary. While clinical utility as biomarker for diagnostic purposes might be limited when considering the cost (Grzenda & Widge, 2020), it is more feasible to use them as endophenotype in the development or evaluation of potential treatment options. For instance, experimental studies targeting dysregulated networks using non-invasive brain stimulation techniques could elucidate whether inducing a neural stress response more closely resembling a response associated with low negative affectivity also changes how stress is experienced behaviorally. Alternatively, one could evaluate whether treatments targeting trait-like negative affect, for example, behavioral therapy changing coping behavior and negative outcome expectations change the spatio-temporal neural stress response. Ultimately, this might enable personalized treatment or interventions in high-risk populations targeting the

systems corresponding to individual symptom profiles across levels ranging from genetic risk to maladaptive behavioral stress reactivity.

Third, the generalizability of the results should be assessed on different levels ranging from narrower replications to validation in real-life settings (Yarkoni, 2019). The generalizability of the results to other data sets should be tested with a replication in an independent although methods such as cross-validation and hierarchical model estimation help increase reliability and reduce overfitting (Farahibozorg et al., 2021; Vabalas et al., 2019; Varoquaux et al., 2017). In a next step, generalization to other types of stressors should be investigated since stress reactivity is dependent on the exact protocols (Dickerson & Kemeny, 2004; Goodman et al., 2017; Noack et al., 2019). Illustratively, we were unable to replicate hippocampal FC networks predicting subjective stress reactivity in a threat-induction stress paradigm using a psychosocial stress task (Kühnel et al., 2020). Thus, the generalizability of the dynamic signatures to other laboratory tasks needs to be evaluated. Next, it is also necessary to investigate how well dimensions of stress reactivity such as negative affectivity predict naturalistic behavior (Amirkhan, 1994; Chesney et al., 2006). In the same way it has to be evaluated whether the association with dynamic spatio-temporal signatures generalizes also predicts naturalistic behavior (Yarkoni, 2019). For instance, one could relate the dynamic signatures derived in the lab to stress reactivity measured outside the lab in response to real-life stressors by using ecological momentary assessment or continuous cardiovascular monitoring (e.g., Hur et al., 2021). Ultimately, a longitudinal prediction of maladaptive stress responses and lasting mental health problems is central to determine whether and how increased risk or maladaptive spatio-temporal stress signatures lead to mental disorders (e.g., Zhang et al., 2021). However, the study only includes one cross-sectional assessment, precluding causal conclusions (Siddiqi et al., 2022). Therefore, longitudinal studies or experimental designs that modulate network connectivity are necessary to disentangle how altered stress processing, trait-like negative affectivity, and acute depressive or anxiety symptoms influence each other.

Fourth, the first chapter of the thesis shows that a cortisol response elicited by a protocol variation that is necessary to measure cortisol levels induces interindividual variability that still affects the response to the following stress task. Similar effects could also be induced by other parts of the procedure that are necessary to measure the stress response. For example, the fMRI scanner itself can induce a confounding cortisol response (Gossett et al., 2018; Muehlhan et al., 2011). Further, repeatedly asking participants about their mood or affect state could alter the measured subjective response as introspection affects emotions (Herwig et al., 2010). Therefore, measurement methods and their influence on the response should be systematically investigated and carefully considered and in future studies.

1.11 Conclusion

Chronic stress is one of the most prominent risk factors for the development of mood and anxiety disorders. Hence, a dysregulated acute stress response, especially of the HPA axis, has been one of the main targets in the search of biomarkers as well as of a mechanistic understanding of mood and anxiety disorders (Lupien et al., 2017). Notably, the focus has increasingly shifted from a blunted or excessive acute response to considering the dynamics of the complete stress response from anticipation until recovery (Kim et al., 2015; McEwen, 1998). The studies included in the thesis extend the work on dynamic stress responses by first investigating the effect of multiple stress hits on the system, followed by an in-depth characterization of dynamic brain response trajectories and their association with trait-like (mal)adaptive stress responsivity. A first cortisol response during anticipation affects stress response dynamics across all levels of the stress response (i.e., subjective, cardiovascular, neural, and endocrine) by inducing a habituation effect on the acute response (subjective, and endocrine) and particularly also by an acceleration of stress recovery (cardiovascular, neural). Zooming in on the dynamics of the brain's response to an acute psychosocial stressor, the thesis highlights four subnetworks that show differential changes in connectivity in response to stress. Specifically, FC changes in the subnetwork dominated by salience network connectivity and activation of the insula were central in distinguishing the current stress state and predicting corresponding heart changes. Moreover, they predicted negative affectivity, a trait-like marker for amplified negative responses to stress. On a methodological level, the results of the studies highlight the importance of densely measuring and modeling individual stress responses from anticipation until the system has recovered, to improve our understanding of inter- and intraindividual changes in response to stress. On a mechanistic level, spatio-temporal trajectories of particularly salience network connectivity may be key for orchestrating the bodily stress response. Crucially, signatures differ depending on trait-like negative affectivity, thereby providing a potential endophenotype that can guide future studies across multiple levels ranging from genetics to therapeutic targets. For instance, interindividual differences in genes regulating stress reactivity might provide a link between individual risk, associated alterations in acute stress reactivity, and the development of psychiatric disorders. Likewise, underlying mechanisms in dynamic traces of stress can be investigated in animal studies targeting structures such as the insula. Importantly, this phenotype may ultimately prove to be valuable for precision psychiatry by either revealing a transdiagnostic dysregulation that characterizes a specific subgroup of patients or by providing a target for evaluating or targeting treatments such as neurostimulation.

2. Psychosocial stress reactivity habituates following acute physiological stress

2.1 Summary

To evaluate whether an independent, preceding cortisol response leads to sensitization or habituation of the stress system, we investigated the effects of intravenous catheter placement (IVP) 60 minutes before a psychosocial stress task on subsequent stress reactivity on the endocrine, subjective, cardiovascular, and neural level. We included 67 self-reportedly healthy individuals from the BeCOME study that investigates biological dimensions of mood and anxiety disorders. Within this study, all participants perform a psychosocial stress task including a prestress anticipation phase, stress phase, and poststress recovery phase during fMRI imaging. Crucially, there was substantial interindividual variation in the response to IVP and approximately 35% of the sample showed a significant cortisol response. Subsequently, we assessed differences in in heart rate, negative and positive affect, cortisol response, and brain activation during stress and stress recovery between IVP-responders and non-responders. Moreover, we correlated the magnitude of the IVP cortisol response with the responses to the psychosocial stress task.

First, the cortisol response was reduced in IVP responders compared to non-responders. Second, this reduction was mirrored on the subjective and autonomous level, where we observed reduced negative affect after the task as well as reduced heart rate increases particularly during stress recovery, although effects during acute stress and stress recovery were highly correlated, preventing any conclusions regarding specificity. Last, while we did not observe any differences in whole-brain activation patterns during stress or stress recovery, neural similarity, a measure capturing stress-induced changes irrespective of exact localisation or directionality, between the anticipation and recovery phase was higher in IVP responders at the voxel level as well as at the region of interest level suggesting faster stress recovery back to baseline levels. Taken together, our results suggest that a preceding cortisol response leads to habituation of subsequent stress responses even when the preceding stressor is presumably aversive. Moreover, the results highlight the importance of high-frequency cortisol measurements throughout the complete procedure especially when investigating potential biomarkers, to identify possible sources of interindividual variation in stress reactivity.

2.2 Contributions and reference

The study “Psychosocial stress reacitivity habituates following acute physiological stress” was published in *Human brain mapping* in June, 2020. PGS and EBB were responsible for concept and design; IGE, MC, and PGS validated the paradigm and procedure; AK performed data analyses and NBK contributed to data analysis; AK wrote the manuscript; AK, NBK, IGE, MC, PGS, MW, and EBB provided critical revision of content

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Psychosocial stress reactivity habituates following acute physiological stress

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Abstract

Acute and chronic stress are important factors in the development of mental disorders. Reliable measurement of stress reactivity is therefore pivotal. Critically, experimental induction of stress often involves multiple “hits” and it is an open question whether individual differences in responses to an earlier stressor lead to habituation, sensitization, or simple additive effects on following events. Here, we investigated the effect of the individual cortisol response to intravenous catheter placement (IVP) on subsequent neural, psychological, endocrine, and autonomous stress reactivity. We used an established psychosocial stress paradigm to measure the acute stress response (*Stress*) and recovery (*PostStress*) in 65 participants. Higher IVP-induced cortisol responses were associated with lower pulse rate increases during stress recovery (b= -4.8 bpm, p= .0008) and lower increases in negative affect after the task (b= -4.2, p= .040). While the cortisol response to IVP was not associated with subsequent specific stress-induced neural activation patterns, the similarity of brain responses *Pre-* and *Post-Stress* was higher IVP- cortisol responders (t(64)= 2.35, p= .022) indicating faster recovery. In conclusion, preparatory stress induced by IVP reduced reactivity in a subsequent stress task by modulating the latency of stress recovery. Thus, an individually stronger preceding release of cortisol may attenuate a second physiological response and perceived stress suggesting that relative changes, not absolute levels are crucial for stress attribution. Our study highlights that considering the entire trajectory of stress induction during an experiment is important to develop reliable individual biomarkers.

Key words: stress, fMRI, HPA Axis, cortisol, habituation, representational similarity

1. Introduction

Acute stress and possible maladaptive responses such as increased anxiety, extensive rumination and impaired cognitive functioning (Mizoguchi et al., 2000) are important factors in the etiology of affective disorders (McEwen, 2004). An important biomarker quantifying the stress response and linking it to personality traits and disease is the hypothalamus–pituitary–adrenal (HPA) axis response to standardized stress tests (Foley and Kirschbaum, 2010), such as the Trier Social Stress Task (TSST) (Kirschbaum et al., 1993) and adaptations suitable for exploration through functional imaging (fMRI) (Elbau et al., 2018; Noack et al., 2019). Whereas stress is an integral part of everyday life, responding to repeated stressful experiences can unveil inter-individual differences that have been linked to psychopathology before (Grillon et al., 1996; McEwen, 1998; McLaughlin et al., 2010). Decades of preclinical and human research have demonstrated the interdependence of multiple stressful events often leading to habituation or sensitization of acute responses to impending stress (Belda et al., 2015; Grissom and Bhatnagar, 2009; Petrowski et al., 2012; Pitman et al., 1990). However, there is little evidence from multimodal experimental studies on potential carry-over effects of directly preceding stress suggesting an implicit assumption that sequential stress effects are independent and additive. Here, we sought to bridge this gap by investigating inter-individual differences in cortisol responses to a stressful precedence (here: placement of an intravenous catheter) on the experience of psychosocial stress.

Consequently, the basal state of the stress system at the time the stressor plays an important role in modulating endocrine stress responses (Dickerson and Kemeny, 2004; Juster et al., 2012; Kudielka et al., 2004). Alterations in the basal HPA axis state may even affect the cognitive appraisal of the stress-induced physiological changes, thereby altering the emotional response (Folkman et al., 1986; Ursin and Eriksen, 2004). The TSST has been validated extensively and a number of influencing factors have been characterized to date (Allen et al., 2014). For instance, time of day (Kudielka et al., 2004), timing of cortisol measurements (Dickerson and Kemeny, 2004; Liu et al., 2017), composition and feedback (e.g. neutral vs. negative) of the panel, sex and menstrual cycle (Childs et al., 2010; Liu et al., 2017) have been shown to impact stress reactivity. One crucial factor that may influence basal states is the intravenous catheter placement (IVP) for the repeated assessment of serum cortisol levels (Dickerson and Kemeny, 2004; Goodman et al., 2017; Kudielka et al., 2004). Experimental evidence for the importance of the basal HPA axis state comes from studies showing that a pharmacological increase of cortisol before the TSST reduced subjective stress after the task (Het and Wolf, 2007). Similarly, endogenous cortisol increases induced by either physical exercise or anticipation of a stress task or the MRI were associated with a reduced endocrine or physiological response to the psychosocial stressor, albeit at a group level (Gossett et al., 2018; Juster et al., 2012; Zschucke et al., 2015). Likewise, reduced cortisol responses to the TSST as a result of two subsequent sessions on the same day indicate that biological habituation of the HPA axis may be relevant for repeated stressors in a short time window (Höhne et al., 2014). Lasting effects of cortisol have also been described for functional connectivity at rest (Vaisvaser et al., 2013) and task-related activity. For example, an unrelated, previously

induced cortisol response altered the neural response to the imaging stress task (Zschucke et al., 2015) and other tasks (Maier et al., 2015) even up to 60 minutes later (Joëls et al., 2011). Collectively, this suggests that a preceding acute cortisol response may have lasting effects on the endocrine, physiological, neural and psychological response to subsequent experimental stressors.

To evaluate the interdependence of stressful events and how it may affect potential biomarkers of stress, we quantified the effect of inter-individual differences in cortisol responses elicited by IVP on the subsequent stress response to a multimodal psychosocial stress test. A recent meta-analysis (Goodman et al., 2017) showed that cortisol responses to the TSST are indeed influenced by IVP, with effects sizes of the cortisol response being significantly higher in studies with IVP versus without. However, other confounding factors such as interindividual differences in cortisol response to IVP, timing of IVP, or the different methods used to quantify the cortisol response (saliva vs. serum) were not controlled for and effects on other levels of the stress response were not evaluated. Therefore, we first characterized the cortisol response elicited by IVP before a stress task. We then tested if this IVP-induced increase in cortisol altered the stress response to a subsequent standardized fMRI stress task. Critically, we assessed the stress reactivity on multiple levels including neural (fMRI), autonomous, endocrine, and subjective read-outs. Moreover, the task was separated into three phases of arithmetic, starting with a control condition without psychosocial stress, followed by the actual psychosocial stressor and ending again with control condition without psychosocial stress. This enabled us to also assess the fast stress recovery during the post stress phase, which may show greater sensitivity to individual stress-response profiles. We investigate if a stronger preceding IVP-induced cortisol response would alter the stress response to the subsequent stress task. According to habituation (Gossett et al., 2018; Juster et al., 2012) or sensitization (Goodman et al., 2017) of the stress system, a stronger IVP-induced cortisol response could either exacerbate or limit the magnitude of a second, task-induced response.

2. Methods

2.1 Participants

The sample recruited as part of the Biological Classification of Mental Disorders (BeCOME) study at the Max Planck Institute of Psychiatry, registered on ClinicalTrials.gov: NCT03984084). The BeCOME study characterizes participants with a broad spectrum of affective, anxiety, and stress-related mental disorders as well as unaffected individuals. It includes various behavioral and functional imaging tasks measured across two days (Brückl et al., submitted). For the present study we included a subsample of 67 participants (26 women, M_{age}= 32.4 years ± 9.7) that contacted the institute as healthy control participants. All participants underwent a comprehensive, computer-based, standardized diagnostic interview (CIDI) in which diagnoses are derived by an automatically evaluated, standardized, DSM-IV-based algorithm. We did not exclude participants that received a diagnosis and thus capture a sample of participants self-identifying as healthy yet showing symptoms that would be considered subclinical or lead to a diagnosis in multiple cases. Briefly, 48% (n= 32) did not have any current or lifetime diagnosis, while 40% (n= 27) received at least one (lifetime) diagnosis belonging to the anxiety disorders spectrum including specific phobias, 19% (n= 13) a substance use-related diagnosis and 7% (n= 5) a mood disorder (See table S1 for details). However, none of the participants reported any present medication for their psychiatric symptoms.

To maximize the sample size, we excluded participants with missing or low-quality data for each analysis separately. More specifically, we excluded participants because of missing cortisol saliva (n=2) samples from all analyses, and serum samples (n= 12) from analyses regarding serum cortisol responses to the stress task (both insufficient biological material). Moreover, we excluded 12 participants from analyses regarding pulse rate as their signal quality was too low for reliable peak detection.

2.2 Experimental procedure

The imaging stress task (Figure 1) was included in the fMRI session on the second BeCOME study day (Brückl et al., 2020). All participants previously took part in the fMRI session on the first study day and consequently none of the participants was fMRI naïve. On this day, participants arrived at the scanner at approximately 10 am. Upon arrival, the first saliva sample was taken to measure basal cortisol levels. Subsequently, the IV catheter was placed and tested for permeability for repeated serum sampling measurements during and after the stress task. Problems during the procedure (e.g. failed first or multiple IVP attempts) were recorded by the physicians. After that, participants were familiarized with the task and the response options. Electrodes were placed on the palm of the left hand for the measurement of skin conductance and on the back for electrocardiography. A pulse oximeter was placed on the fingertip to measure pulse rate. Before entering the scanner (21.8 minutes ± 7.6 after IVP), we took another saliva sample to assess cortisol increases related to the IVP. The fMRI session started with a T2-weighted high-resolution image for spatial normalization, followed by an emotional face

matching task and a pre-stress resting state. Immediately before the stress paradigm, participants rated their current affective state using the previously used (Elbau et al., 2018) *Befindensskalierung nach Kategorien und Eigenschaftsworten* (BSKE, for details see SI). Approximately 60 minutes (64.6 minutes ± 8.7) after IVP, the stress task started. A 60 minute interval is generally recommended for recovery of the cortisol concentrations back to baseline after IVP (Allen et al., 2014). The task consisted of a PreStress, Stress, and PostStress phase and lasted for about 25 minutes. Multiple blood samples were taken during task performance (Figure 1). After completion of the task, the current affective state was assessed again with the BSKE and saliva and blood samples were taken. A 30-minute rest period lying outside the scanner was followed by a concluding assessment of subjective affect, blood and saliva cortisol samples, and post-task resting state fMRI. At the end of the session, participants were debriefed by the investigator.

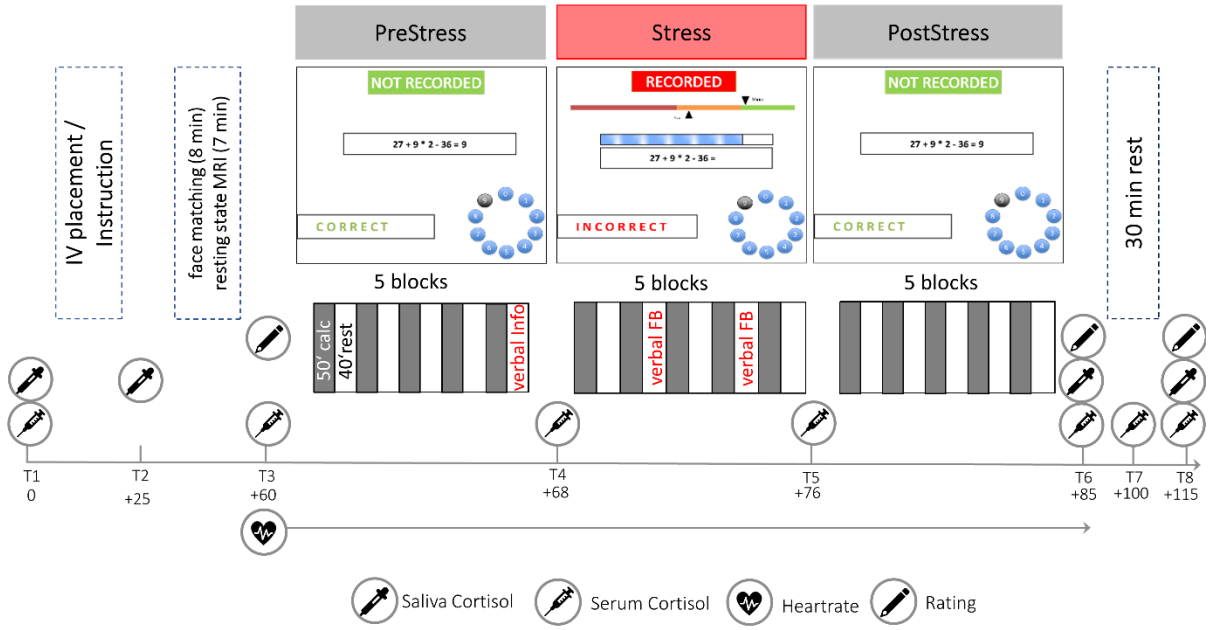

Figure 1: Schematic summary of the procedure and task. Before the stress phase, participants were informed about being recorded in the following trials. Additional aversive verbal feedback (verbal FB) about unsatisfactory performance was given in the 2nd and 4th rest period of the Stress condition. The first serum and saliva samples were taken directly after IV placement.

2.3 Paradigm

Psychosocial stress was induced by an imaging stress task previously reported by Elbau et al. (2018), with minor changes regarding the aversiveness of the feedback and the number of task blocks. As in previous versions of the task, participants had to solve mental arithmetic problems either in a control condition without time pressure and negative feedback or under stress with a time limit and negative feedback. Critically, the task was partitioned into three

phases, PreStress, Stress, and PostStress, each consisting of five 50 second blocks of arithmetic interleaved with five 40 second blocks rest (fixation cross). During an arithmetic block, participants were presented an arithmetic problem with a solution between 0 and 9. Arithmetic problems varied in their difficulty across three levels and difficulty was balanced across the three conditions. The correct answer was chosen using a response box allowing to navigate a two-button dial wheel system. After selecting the answer, the screen 'froze' for an anticipation phase (2.5 ± 1s, jittered) that was followed by the feedback ('correct', 'incorrect' or 'timeout', presented for 660ms). During PreStress and PostStress, participants had 10.5 seconds to respond and no further evaluative feedback or cues were given. Before Stress, participants were informed that answers are now 'recorded'. During stress, time to solve the arithmetic was generally limited to 4.5 seconds, and in part self-adaptive depending on the participant's preceding performance. Further, a time bar indicated how much time was left, inducing further time pressure, and a performance indicator showed that current performance was below group average ('in the red area'). Two instances of scripted negative verbal feedback in two rest periods informed the participants about their sub-par performance and pushed them to work harder

2.4 Data acquisition

2.4.1 Cortisol sampling (serum and saliva) and analysis

Cortisol concentrations were measured repeatedly before, during, and after the task in saliva and/or serum (Figure 1). Salivary cortisol was sampled directly at arrival before IVP (T1), 20 minutes after IVP to quantify potential effects of the placement itself (T2) and additionally directly after the stress paradigm (T6) and 30 minutes after the end (T8) using salivettes cortisol code blue with a synthetic swab (Sarstedt AG & Co., Nümbrecht, Germany). After collection, all probes were centrifuged and stored at -80° C until further processing. Salivary cortisol concentrations were measured with electro-chemiluminescence-assay (ECLIA) kit (Cobas®, Roche Diagnostics GmbH, Mannheim, Germany). The detection limit was 1090 pg/mL. The %CV (coefficient of variation) in saliva samples with varying concentrations was between 2.5% and 6.1% for intra-assay variability and between 3.6% und 11.8% for inter-assay variability.

To assess the HPA-axis response to the psychosocial stress task with a higher temporal resolution, we additionally repeatedly measured serum cortisol. It was sampled at seven time points, first directly after IVP and then in 8-minute intervals starting directly before the task and ending after the 30-minute rest period. After collection, all probes were centrifuged and stored at -80° C until further processing. Serum cortisol was determined using an Enzyme-linked Immunosorbent Assay (ELISA) kit (IBL Hamburg, Germany). The standard range was 20 – 800 ng/mL. The %CV in serum samples was between 2.6% and 3.5% for intra-assay variability and between 2.1% und 5% for inter-assay variability.

2.4.2 Physiological recording and preprocessing

The autonomous stress response was measured throughout the complete task using photoplethysmography (PPG), electrocardiography, and skin conductance. The PPG data was acquired with an MR compatible pulse oximeter (Nonin Medical Inc., Plymouth MN, USA) attached to the pulp of the left ring finger. PPG data, sampled at 5 kHz, was amplified using a MR compatible multi-channel BrainVision ExG AUX Box coupled with a BrainVision ExG MR Amplifier (Brain Products GmbH, Gilching, Germany) and recorded with BrainVision Recorder software 1.0. After down-sampling to 100 Hz, RR-intervals were detected using the Physionet Cardiovascular Signal toolbox (Vest et al., 2018). Success of detection of beat positions was evaluated by visual inspection. Measurements with insufficient data-quality leading to failed detection of beat positions were excluded (n= 12). Subsequent analysis of the pulse rate was based on the derived RR-intervals and conducted with the RHRV package (Rodríguez-Liñares et al., 2008) for R. Further preprocessing involved the exclusion of implausible interbeat-intervals (IBI). We filtered out IBIs shorter than 0.3 s and longer than 2.4s and excluded IBIs showing excessive deviations from the previous, following, or running average (50 beats) IBI. The threshold for excessive deviations was updated dynamically with the initial threshold set at 13% change from IBI to IBI (Vila et al., 1997).

2.4.3 fMRI data acquisition and preprocessing

MRI data were acquired on a GE 3Tesla scanner (Discovery MR750, GE, Milwaukee, U.S.A.). The functional data were T2*-weighted echo-planar images (EPIs) consisting of 755 volumes for the stress task (details in the SI). All fMRI data preprocessing and analysis was performed in Matlab 2018a (The Mathworks Inc., Natick, MA, USA) and SPM12 (Statistical parametric mapping software, version 12; Wellcome Department of Imaging Neuroscience, London, UK). First, data was slice-time corrected and realigned to the first image of the task to correct for head motion. For spatial normalization, a single T2*-weighted EPI (details in the SI) image acquired with a longer repetition time and minimum echo time was segmented using the unified segmentation scheme. While susceptibility induced signal distortions are different at different echo times, this EPI image has the same geometrical distortions as the functional images, but with higher contrast-to-noise ratio. The better match between this image and the fMRI volumes enables successful anatomical segmentation and non-linear transformation to atlas space. Extracted gray matter and white matter segments were used for DARTEL (Ashburner, 2007) normalization to MNI templates. Functional images were co-registered to the single EPI image and normalized by applying the DARTEL-derived transformation matrix. Data was interpolated with a resolution of 2x2x2 mm. The last step was the smoothing of the data with a 6x6x6 mm FWHM kernel. During the realignment, the six head motion-parameters were extracted for later use as nuisance covariates. Additionally, we calculated the framewise displacement for all six parameters and extracted physiological noise components based on aCompCor (Behzadi et al., 2007). We extracted the voxel-wise timeseries of the normalized but unsmoothed functional data from thresholded (p> .90) white matter and cerebrospinal fluid segments, performed PCA, and used the first five components of each segment as physiological noise covariates.

2.5 Data analysis

2.5.1 Cortisol response to IVP

The cortisol response elicited by IVP was estimated using salivary cortisol measures. This response was calculated as the increase in salivary cortisol from T1 to T2 ($\Delta Cort_{IVP}$= $Cort_{T2}$ - $Cort_{T1}$). Further, we classified participants into responders and non-responders to the IVP based on a conservative cut-off of $\Delta Cort_{IVP}$> 2.5 nmol/l (0.91 ng/mL, Wust et al., 2000) previously used in similar studies (Lueken et al., 2012; Muehlhan et al., 2011) to test if marked IVP-induced cortisol responses alter stress task reactivity. All subsequent analyses were primarily based on the comparison between IVP responders and non-responders, but quantitative analyses based on $\Delta Cort_{IVP}$ were also performed.

2.5.2 Stress response to the psychosocial stress task

To delineate effects of psychosocial stress and IVP on cortisol concentrations over time, we quantified the HPA axis response to the task using serum cortisol measurements. We calculated the area under the curve (AUC) values starting at the beginning of the stress task and ~60 minutes after IVP, a time-interval frequently recommended to aid recovery of the cortisol system. Thus, we included serum cortisol measures from the time point T3 until T8, 30 minutes after the end of the task. Cortisol responses may be partly offset by declining cortisol concentrations over the day starting shortly after the morning cortisol peak. Therefore, we additionally calculated cortisol concentrations corrected for a linear circadian trend between T3 and T8 and used those values to subsequently derive a circadian corrected AUC ($AUC_{Circ,}$ for details see SI) to assess if the psychosocial stressor elicited an HPA axis response above the circadian decline. This previously used and validated (Elbau et al., 2018) approach is sensitive to small cortisol increases but does not overestimate stress effects, making it suitable to assess the success of HPA axis induction by the stress task across the whole group. However, the serum-cortisol AUC-values still incorporate IVP-related effects. Moreover, serum cortisol values may not have returned to their physiological circadian level with the last available measurement. Consequently, we used the AUC values derived from uncorrected serum cortisol concentrations to assess interindividual differences induced by the IVP.

Autonomous stress effects elicited by the stress task were estimated as change in average pulse rate (beats per minute, bpm) during the arithmetic blocks in the Stress condition compared to the arithmetic blocks in the PreStress condition (ΔHR_{Stress}= HR_{Stress} - $HR_{PreStress}$). In the same way, the lasting effects of stress during the acute recovery (PostStress) phase were calculated as $\Delta HR_{PostStress}$= $HR_{PostStress}$ - $HR_{PreStress}$.

Subjective stress effects elicited by the stress task were estimated as the change in positive and negative affect after the task (ΔPos/ΔNeg = Positive/Negative affect(T6) - Positive/Negative affect(T3)). As in previous work (Elbau et al., 2018), we used 15 items of the BSKE to assess negative and positive affect and calculated sum scores for the relevant items (for details see SI).

The effects of cortisol induced by IVP on autonomous, subjective or serum HPA responses to the subsequent stress task were assessed with multiple linear regression models including either the responder status to IVP or the cortisol increase ($\Delta Cort_{IVP}$) as predictor and sex, age, and presence of any lifetime psychiatric diagnosis (coded yes/no) as covariates.

2.5.3 fMRI data

The first-level general linear models (GLM) were built using individual onsets and durations of all task-blocks extracted from the log files for each participant. The task was modelled with three regressors, each modeling the five arithmetic blocks (60s) of the conditions PreStress, Stress and PostStress, respectively. In addition, we included two regressors modeling individual motor responses and verbal feedback during the Stress phase. Nuisance regressors were the six movement parameters derived from realignment, their derivatives, and five physiological noise components extracted from white matter and cerebrospinal fluid each. Data were high pass filtered with a cut-off of 256s. The contrasts of interest, *Stress – PreStress,* to assess acute psychsocial stress, and *PostStress – PreStress,* to assess effects of fast stress recovery, were estimated for each participant. To additionally describe effects on a network level, we aggregated stress effects by calculating mean betas within networks (Yeo et al., 2011) for each participant and contrast and tested for significant changes within one network across participants.

To test the effects of IVP-induced cortisol responses on the subsequent neural stress response to the psychosocial stressor, we performed whole-brain voxel-wise multiple regression analyses using the contrast images derived in the first-level statistics. Either $\Delta Cort_{IVP}$ or responder status were included as predictor and sex, age, and lifetime psychiatric diagnosis (no/yes) as covariates. In addition to this cluster-based approach, we again used aggregated betas within networks to compare neural stress responses in IVP-responders and non-responders. We depict t-values (i.e., a ratio of the beta coefficients and their variability) in Figure 3 to ease their comparison.

However, this approach may mask individual variation in the direction or localization of stress effects. To capture individual neural stress effects independent of their directionality and localization, we calculated within-participant similarity of the neural activity during PreStress compared to Stress and PostStress, respectively. To this end, we extracted mean beta estimates of the conditions (PreStress, Stress, and PostStress) from 268 regions of interest (ROIs) spanning the whole brain using an established brain parcellation (Shen et al., 2013) to assess stress effects on the ROI level. Representational similarity was then calculated as the Pearson correlation between the activity PreStress and Stress or PressStress and PostStress across all ROIs for each participant separately. In addition, we used voxel-wise beta coefficients and estimated individual similarity within functional Yeo networks (Yeo et al., 2011) to test an alternative level of aggregation. Correlation coefficients were Fisher's z-transformed for further parametric analyses. Effects of IVP-induced cortisol on neural similarity during and after stress was tested by applying linear models including sex, age, lifetime diagnosis, and average framewise displacement as covariates.

2.5.4 Statistical threshold and software

Statistical analyses were performed in R v3.5.1. (R Core Team, 2018). To account for non-normal distributions of the cortisol responses, we additionally bootstrapped all regression estimates (2,000 resamples). As the current literature did not converge to suggest a heightened or attenuated stress response after IVP, we used two-sided tests with a significance threshold $p < .05$ for all effects of interest. For whole-brain fMRI analyses, the voxel threshold was set at $p < 0.001$ (uncorrected). Clusters were considered as significant with an FWE cluster-corrected p-value threshold of $p_{cluster.FWE} < .05$.

3. Results

3.1. The imaging stress task induced autonomous, subjective, and neural stress responses

First, we assessed if stress induction by the imaging stress task was successful. As expected, stress induction increased the pulse rate in the Stress (mean ΔHR_{Stress}= 8.17 bpm, t(55)= 9.34, $p <$. 0001) and PostStress (mean $\Delta HR_{PostStress}$= 1.42 bpm, t(55)= 2.11, p= .038) phase. Still, it recovered significantly (mean $\Delta HR_{Stress\text{-}PostStress}$= -6.74 bpm, t(55)= 8.39, $p <$ .0001) after stress (see Figure 2C-D). Positive affect was decreased (mean ΔPos(T6)= -1.81, t(66)= -3.30, p= .0002) and negative affect increased (mean ΔNeg(T6)= 6.16, t(66)= 6.48, p< .0001) directly after the task (Figure 2E). In contrast, only positive affect was still decreased (mean ΔPos(T8)= -1.13, t(66)= -2.16, p= .034) 30 minutes later while negative affect had recovered to levels slightly below baseline (mean ΔNeg(T8)= -0.82, t(66)= -1.26, p= .21, Figure 2E). Both, pulse rate increases in the Stress and PostStress phase as well as affect changes directly and 30 minutes after the task, were positively correlated (rs between 0.63 and 0.77, all $ps <$ .0001) indicating that interindividual differences of the autonomous and subjective stress response also persist during the recovery period. The task elicited a significant serum cortisol response (AUC_{Circ}= 459 ng/ml*min, t(51)= 3.69, p= .0005) when taking into account the approximated circadian cortisol decline for each individual. Eighteen participants would be classified as responders with a peak cortisol response higher than 55 nmol/L (19.99 ng/mL, equivalent to 2.5 nmol/L in threshold in saliva).

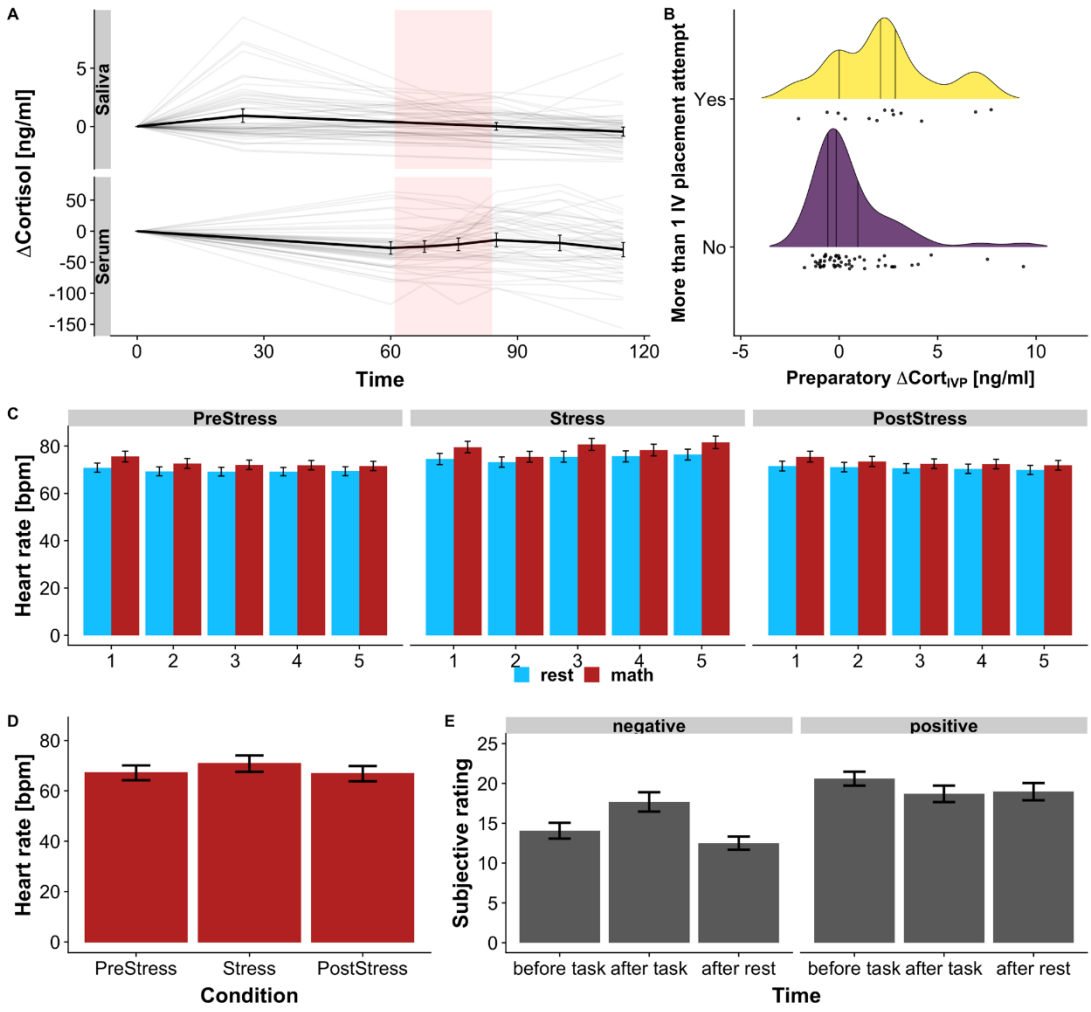

Figure 2: The intravenous catheter placement (IVP) and the stress task increased stress levels. A) Cortisol response (ΔCortisol) over time. IVP just before T1 increased average salivary cortisol at T2. Thin lines depict individual cortisol profiles, thick lines depict the group average. Shaded rectangles indicate the stress task phase. B) IVP- induced cortisol responses were higher after complicated placement, for example if more than one attempt was needed. C) The average pulse rate was higher during the cognitive task (math) compared to rest phases across all task blocks. D) The average pulse rate in math phases of the Stress condition was higher compared to PreStress and PostStress. Notably, the average pulse rate did not completely recover. E) Stress increased negative emotions and decreased positive emotions. Increases in negative emotions were transient and recovered back to baseline levels, while positive emotions remained reduced. Error bars depict 95% confidence intervals.

Likewise, stress-induced changes in neural activity, as assessed within the contrast PreStress-Stress, mapped to increased activity in primary and secondary visual as well as lateral parietal cortex and decreased activity in the default mode network, including the posterior cingulate cortex (PCC), precuneus and lateral parietal (angular gyrus) and temporal cortex, dorsomedial prefrontal cortex, thalamus, and insula (Figure 3A). Consistent with this voxel-wise approach, at the network level, increases in activity were predominantly observed in the visual and the dorsal attention network (Yeo et al., 2011), while deactivation were observed in the default mode network (Figure 3B). Moreover, the deactivation of the default mode network was still visible in the PostStress phase, while activation of the dorsal attention network recovered closer back to baseline (Figure 3E).

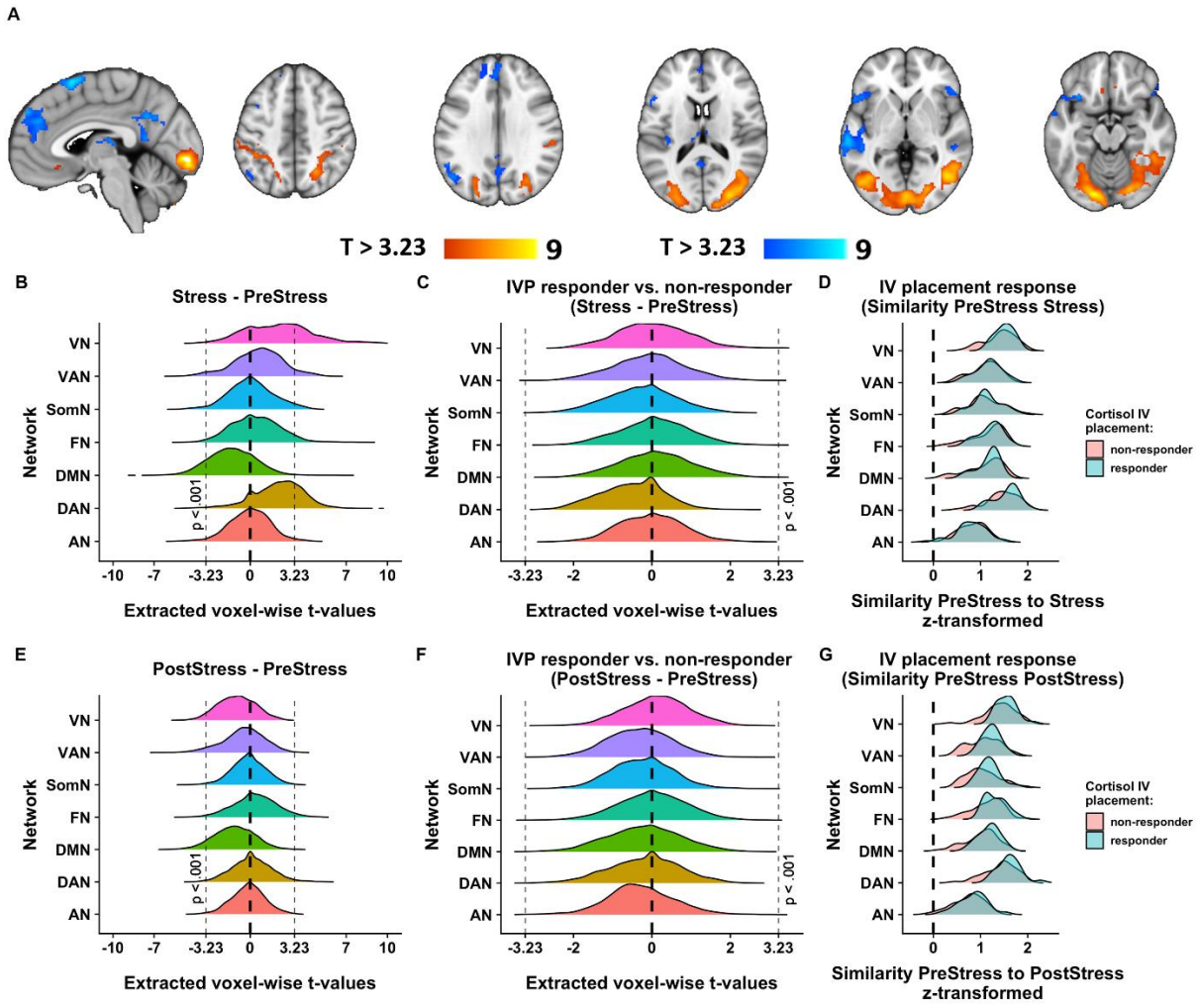

Figure 3: Changes in stress-induced brain activity depends on the IVP cortisol response. A) Stress-induced (Stress - PreStress) activation (warm colors) and deactivation (cool colors) across all participants, voxel-threshold p < 0.001. B) Activity during stress was reduced in the default mode network (t(66)= -3.24, p = .0018) and increased in the dorsal attention (t(66)= 5.11, p <. 0001) and visual network (t(66)= 4.9, p <.0001). C) No network-specific differences between comparing IVP responders to non-responders in the contrast Stress - PreStress. Less than 100 voxels exceeded the t-value threshold corresponding to $p_{voxel.uncorrected}$ < .001 (t = 3.23) and no clusters reached significance in whole brain analyses. D) Intraindividual similarity (z-transformed Pearson correlation) between voxel-wise neural activity during Stress compared to PreStress was not different in IV responders. E) Activity after stress remained reduced in the default mode network (t(66)= -3.9, p = .00017) but recovered in all other networks F) IVP responders and non-responders did not differ in network-specific activity in the contrast PostStress - PreStress. Less than 100 voxels exceeded the t-value threshold corresponding to $p_{voxel.uncorrected}$ < .001 (t = 3.23) and no clusters reached significance in whole brain analyses. G) Intraindividual similarity (z-transformed Pearson correlation) between voxel-wise neural activity during PostStress compared to PreStress was higher in IVP responders across functional networks. B) – G) depict the density of voxel-wise extracted t-values for the following functional networks: VN = Visual Network, VAN = Ventral attention network, SomS = Somatosensory network, FN = Frontoparietal network, DMN = default mode network, DAN = dorsal attention network, AN = Limbic network

3.2. IVP increased salivary cortisol

The placement of the IV led to a significant salivary cortisol response 20 minutes later (T1, *mean* $\Delta Cort_{IVP}$= 0.93 ng/ml, SD $\Delta Cort_{IVP}$= 2.29 ng/ml, t(64)= 3.27, *p*= 0.001, p_{boot}< .001, Figure 2; raw cortisol concentrations Figure S1). Importantly, 35.4% (n=23) of the participants reacted to IVP with a cortisol response larger than 2.5 nmol/l (0.91 ng/mL, Wust et al., 2000), indicating substantial interindividual differences. Differences in cortisol response to IVP were not dependent on baseline cortisol concentrations (serum: t(52)= -0.18, *p*=.85; saliva: t(63)= -0.03, *p*=.98). Serum and salivary cortisol at baseline were highly correlated (r=.61, *p*<.0001). Of note, cortisol responses to IVP were higher in participants for whom more than one attempt was needed until success (b=1.85 ng/ml, t(60)= 2.65, *p*= .010, Figure 2B). In contrast, reporting at least one symptom of needle phobia was not predictive of the cortisol response to IVP (b= -1.13 ng/ml, t(60)= -1.11, *p*= .27). Responders to IVP did not differ from non-responders with respect to various other demographic and psychopathological variables (Table 1).

Table 1: Sociodemographic and psychopathological information of IVP responders and non-responders.

	IVP-responder N=23	IVP non-responder N=42	Statistic (χ^2 or t-value)	*p*
Age	32.78 ± 8.71	31.52 ± 9.97	-0.53	.60
Sex: female	7	18	0.52	.47
Problems IVP	9	4	8.1	.004**
At least one symptom of needle phobia	1	5	1.01	.31
Depression-related diagnosis (F3)				
12-month	0	4	2.22	.14
lifetime	1	4	0.49	.48
Anxiety-related diagnosis (F4)				
12-month	2	10	2.02	.15
lifetime	7	19	1.42	.23
Substance abuse disorders (F1)				
12-month	2	1	1.47	.23
lifetime	3	10	0.91	.34
Other psychiatric disorders				
12-months	0	0	n.a	n.a.
lifetime	3	2	1.46	.23
Any lifetime psychiatric disorder: yes	9	25	2.48	.12

Note: ** p < .01, IVP = Intravenous catheter placement, Diagnoses are derived from the automatically evaluated CIDI-interview

3.3 The endocrine response to psychosocial stress was lower in IVP-responders

To investigate the effects of IVP on the cortisol response trajectories, we tested if a strong response to the IVP alters stress task reactivity. The endocrine response to the stress task ($AUC_{serum.T3-T8}$) was lower in IVP responders compared to non-responders (difference= -1459 ng/ml*min, *p*= .013, CI_{boot}= [-2584 ng/ml*min to -264 ng/ml*min], Figure 4B). Critically, serum cortisol levels before the start of the task were lower than at baseline (*mean* $\Delta SerumCort_{T3}$ = -27.3 ng/ml, t(53)= -5.75, *p*< .001, Figure 4A) across the whole sample, but changes of serum cortisol between baseline and the start of the task (T3) were dependent on the cortisol response to IVP with responders having significantly higher cortisol changes than non-responders (t(50)= -2.78 ng/ml, *p*= .008, correlation $\Delta Cort_{IVP}$: r= .41, p= .002, Figure 4A). Collectively, this indicates that IVP alters the cortisol system for at least the following 60 minutes potentially influencing the cortisol response to the subsequent stress task.

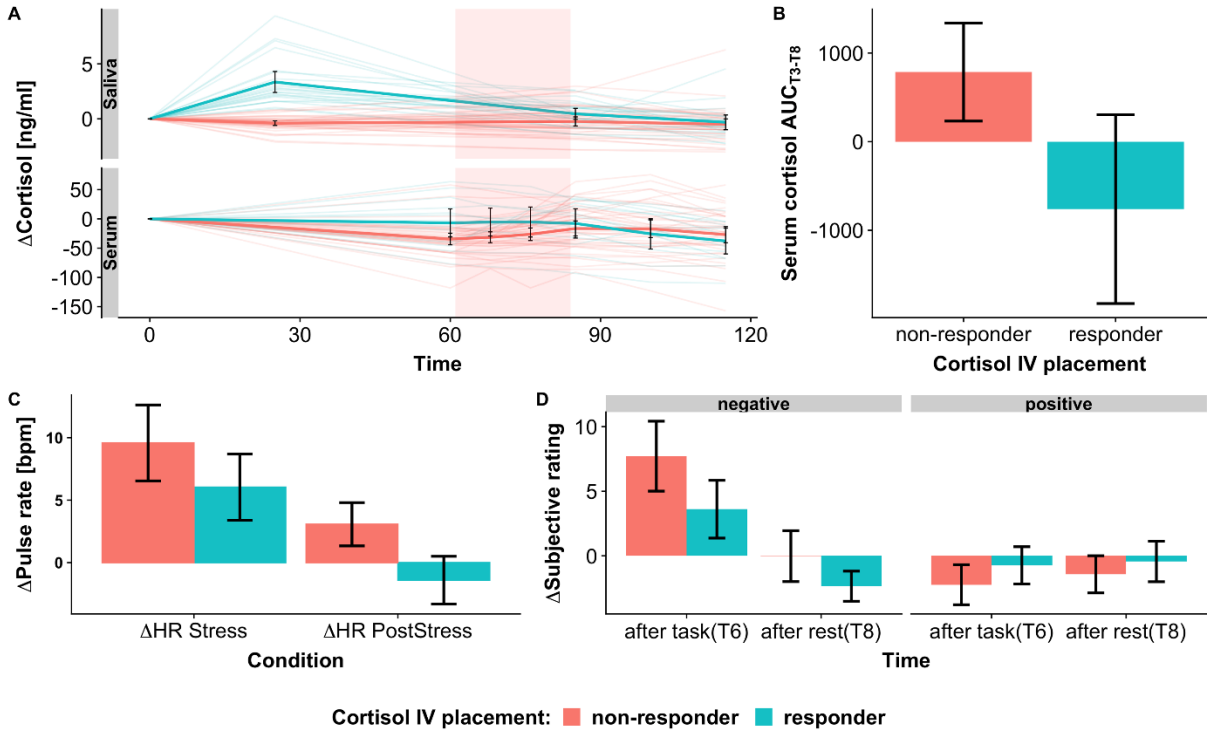

Figure 4: Response to the stress task depends on IVP response. Cortisol responders ($\Delta Cort_{IVP}$ > 2.5 nmol/l, (Wust et al., 2000)) to the intravenous catheter placement (IVP) show reduced endocrine, autonomous, and subjective reactivity to the stress task. A) Cortisol response (ΔCortisol) over time. IV placement before T1 increases salivary cortisol at T2. Note that serum cortisol values were still slightly elevated in responders compared to non-responder even 60 minutes after IVP. Thin lines depict individual cortisol profiles, thick lines depict the mean cortisol response in IVP-responders/non-responders. Shaded rectangles indicate the task phase. B) Serum cortisol response to the stress task (AUC_{T3-T8}) is reduced in IVP responders compared to non-responders. C) The pulse rate response to the stress task is reduced in cortisol responders to IV placement, especially in the PostStress phase. D) Increase in negative emotions is reduced in non-responders compared to responders. Positive affect is unaffected. Error bars depict 95% confidence intervals.

3.4 Reduced stress reactivity and facilitated recovery in IVP-responders

The reduced endocrine response in IVP responders was mirrored in a reduced autonomous and subjective response predominantly in the PostStress recovery phase. Here, lasting pulse rate increases during PostStress compared to PreStress were 4.9 bpm (n= 54, p= .0006, CI_{boot}= [-7.39 to -2.65]) lower in IVP responders (see Figure 4C). Likewise, increases in negative affect directly after the PostStress condition of the task were reduced by 55% (b= -4.47, p= .034, CI_{boot}= [-8.15 to -0.82]) in IVP responders compared with non-responders. In contrast, positive affect and pulse rate increases during stress were not significantly different in responders compared to non-responders (Figure 4D, Table 2). Interestingly, IVP-responders had a significantly higher pulse rate already in the PreStress phase (b= 8.30, p= .020, CI_{boot}= [0.84 – 15.13]). In contrast, there were no differences in the affective state (positive: b= 0.23, p= .81, CI_{boot}= [-1.42 to 1.80], negative: b= 0.51, p= .67, CI_{boot}= [-1.66 to 2.64]) directly before the task (T3). Comparable results were obtained when using the quantitative salivary cortisol response to IVP as a predictor (Table 2, Figure S3).

Table 2: Cortisol response to IV placement influences the stress response to the subsequent psychosocial stress task

	$\Delta Cort_{IV}$			Reponder /Non-responder		
	b	P	CI_{boot}	b	P	CI_{boot}
Cortisol (N = 54)						
AUC [ng/ml*min]	-245	.049	[-487 to -40]	-1459	.013	[-2584 to -264]
Pulse rate (N = 54)						
PreStress [bpm]	1.27	.087	[0.03 to 3.05]	8.30	.020	[0.85 to 15.12]
ΔStress [bpm]	-0.71	.13	[-1.79 to 0.01]	-4.45	.050	[-8.72 to -0.53]
ΔPostStress [bpm]	-0.64	.035	[-1.51 to -0.18]	-4.93	.0006	[-7.39 to -2.64]
Subjective (N = 65)						
Positive PreTask	0.11	.58	[-0.24 to 0.38]	0.23	.81	[-1.41 to 1.80]
Negative PreTask	0.23	.34	[-0.27 to 0.67]	0.51	.67	[-1.67 to 2.64]
ΔPositive	0.25	.32	[- 0.15 to 0.84]	1.72	.15	[-0.39 to 4.09]
ΔNegative	-0.89	.043	[-1.83 to -0.13]	-4.47	.034	[-8.15 to -0.82]
Neural (ROI) (N = 65)						
Similarity Pre-Stress	0.02	.19	[-0.01 to 0.04]	0.09	.22	[-0.06 to 0.22]
Similarity Pre-Post	0.03	.049	[0.002 to 0.05]	0.16	.024	[0.02 to 0.30]

Note: Regression weights from linear models including the different cortisol measures as predictor and age, sex, lifetime-diagnosis status (and framewise displacement for neural similarities) as covariates. CI: bootstrapped 95% confidence intervals.

In contrast, region-specific, neural activity before stress (PreStress), during stress (Stress - PreStress) or recovery (PostStress - PreStress) was not different in IVP responders compared to non-responders, as whole-brain voxel-wise analysis revealed no significantly different clusters even without further correction for multiple comparisons. Moreover, additional network-level analysis showed that there were no low-intensity shifts in activity in any of the main functional networks (Yeo et al., 2011)(Figure 3C & 3F). Nevertheless, neural similarity between PostStress and PreStress neural activity, a measure capturing stress-induced changes that are not necessarily region-specific or in the same direction between individuals, was higher in IVP responders. We assessed similarity of stress responses using either an aggregation at the network and one at the ROI level. In both analyses, similarity was significantly higher in IVP responders (ROI: b= 0.23, p= .003, CI_{boot}= [0.10 - 0.35] Figure S2; Network: b= 0.06, p= .028, Figure 3G). Following correction for the described nuisance effects (age, sex, diagnosis, average FD), the difference remained significant at the ROI level but not for the network aggregation (ROI: b= 0.16, p= .024, CI_{boot}= [0.02 - 0.30] Figure S2; Network: b= 0.04, p= .127, Figure 3G) suggesting that the latter analysis was more affected by confounds. Collectively, the results suggest faster recovery to baseline levels in IVP responders, perhaps due to the earlier trigger of the HPA axis response.

4. Discussion

Stress reactivity is often quantified using validated and standardized procedures (Allen et al., 2014; Kirschbaum et al., 1993) as reliable quantification within as well as between individuals of stress reactivity is crucial for the identification of response profiles predictive of psychopathological risk. Nonetheless, there are numerous variations of protocols across studies and even slight modifications may elicit a preceding cortisol response that alters the baseline state of the HPA axis and thereby influences the individual response to the main experimental stressor (Goodman et al., 2017). One frequent protocol modification is the placement of an IV to measure serum cortisol across time. Here, we investigated if individual differences in cortisol responses to IVP are associated with altered reactivity to a subsequent psychosocial stress task. IVP elicited a relevant cortisol response in over 30% of the sample. Moreover, in those participants, cortisol levels remained elevated up to the start of the stress task and a blunted cortisol response was elicited by the task. This was paralleled on the autonomous, neural, and subjective level, which all showed less reactivity to the task or faster return to baseline in IVP-cortisol responders. This is in line with previous observations that stress reactivity is reduced in case of higher baseline cortisol (Dickerson and Kemeny, 2004; Kudielka et al., 2004). Task-unrelated prior cortisol responses may thus limit the individual response to a subsequent psychosocial stressor and confound inter-individual differences in stress reactivity.

Our finding that pre-task IVP-induced cortisol increases reduced the endocrine response to a subsequent psychosocial stress task could be explained by habituation of the HPA axis. This has previously been described after repeated participation in a stress task on the same day, indicating the possibility of desensitization of the HPA axis within a certain time window

of repeated stimulation (Höhne et al., 2014). Importantly, habituation may extend to stressors unrelated to the stress task such as physical exercise (Zschucke et al., 2015). The attenuating effects of a first cortisol response could be related to glucocorticoid receptor (GR)-mediated negative feedback on the HPA axis at the level of the pituitary and the brain (Herman et al., 2005; Ulrich-Lai and Herman, 2009) that would counteract the response to a second stimulus.

The attenuated endocrine response to the task was mirrored by reduced autonomous, psychological, and neural stress reactivity which may arise for different reasons. For instance, the IVP-induced cortisol response could attenuate a second cortisol response and this, in turn, could translate to lower autonomous, neural, and psychological responses. Exogenous administration of steroids has been associated with acute increases in heart rate and decreased heart rate variability (Adlan et al., 2018; Dodt et al., 2000) and changes in neural activity of the hippocampus (Symonds et al., 2012). While a previous study showed that cortisol increases self-reported arousal (Abercrombie et al., 2005), there is little evidence for acute cortisol effects on mood (Putman and Roelofs, 2011). Still, cortisol predominantly improved mood in response to subsequent stress challenges (Het and Wolf, 2007; Soravia et al., 2006), comparable to the attenuated negative emotional response to the stress task in our study. Therefore, reduced stress reactivity across response systems as observed in our study could also reflect the previously proposed restorative role of delayed GR-mediated processes (Kloet et al., 2005) elicited by the cortisol response to the IVP.

Alternatively, the preceding HPA axis response to IVP could have induced persistent changes in heart rate or mood that subsequently tune the response to the psychosocial stress task. Stress responses are initiated by brain circuits that integrate psychological information, such as salience, valence, and context on the stressor with current homeostatic information (Ulrich-Lai and Herman, 2009). For example, homeostatic indices of resting autonomous functioning have been shown to predict the cortisol response to a stress task (Weber et al., 2010). Comparably, IVP-responders showed increased task-associated pulse rate in the PreStress phase, indicating potentially lasting effects of the pre-task stress response. This was accompanied by an attenuated response to the psychosocial stressor suggesting limited excitability to subsequent stimuli. Lasting changes in mood, context, or expectations about the following task could also influence the response to the stress task (Salzmann et al., 2018). However, IVP-responders did not differ in their self-reported mood directly before the stress task. Nonetheless, the cognitive appraisal of physiological responses is crucial for the generation of the emotional response (Folkman et al., 1986; Ursin and Eriksen, 2004) and is also influenced by pre-stress expectations and other cognitive strategies (Gaab et al., 2005; Jamieson et al., 2018). Thus, the attenuated negative response to the stress task in IVP responders may suggest that any additional physiological response induced by the psychosocial stressor was perceived as less aversive than the relief of physiological stress from the IVP-induced response leading to an attenuated negative appraisal.

Contrary to our hypothesis, cortisol responses induced by IVP did not reduce baseline activity or neural stress reactivity in specific brain regions, specific clusters in whole-brain voxel-wise analysis or even on a broader network level. Critically, the psychosocial stressor

in the task induced the expected increase in activity in the dorsal attention and visual networks and stronger deactivation in the DMN (Dedovic et al., 2009; Elbau et al., 2018). Interestingly, the DMN still maintained a stronger deactivation in the PostStress task phase, which is in line with previously reported changes in connectivity of the default mode network up to two hours after stress induction (Veer et al., 2011; Zhang et al., 2019). However, those stress induced changes of activity in the dorsal attention, visual, and default mode network did not differ between IVP responders and non-responders. Likewise, yet in contrast to previous reports (Zschucke et al., 2015), we did not observe any differentially activated clusters in participants showing a IVP cortisol response. One explanation for the diverging results could be the high heterogeneity of imaging stress studies with regards to specific procedures, leading to variable group-level stress effects and little convergence (Kogler et al., 2015; Noack et al., 2019). Likewise, neural effects may be masked by high inter-individual variability of the localization and maybe even directionality of the neural stress effects. Recently, representational similarity analysis has been used to re-identify participants with high accuracy across different tasks analogous to “fingerprinting” (Finn et al., 2015). Due to the high reliability of individual connectomes or specific task-induced brain activation patterns (Fröhner et al., 2019), representational similarity can be used to track changes from an individual baseline regardless of the direction. Indeed, within-participant similarity between the PreStress and PostStress condition was higher in IVP responders suggesting faster recovery back to PreStress neural activity.

Differences between IVP responders and non-responders were predominantly observed in the PostStress phase for autonomous as well as neural responses, while acute changes under stress were less affected. Comparably, pre-task exercise stress did not alter acute HR increases (Hamer et al., 2006) to a subsequent stressor, but changes in stress recovery after pre-treatment with cortisol have been reported (Soravia et al., 2006). One explanation may be stronger influence of high-level interindividual differences in moderating factors such as coping or resilience on post stress recovery (Lü et al., 2016). Likewise, preservative cognitions or extended rumination after stress have been related to longer lasting physiological alterations after stress and are likely also supported by lasting alterations in neural activity (Brosschot et al., 2006; Ottaviani et al., 2016). Nonetheless, specificity of effects for the PostStress phase is limited, as the responses in both conditions were highly correlated.

This study has several limitations. First, we assessed the impact of an IVP-induced cortisol response on a subsequent stress response within participants. This is necessary to capture the individual variability in the response to IVP and determine effects of a preceding cortisol response on the subsequent stress response. However, we did not include a control condition where the same participants or a control group took part in the stress task without prior IVP. Therefore, future studies are necessary to confirm that stress reducing effects of pre-task IVP are only present in responders. Also, we cannot identify which exact factor of the IVP procedure caused the HPA axis response (needle phobia, painful procedure). Nonetheless, the effects of any adaptations to the procedure that could induce a pre-task cortisol response, should be assessed by repeated cortisol measurements even before the start of the task. Second, we only assessed the cortisol response to IVP and did not concurrently measure

pulse rate or the subjective experience of blood taking. However, this information may help to understand how the appraisal of the different physiological responses influences subsequent stress reactivity (Gaab et al., 2005). Third, other parts of the procedure, for example anticipation of the MR environment, may also lead to additional inter-individually different perturbations of the stress system that consequently alter stress reactivity (Muehlhan et al., 2011). However, none of the participants were MRI-naïve, reducing potential confounding by individual differences in previous MRI-exposure. Fourth, a number of other confounding factors, such as hormonal status, use of contraceptives and importantly time of day may also influence results. As all sessions started at around 10 am, we cannot generalize our results to other times of the day beyond the afternoon, when cortisol baseline levels are lower.

In summary, the IVP led to a significant cortisol response in 35% of the participants. Critically, in these IVP responders, reactivity to the psychosocial stress task was significantly reduced including lower endocrine, subjective, autonomous, and neural responses. These effects were found despite a delay of about 60 minutes between IVP and the start of the stress task, a time frame that has often been considered as sufficient to avoid carry-over effects. Collectively, our results suggest that an unrelated cortisol response that is induced before a psychological stressor may have beneficial, stress-reducing effects in a consecutive stressful situation. Interestingly, this is not only the case for 'positive' stressors such as exercise (Zschucke et al., 2015), but also for presumably aversive stressors such as placement of an IV. Moreover, the study further emphasizes the importance of high frequency cortisol assessment in stress studies to identify sources of individual variability in responsivity. Thus, high heterogeneity in the specifics of measurements (mode, frequency, invasiveness) and interindividual differences in the response to different parts of the procedures may reduce the meta-analytic convergence across studies calling for a stronger emphasis on standardization of procedures and replicability.

Author contributions

EBB and PGS were responsible for the study concept and design. IGE, MC and PGS validated the paradigm and procedure. AK performed the data analysis and NBK contributed to analyses. AK wrote the manuscript. All authors contributed to the interpretation of findings, provided critical revision of the manuscript for important intellectual content and approved the final version for publication.

Financial disclosure

The authors declare no competing financial interests.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information:

Psychosocial stress reactivity habituates following acute physiological stress

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Assessment of subjective stress experience (BSKE scales)

The BSKE (Befindlichkeitsskalierung durch Kategorien und Eigenschaftswörter, Janke, 1994) scales are a short version of the more extensive Eigenschaftswörterliste (EWL, (Janke and Debus, 1978) developed to assess the current emotional state across positive and negative dimensions. The scale consists of 15 items (emotions / states) and participants were asked to rate their current state/feeling ("I feel …") on 6-point scale ranging from 1 ("not at all / gar nicht") to 6 ("very strongly / sehr stark"). We calculated sum scores including the items activity, wakefulness, self-certainty, focus, and relaxed state of mind for positive affect and including the items internal and external agitation, anxiety, sadness, anger, dysphoria, sensitivity as well as three items assessing somatic changes for negative affect.

Janke, W., 1994. Befindlichkeitsskalierung durch Kategorien und Eigenschaftswörter: BSKE (EWL) nach Janke, Debus, Erdmann und Hüppe. Test und Handanweisung. Unveröffentlichter Institutsbericht, Lehrstuhl für Biologische und Klinische Psychologie der Universität Würzburg.

Janke, W., Debus, G., 1978. Die Eigenschaftswörterliste: EWL. Verlag für Psychologie CJ Hogrefe.

fMRI Imaging parameters:

The following scanner settings were used for acquisition of echo-planar images (EPI) for the imaging stress task: 42 oblique slices, oriented along the AC-PC plane, covering the whole brain, interleaved ascending acquisition order, TR= 2s, TE= 40ms, 64 × 64 matrix, field of view = 200 × 200 mm, voxel size = 3.5 × 3.5 × 3 mm. Additionally, the measurements included single EPI (T2*-weighted) volume with the same settings as the fMRI sequence, but a longer TR of 10s. This single EPI volume has the same geometric distortions as the fMRI images combined with a higher contrast-to-noise ratio and less signal drop-out and was used for segmentation and subsequent normalization to correct for field distortions.

Calculation of Circadian corrected AUC values:

In short, an individual linear baseline over time was calculated from the e cortisol assessment before the start of the stress task (T3) and the last measurement approximately 20 minutes after the end of the stress task (T8): $Cortisol_{circ}(T) = \frac{Cortisol\,(T8) - Cortisol\,(T3)}{T8} * T + Cortisol\,(T3)$, where T is any time starting from the onset of the stress task (T3) and T3 and T8 are the times of the 3rd and 8th cortisol measurement respectively.

The corrected cortisol response for each timepoint was then determined as a difference between the measured cortisol concentration at each timepoint and the projected baseline cortisol level at that time: $Cortisol_{circ.cor} = Cortisol\,(T) - Cortisol_{circ}\,(T)$. Lastly, we calculated

the area under the curve using the corrected cortisol concentrations for the timepoints T3 until T8 and the appropriate individual time intervals.

Figures

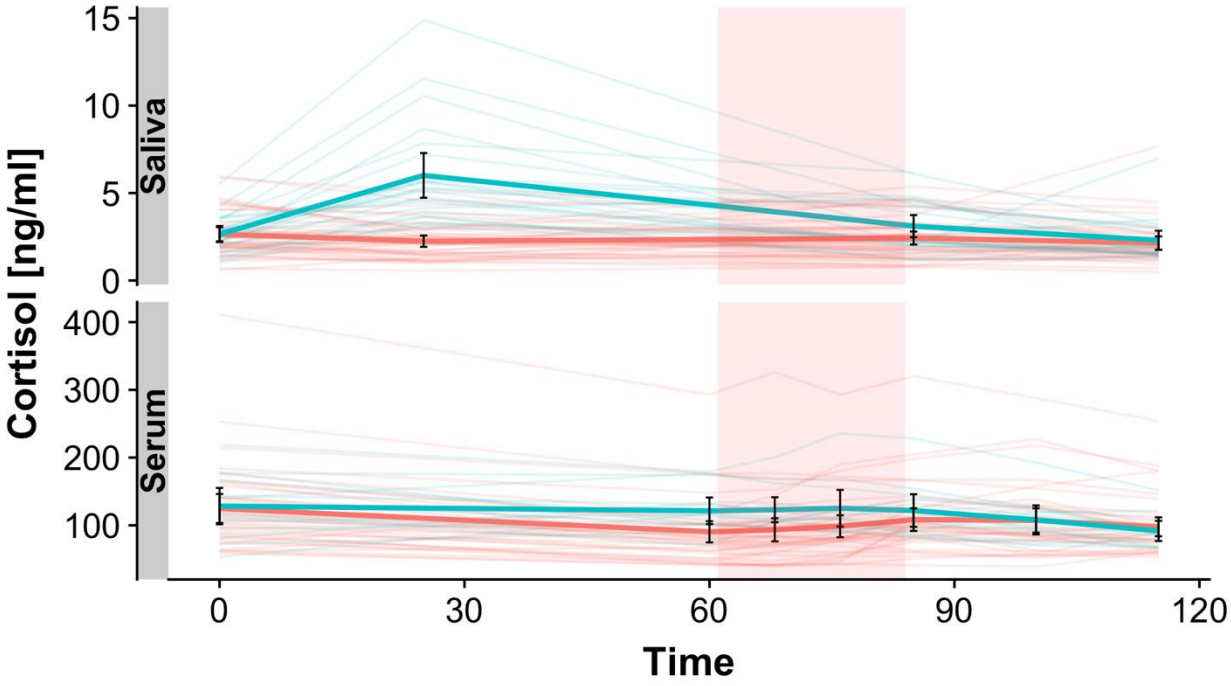

Figure S1: Cortisol concentrations in blood and saliva across time. Cortisol response (∆Cortisol) over time. IV placement before T1 increases salivary cortisol at T2. Note that serum cortisol values were still slightly elevated in responders compared to non-responder even 60 minutes after IVP. Red depicts non-responders, blue responders (∆CortIVP > 2.5 nmol/l / 0.91 ng/mL) to IV placement. Thin lines depict individual cortisol profiles, thick lines depict the mean cortisol response in IVP-responders/non-responders. Shaded rectangles indicate the task phase.

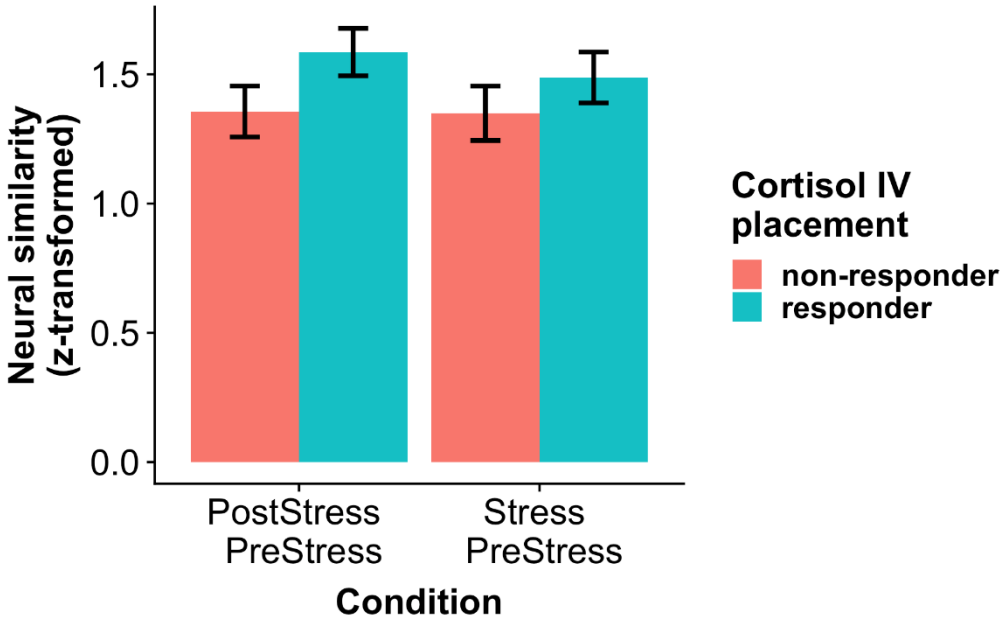

Figure S2: Intraindividual similarity between neural activity PreStress and PostStress is higher in IV placement responders compared to non-responders (b= 0.16, p= .024, CIboot= [0.02 - 0.30]). Y-axis depicts neural similarity (z-transformed correlation) between neural activity across regions of interest. Error bars indicate the 95% confidence intervals.

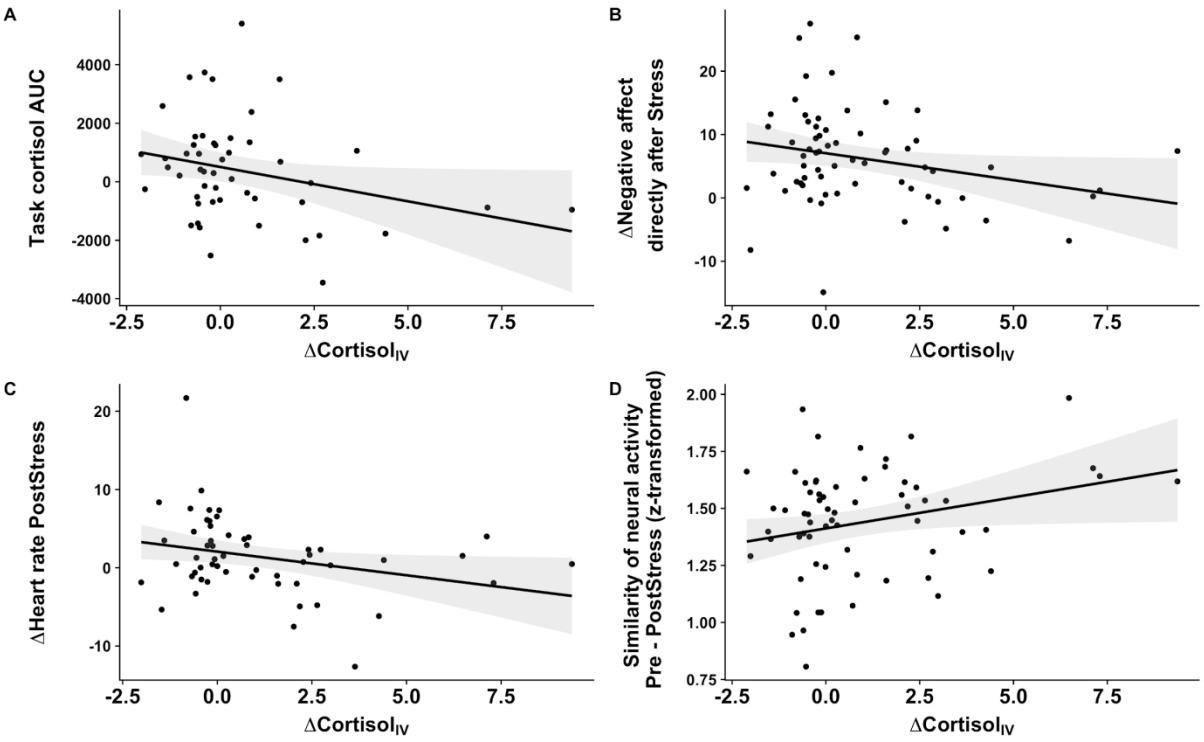

Figure S3: IV placement (IVP) induced cortisol ($\Delta Cortisol_{IVP}$ always on the x-axis) increases influence the endocrine, autonomous, subjective, and neural response to the stress task. A) Cortisol response (Serum cortisol AUC) to the stress task is lower after high cortisol responses to IVP B) Negative affect (ΔNegative at T6) is less increased after the stress task after high cortisol responses to IVP. C) Heart rate increases in the PostStress ($\Delta HR_{PostStress}$) condition are reduced after high cortisol responses to IV placement. D) ROI similarity of neural activity Pre- and PostStress indicating stress recovery to baseline is higher after high cortisol responses to IVP. Linear regression lines are corrected for age, sex, and lifetime diagnosis status (and average FD for neural similarity). Shaded areas depict 95% confidence intervals.

Table

Table S1: Current and lifetime prevalence of psychiatric disorders identified using the CIDI in the present sample.

	12-months diagnosis N(%)	**Lifetime diagnosis N(%)**
Substance use disorders (F1)	3 (4%)	13 (19%)
Mood disorders (F3)	4 (6%)	5 (7%)
Anxiety-related disorders (F4)	12 (18%)	27 (40%)
Other disorders	0 (0%)	7 (6%)
No diagnoses	51 (76%)	32 (48%)
1 diagnosis	13 (19%)	23.(34%)
2 diagnoses	2 (4%)	9 (13%)
3 and more diagnoses	0 (0%)	3 (4%)

Note: Lifetime diagnosis status (dummy-coded yes/no) was used as a covariate in all analyses.

3. Spatiotemporal dynamics of stress-induced network reconfigurations reflect negative affectivity

3.1 Summary

The goal of this study was to identify spatio-temporal trajectories of brain network connectivity in response to stress and subsequently evaluate whether individual trajectories differ between participants with vs. without mood and anxiety disorders or depending on transdiagnostic dimensions capturing trait-like behavioural maladaptive stress reactivity. To this end, we analyzed data from 217 participants of the BeCome study that completed a psychosocial stress task. We used hierarchical mixed-effects models to derive block-wise FC and activation changes throughout all stress phases (anticipation vs. stress vs. recovery) compared to a resting baseline. Models were based on extracted timeseries from a predefined network previously implicated in stress reactivity. To validate that the trajectories from the four derived subnetworks carry relevant individual information, we first successfully used individual trajectories to predict intraindividual stress states as well as corresponding changes in heart rate using support vector machines. We then investigated whether individual trajectories also predicted interindividual differences in psychopathological dimension using elastic net regression. In addition to diagnostic information of the last 12 months, we derived dimension of trait-like stress reactivity and general negative affect using non-negative matrix factorization across state (Becks depression inventory II) and trait (anxiety, coping, intolerance of uncertainty) questionnaires.

The results show that dynamic changes in FC but not activation across four subnetworks (i.e., DMN-dominated, salience network dominated, cross-clique connections, and a limbic network) recover stress phases and heart rate changes. In contrast both, FC and activation change trajectories predict negative affectivity but not the presence of a mood or anxiety disorder. Critically, salience network connectivity and insula activation changes contributed substantially to the prediction of stress phases as well as interindividual differences in negative affectivity, indicating that the salience network with the insula as a core hub are crucial in mediating (bodily) stress reactivity and a dysregulation may be present in transdiagnostic high negative affectivity which is common risk factor mood and anxiety disorders. Consequently, the results might drive translational research that further elucidates underlying molecular or circuit level mechanisms of the spatio-temporal reconfigurations and corresponding alterations in psychopathology as well as establish directionality or causality of effects for instance by perturbing salience network processing using neurostimulation. Eventually, stress induced changes in salience network response might be a promising endophenotype for patient stratification or treatment of specific transdiagnostic symptoms of psychiatric disorders.

3.2 Contributions and reference

The study “Spatiotemporal dynamics of stress-induced network reconfigurations reflect negative affectivity” was published in Biological Psychiatry in January 2022. EBB, PGS and the BeCome working group were responsible for the study concept and design. MC and PGS validated the paradigm and procedure. AK and NBK conceived the method and AK performed the data analysis. AK wrote the first draft of the manuscript and NBK contributed to the writing. All authors contributed to the interpretation of findings, provided critical revision of the manuscript for important intellectual content.

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Spatio-temporal dynamics of stress-induced network reconfigurations reflect negative affectivity

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Abstract

Background: Maladaptive stress responses are important risk factors in the etiology of mood and anxiety disorders, but exact pathomechanisms remain to be understood. Mapping individual differences of acute stress-induced neurophysiological changes, especially on the level of neural activation and functional connectivity (FC), could provide important insights in how variation in the individual stress response is linked to disease risk.

Methods: Using an established psycho-social stress task flanked by two resting-states, we measured subjective, physiological, and brain responses to acute stress and recovery in 217 participants with and without mood and anxiety disorders. To estimate block-wise changes in stress-induced activation and FC, we used hierarchical mixed-effects models based on denoised timeseries within predefined stress-related regions. We predicted inter- and intra-individual differences in stress phases (anticipation vs. stress vs. recovery) and transdiagnostic dimensions of stress reactivity using elastic net and support vector machines.

Results: We identified four subnetworks showing distinct changes in FC over time. FC but not activation trajectories predicted the stress phase (accuracy: 70%, p_{perm}<.001) and increases in heart rate (R^2=.075, p_{perm}<.001). Critically, individual spatio-temporal trajectories of changes across networks also predicted negative affectivity (ΔR^2=.075, p_{perm}=.030), but not the presence or absence of a mood and anxiety disorder.

Conclusions: Spatio-temporal dynamics of brain network reconfiguration induced by stress reflect individual differences in the psychopathology dimension negative affectivity. These results support the idea that vulnerability for mood and anxiety disorders can be conceptualized best at the level of network dynamics, which may pave the way for improved prediction of individual risk.

1. Introduction

Stressful situations occur frequently in life and an adaptive response is critical for mental health (1). Congruently, maladaptive stress responses such as prolonged anxiety, extensive rumination, and negative coping strategies are common symptoms of mental disorders, specifically mood and anxiety disorders (2–5). Physiologically, maladaptive stress responses are mirrored in dysregulated endocrine (6–9) and autonomous adjustments (10).

Stress responses can be divided into three phases: anticipation (11,12), acute (13,14) stress, and recovery (15–17) and alterations in mood and anxiety disorders occur across phases (13,14). Depression has been associated with increased endocrine stress responses (9,18-21). Depression-related personality characteristics such as negative affectivity or trait anxiety (22,23) with shared genetic signatures (24) also affect endocrine stress reactivity across phases (25–27). Moreover, negative affectivity is associated with negative emotional responses to stress (28) and moderates the effect of stressful life events on depression (29). Specifically, mood and anxiety disorders show maladaptive stress-related cognitions (30,31). For instance, negative coping styles and excessive rumination in depression are associated with slower stress recovery (32–35), whereas distraction is associated with faster recovery (36,37). Resilient coping styles, such as cognitive reappraisal (38) or using social support (39), showed faster recovery (40) and reduced anticipatory stress (41).

On the neural level, stress responses are characterized by dynamic shifts in the salience (SN), default mode (DMN), and fronto-parietal networks (42,43). Consequently, changes in FC between key network nodes have been reported (44,45) up to 40min after stress. Mood and anxiety disorders consistently show dysregulation within this network of stress-related regions (46), suggesting that brain networks implicated in acute stress reactivity are also chronically affected in disorders. Comparably, previous work in healthy participants or adolescents with mental disorders has shown that trait anxiety is associated with altered stress-induced activation (47,48). However, most studies focus on average stress-induced activations during the task. Hence, little is known about dynamic changes within the stress-related regions across stress phases although emerging evidence has highlighted the importance of dynamic network reconfigurations in mental disorders (49,50). Likewise, task-induced changes in FC improve the correspondence with phenotypic differences compared to resting FC and have been proposed as promising target to track alterations in mental disorders (51,52). Therefore, identifying individual signatures of stress reactivity incurring risk for psychopathology could help pinpoint potential intervention targets (i.e., for non-invasive brain stimulation techniques 53) and improve means to study network perturbations in clinical trials.

Here, we used a hierarchical model of stress-induced changes in activation and FC to characterize trajectories of network reconfigurations across the stress phases. Using individual FC signatures of stress adaptation, we identified dynamic FC changes differentiating between stress phases and predicting interindividual differences in negative affectivity. We thereby provide a link between acute stress reactivity and psychopathology.

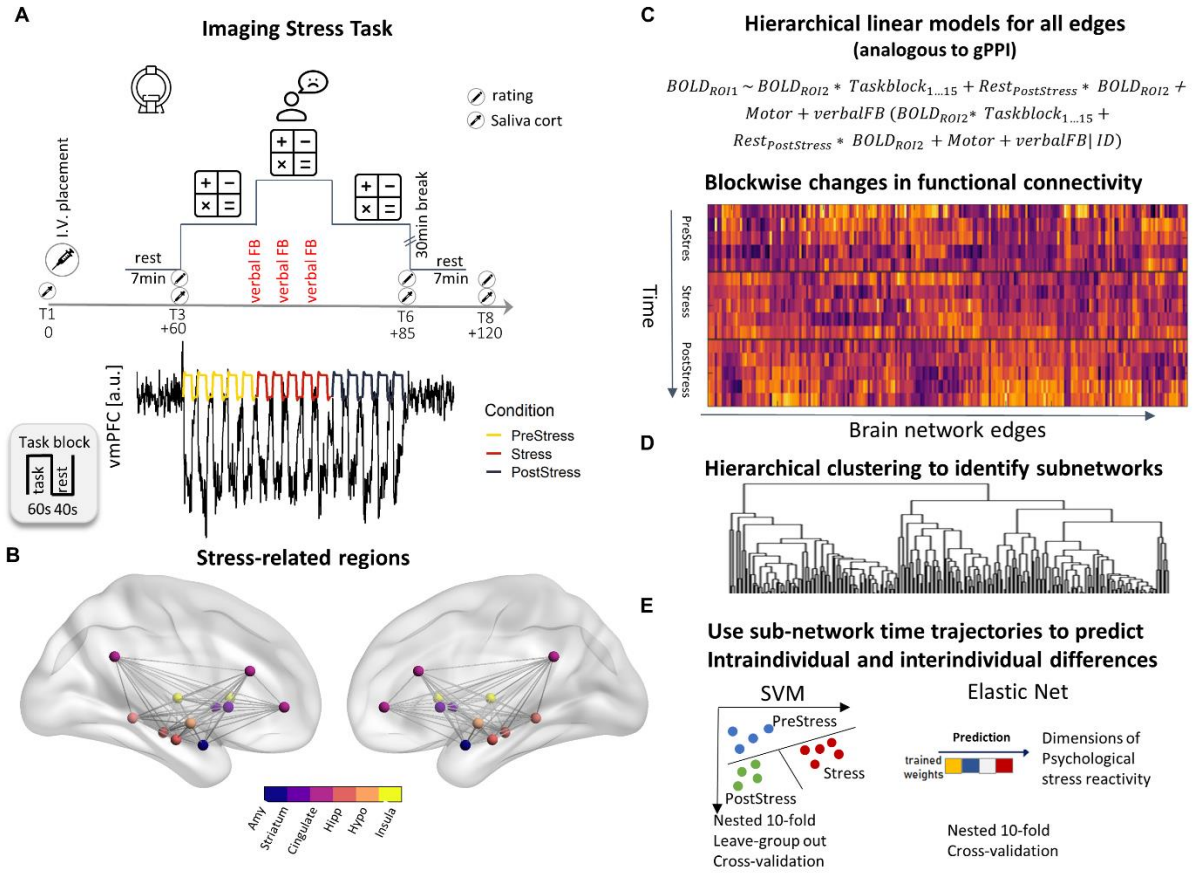

Figure 1: Schematic overview of task design and analyses. A) The psycho-social stress task consists of 15 blocks (50s each) of arithmetic problems interleaved with rest blocks (fixation cross, 40s each). The first five blocks are without aversive feedback (*PreStress*), followed by five blocks with negative feedback and time constraints (*Stress),* and another five blocks without aversive feedback (*PostStress*). Illustratively, we depict the average time series of the vmPFC after denoising across all measurements, which tracks the structure of the paradigm. B) Stress-induced changes in activation and functional connectivity (FC) from block to block are characterized for all regions and edges within predefined stress-related regions (Figure S3). C) Changes in activation and FC for each block are estimated using a hierarchical extension of generalized psychophysiological interactions (gPPI) estimated with one hierarchical linear model for each edge of the network, leading to group-level estimates of task-induced FC change for each block and 210 edges. D) For further predictive analyses, edges with similar changes over time are clustered into four subnetworks using hierarchical clustering. E) Lastly, we use individual-level profiles of the four subnetworks FC changes (average across all edges per subnetwork) to predict either the task phase of unseen blocks (four features per block) or interindividual differences in adaptive vs. maladaptive stress reactivity, vmPFC = ventromedial prefrontal cortex, dACC = dorsal anterior cingulate cortex, Put = putamen, PCC = posterior cingulate cortex, pIns = posterior insula, aIns = anterior insula, pHipp = posterior hippocampus, mHipp = medial hippocampus, aHipp = anterior hippocampus, Amy = amygdala, SVM = support vector machine

2. Materials and Methods

2.1 Participants

The sample was recruited as part of the Biological Classification of Mental Disorders study (ClinicalTrials.gov: NCT03984084, 54). It characterizes participants with a broad spectrum of mood and anxiety disorders including common comorbidities and unaffected individuals. Here, we included 217 participants (140 women, M_{age}=35.1 years±12.1, Table S1). All participants underwent a computer-based, standardized diagnostic interview (12). Diagnoses were derived by a DSM-IV-based algorithm and n=129 (54%) fulfilled the criteria for ≥1 mood or anxiety disorder (ICD-10 code F3-F4, excluding specific phobias) within the last 12 months (Table S2). Only n=9 reported present medication for their psychiatric symptoms. To maximize sample size, we excluded participants with missing or low-quality data for each analysis separately (N=174-217, for details: Tables S4-S6).

2.2 Experimental procedure

The stress task (Figure S1) was included in the second functional magnetic resonance imaging (fMRI) session (11), so participants were not fMRI naïve (13). Upon arrival, the first saliva sample was taken (T1) for cortisol assessment followed by a second sample (T2) approximately 20min later, after placement of an intravenous catheter for additional blood sampling in 73 (33%) participants, and before entering the scanner. After an emotional face-matching task (~12min), a baseline resting-state measurement, participants rated their current affective state using *Befindensskalierung nach Kategorien und Eigenschaftsworten* (BSKE;57; Supplementary Information, SI). The psycho-social stress paradigm was adapted from the Montreal imaging stress task (15), where stress is induced by performing arithmetic tasks with time pressure and negative feedback (16,17) corresponding to a mild laboratory stressor with 47%-65% cortisol responders (18). The task lasted ~25min and included a *PreStress* phase without negative feedback or time pressure, followed by a *Stress* phase with psycho-social stress-induction, and a *PostStress* phase (analogous to *PreStress*). Each phase contained 5 task blocks (60s) interleaved with rest (40s) blocks. We measured heart rate (HR) using photoplethysmography (SI). After completion of the task, affective state was assessed, and saliva samples taken (T6). A 30min rest period lying outside the scanner was followed by a concluding resting-state scan, and assessments of subjective affect and saliva cortisol (T8). In participants with additional blood sampling, samples were taken in the scanner before, during, and after the task (T3-T8).

2.3 Questionnaires

To measure state- and trait-like depressive symptoms and negative affect (19), we included the *Becks Depression Inventory-II* (BDI,62) and the trait subscale of the *State-Trait Anxiety Inventory* (TAI,63). To measure maladaptive and adaptive psychological stress reactivity, we included the *Intolerance of uncertainty scale* (IoU, 64), a stress coping scale (*Stressverarbeitungsfragebogen*,65), and a resilience scale (Resilience-11,66).

2.4 fMRI data acquisition and preprocessing

Briefly, MRI data were acquired on a 3T scanner (Discovery MR750). Functional data were 755 T2*-weighted echo-planar images (EPI) for the stress task and 155 EPIs for each resting-state. Preprocessing was performed in MATLAB 2018a and SPMv12. fMRI data was slice-time corrected, realigned, normalized to the MNI-template using DARTEL (25), and spatially smoothed with a 6x6x6mm^3 full-width at half-maximum kernel (SI).

2.5 Data analysis

2.5.1 Questionnaire data: Non-negative matrix factorization

To extract interpretable dimensions capturing maladaptive stress reactivity from questionnaires, we used non-negative matrix factorization (NNMF, 68). In contrast to other dimension reduction methods, NNMF captures additive latent variables that are intuitively interpretable since all weights are positive. We included all items from the questionnaires after rescaling them between 0 and 1. To ensure stability, we estimated NNMF (*nnmf*, MATLAB 2020b) with 150 iterations and 50,000 replicates. To determine the optimal number of dimensions, we used the elbow method for explained variance (27).

2.5.2 Stress response to the psycho-social stress task

The endocrine stress response was estimated as the change in cortisol concentration between T2 and T6. Since we took blood samples in a subset of participants and cortisol responses to this procedure may confound responses to the task (17), we included a dummy-coded nuisance regressor classifying participants with a response >2.5 nmol/l (0.91 ng/ml, 60,70) at T1 compared to baseline (T0) as pre-task cortisol responders in all analyses.

HR responses to stress were estimated as changes in average HR during arithmetic blocks in the *Stress* or *PostStress* phase compared to *PreStress* (17). The subjective emotional response to stress was estimated as changes in positive and negative affect (sum scores across items) after the task (59,60;SI).

2.5.3 fMRI data

To compare stress-induced changes in activation with earlier studies, we used previously reported first-level contrasts including one task regressor for each task phase (*PreStress*, *Stress*, *PostStress;* SI;60). At the group level, we used voxel-wise multiple regressions. All fMRI and psychometric analyses (whole-brain regressions, elastic net) included age, sex, pre-task cortisol, medication status, and average log-transformed framewise displacement as confounding variables.

To model dynamic FC changes across stress phases, we extracted average timeseries (unsmoothed) from the preprocessed task and the flanking resting states in 21 ROIs. ROIs covered a subset of regions previously reported to show activation- (18,29) and FC changes in stress-related tasks (Figure 1B, 42,71) that are also altered in mood and anxiety disorders (46,72, SI). Regions included the left and right amygdala, hypothalamus, caudate, putamen, anterior, medial, and posterior hippocampus, anterior and posterior insula and one region for the posterior cingulate, dorsal anterior cingulate, and ventromedial prefrontal cortex. Regions were defined using a FC-based atlas (34), except for the hypothalamus (Harvard-Oxford atlas) as the resolution of the Shen atlas was too coarse. Timeseries were detrended (linear), despiked (winsorized at ±4SDs), and residualized with the same covariates as previously reported (16) including the 6 movement parameters, their derivative, and 5 components from white matter and cerebro-spinal fluid, respectively (74, SI). To estimate changes relative to the resting-state baseline before the task, we concatenated timeseries by matching their raw BOLD image intensity (SI).

Analogous to hierarchical generalized psychophysiological interactions (36), we used hierarchical linear models (LME, 76,77) to estimate block-wise changes in activation in 21 ROIs (Figure 1B,S2, Table S7) and their FC (21*20/2 edges). We estimated one model for each edge with all predictors as random effects, simultaneously deriving group-level and regularized individual-level estimates (39–41). Each model included the timeseries of one region (ROI_1) as dependent variable and the timeseries of the other (ROI_2) as independent variable together with one regressor for each of the 15 task blocks (convolved with the SPM hemodynamic response function, HRF) and the interaction of each task-block regressor with the predicting timeseries. Additionally, we included an interaction term for the post task resting-state to account for lasting stress-induced FC changes. To account for changes in activation corresponding to motor responses or verbal feedback, we included two convolved regressors from the first-level GLM (SI). Predictors for interaction terms were mean-centered.

$$BOLD_{ROI1} \sim Taskblock_{1\ldots15} * BOLD_{ROI2} + Rest_{PostStress} * BOLD_{ROI2} + Motor + verbal_{fb} + (Taskblock_{1\ldots15} * BOLD_{ROI2} + Rest_{PostStress} * BOLD_{ROI2} + Motor + verbal_{fb}) | ID$$

To reduce dimensionality, we defined clusters of edges showing similar FC changes over blocks using hierarchical clustering (*eclust,* (42)) with z-standardization and Pearson correlation as distance measure. The number of clusters was determined by evaluating the decrease in total within sum-of-squares (*wss*) with the elbow method leading to 4 distinct clusters (Figure S6).

To evaluate the predictive performance of stress-induced FC changes within the subnetworks, we used machine learning algorithms to predict intra- and inter-individual differences in stress reactivity. First, we predicted task phases (*PreStress*, *Stress*, or *PostStress*) of unseen blocks based on average FC-changes in the 4 subnetworks or activation changes across ROIs using support-vector machine (SVM) classifiers with a radial basis function (one vs. one, *SVC,* scikitlearn (43), Python 3.7.0) with nested 10-fold cross-validation. We used a leave-subject-out approach so that all data from 10% of the participants was in a held-out fold. Second, we used the same approach to predict relative HR changes for each block using support-vector regression (SVR). To test whether predictions provided information in addition to differences between stress phases (i.e., higher HR during stress), we estimated LMEs with the observed HR change (random effect by participant, (44)) for each phase separately. Last, we predicted interindividual differences in psychopathology dimensions derived from NNMF using activation and connectivity (4 clusters) trajectories across task blocks. Since FC changes were relatively stable within conditions, we explored a model with aggregated FC changes within the 5 blocks per condition (Figure S12). Since the models included between 68 (connectivity) and 180 (activation) features, we used elastic net (*lasso*, preset alpha=.5) with nested 10-fold cross-validation. Elastic net performs well if features are correlated and their number is moderately high compared to the observations (45). To account for confounding variables, we included them in the baseline prediction models and evaluated the incremental variance explained by fMRI features. Average log-transformed framewise displacement was not associated with diagnosis status or psychopathological dimensions of stress reactivity (rs<.12, ps>.11). Statistical significance was determined using permutation tests (iterations=1,000; outcome was shuffled with confounders to keep their correlation).

2.5.4 Statistical threshold and software

Statistical analyses were performed in Rv4.0.2 (46). For whole-brain fMRI analyses, the voxel threshold was set at $p_{uncorrected}$<.001. Clusters were considered significant with a cluster-corrected threshold of $p_{cluster.FWE}$<.05. Additional LME models were estimated using lmerTest (47).

3. Results

No difference in average stress-induced responses in mood and anxiety disorders

The task induced stress across multiple levels: positive affect decreased (b=-2.35, p<.001), while negative affect (b=7.6, p<.001, Fig. 2A) increased after the task. Likewise, HR (b=6.5, p<.001, Fig. 2B) increased during stress as well as salivary cortisol (b=.42, p=.007, Fig. 2C). On the neural level, stress led to significant deactivation in the DMN (PCC and angular gyrus), insula, dorsomedial prefrontal cortex as well as activation in the visual and parietal cortex (Fig. 2E).

In contrast to previous reports, average stress reactivity on the physiological, endocrine, or subjective level did not differ between participants with and without mood and anxiety disorders (Fig. 2, Table S3). Likewise, there were no significant whole-brain differences in activation (Fig. 2E).

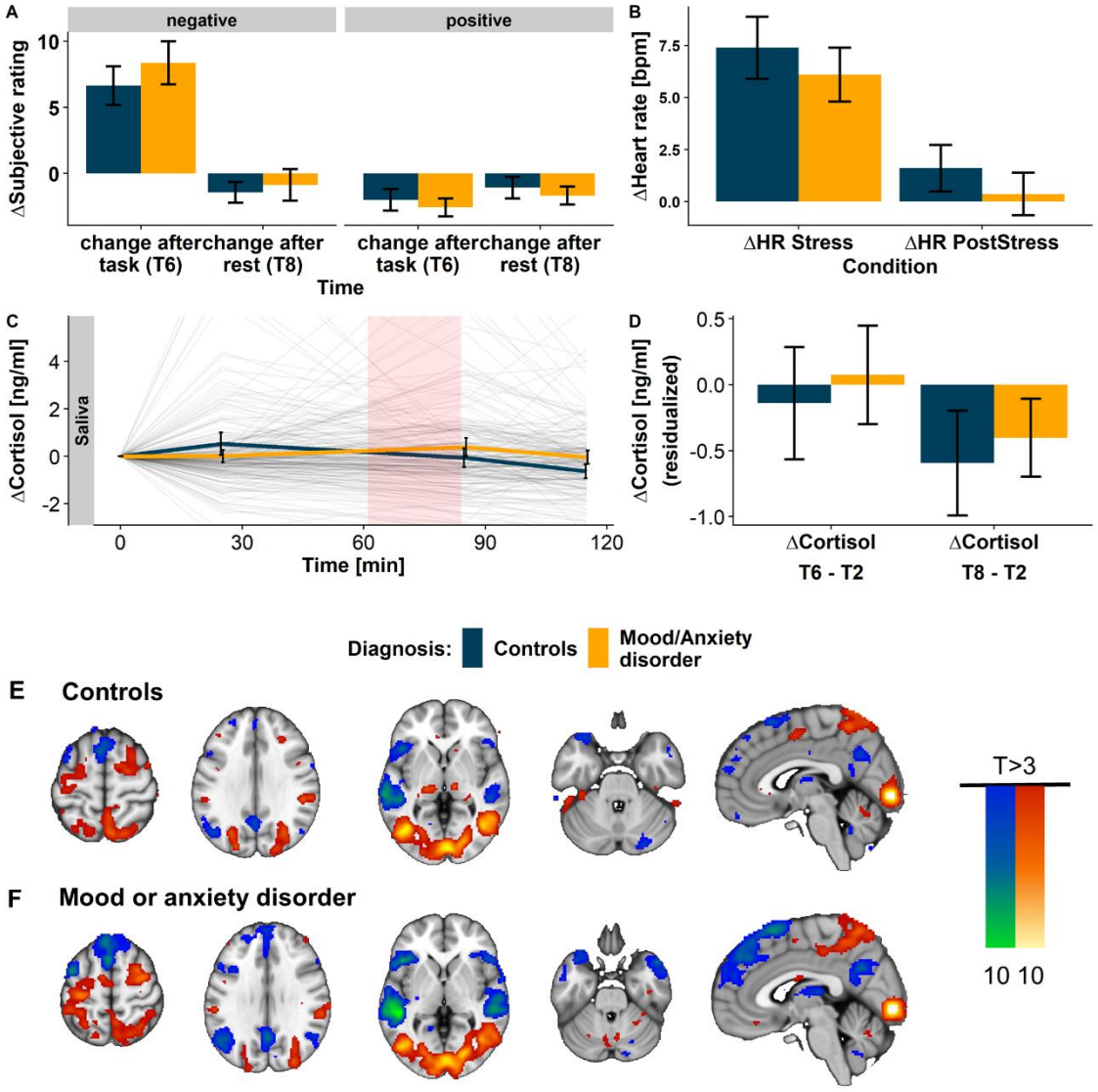

Figure 2: The psycho-social stress task leads to multi-modal stress responses that do not differ between participants with and without mood and anxiety disorders. A) Negative affect increases (Change *PostTask* – *PreTask*: -7.6, *p*<.001) and recovers after stress (Change *PostRest* – *PreTask*: -1.1, *p* = .006), while positive affect decreases (Change *PostTask* – *PreTask*: 2.35, *p*<.001, Fig. 2A) and does not recover back to baseline levels (Change *PostRest* – *PreTask*: -1.4, *p* < .001) in both groups (Supplementary Table S3). B) HR increases during the *Stress* phase and recovers in the *PostStress* phase similarly in both groups. C) The task leads to an increase in salivary cortisol compared to baseline (T0). Thin lines depict individual cortisol trajectories, thick lines show group averages. The shaded area shows the timing of the stress task. D) Cortisol response after the task (T6: 0.24 ng/ml, p=.43) and after a break (T8: 0.22 ng/ml, p=.41) do not differ between groups after taking into account age, sex, pre-task cortisol response, and medication status. E) Stress-induced activation patterns in control participants. F) Stress-induced activation patterns in participants with mood and anxiety disorders are highly similar to control participants (E). All models include age, sex, medication status, and pre-task cortisol response as confounding variables and response variables are residualized accordingly. Error bars depict 95% confidence intervals.

Dynamic connectivity changes predict stress state and changes in heart rate

To assess stress-induced changes throughout stress phases, we concatenated data from the psycho-social stress task and two flanking resting-state scans (Fig. S1). To derive stress-induced changes at a single-block resolution, we used mixed-effects models of fMRI timeseries. By fitting hierarchical models, individual deviations from group averages are recovered more robustly (39–41). While stress-induced changes in activations within stress-related regions were similar across blocks (Figure S4), FC changes were qualitatively and quantitatively discernable across stress phases (Fig. 3B). To reduce dimensions for individual predictions, we identified subnetworks of edges with a comparable stress response using hierarchical clustering. We identified four clusters of subnetworks showing distinct stress-induced changes (Fig. 3, Figure S4-6, Table S8). The blue cluster primarily reflecting cross-clique connections (i.e., 82% of connections between networks, e.g., DMN and SN) showed pronounced FC decreases to stress onset, followed by gradual recovery. In contrast, the yellow cluster, primarily reflecting limbic connections showed increased FC during *Stress* (b_{Stress}=.37 $t(21)$=4.7 p=.00014). In contrast, the green cluster, primarily including DMN edges (i.e., 78% within-DMN connections), showed decreasing FC and the purple cluster, primarily reflecting SN edges (i.e. insula, hypothalamus, amygdala, dACC; (48)), showed increasing FC throughout the task.

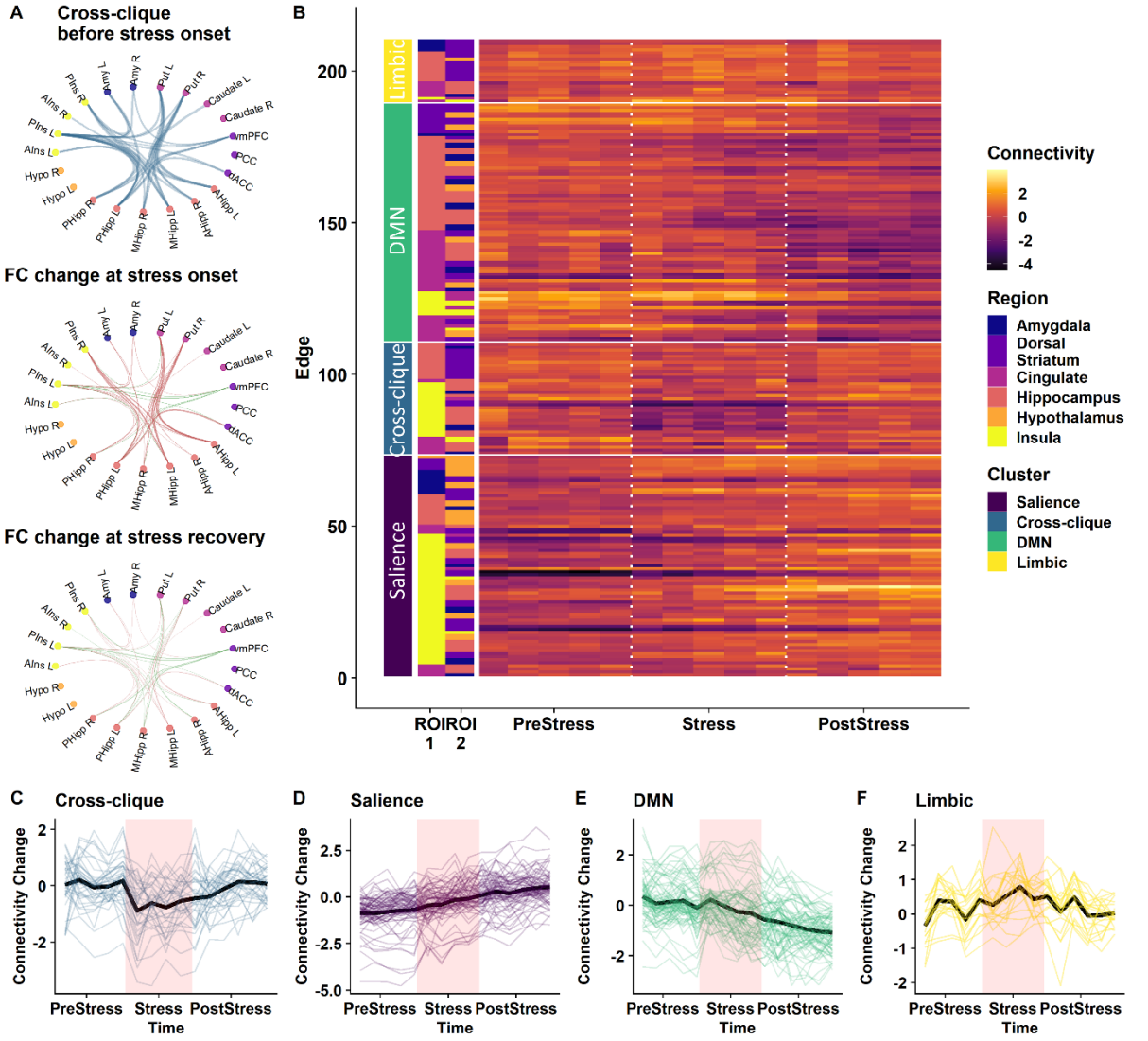

Figure 3: Psycho-social stress leads to characteristic spatio-temporal patterns of functional connectivity (FC) changes. A) The blue cluster reflecting cross-clique connections shows a decrease in FC in response to stress and slowly recovers afterwards. In the first circle plot, line width depicts the change in FC strength in the first block relative to rest for all edges (i.e., estimated FC change for the first block, standardized and rescaled for visualization), line color indicates the blue cross-clique cluster. The second and third plot show the change in FC at stress onset (i.e., first stress block) and at the end of stress recovery (i.e., last *PostStress* block) compared to the beginning of the task (i.e., the difference in estimated FC change at block 6 or 15 and block 1). Red lines indicate decreases in FC and green lines increases, line thickness shows the strength of change. The circle plots for the other 3 networks are shown in the Figure S7. B) FC change (z-standardized) in edges of the predefined network ordered according to the subnetworks identified by hierarchical clustering. C-F) Trajectories of block-wise FC changes (z-standardized) for all four subnetworks (thin lines depict individual edges, thick lines the average across all edges of the subnetwork). vmPFC = ventromedial prefrontal cortex, dACC = dorsal anterior cingulate cortex, Put = putamen, PCC = posterior cingulate cortex, pIns = posterior insula, aIns = anterior insula, pHipp = posterior hippocampus, mHipp = medial hippocampus, aHipp = anterior hippocampus, Amy = amygdala, DMN = default mode network

To verify that these spatio-temporal profiles reflect experimentally induced stress phases, we predicted phases of unseen blocks based on individual-level estimates within the four subnetworks using SVM. Stress-induced FC changes predicted stress phases with high accuracy (70% vs. 33% chance; p_{perm}<.001, individual accuracy *M*=70%±14%, Figure 4A). However, predictions solely based on changes in activation barely exceeded chance levels (40%, Figure 4B). FC features predicted relative changes in HR of each block within participants using SVR (*r*=.29, R^2=.075, p_{perm}<.001, Figure 4C). Successful prediction of HR was not only driven by changes between task phases (e.g., higher HR during stress), but also recovered differences in HR within *Stress* (*p*=.02) and *PostStress* (*p*<.001) phases (Fig. 4D, SI). Stress-induced increases in HR (*Stress–PreStress*) derived from predicted changes in HR for each block corresponded with observed stress-induced effects (*p*s≤.05, Fig. 4E-F). Decreasing or further increasing the number of clusters derived from the hierarchical clustering did not improve the predictive performance (Figure S8). Changes in head movement during stress alone could not explain the successful prediction of stress phases, since a prediction based on motion indices performed barely above chance (43%, SI, Figure S13). To summarize, spatio-temporal profiles of stress-induced responses within the four subnetworks track stress phases and physiological adaptation better than chance, motion, or changes in activation.

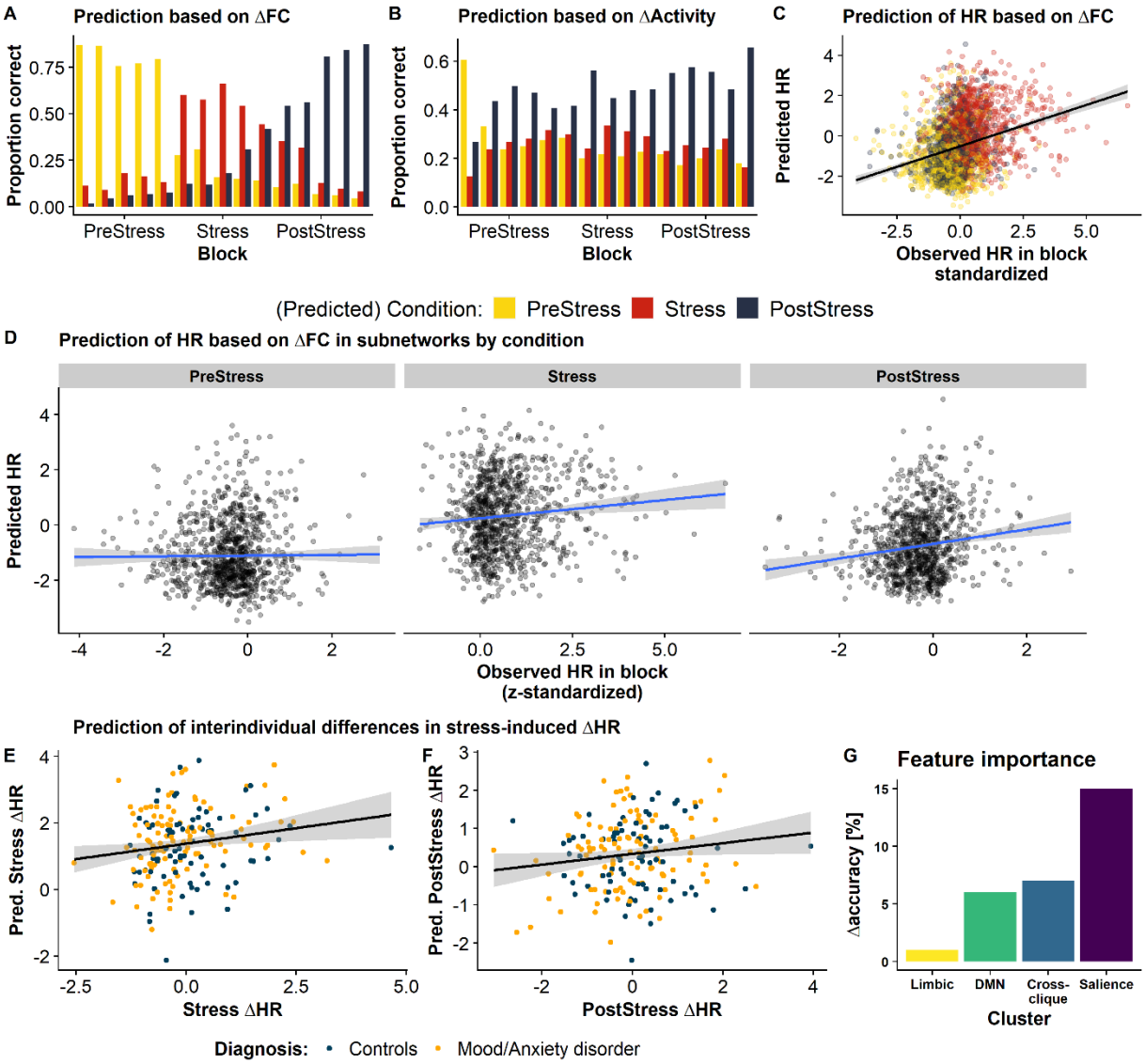

Figure 4: Block-wise changes in functional connectivity (FC) in the four stress-related subnetworks predict stress state and individual changes in heart rate in unseen blocks. A) Block-wise changes in FC predict the current stress phase above chance (70%, p_{perm}<.001). Predictions are best for the *PreStress* condition and the initial stress blocks. In contrast, the transition from *Stress* to *PostStress* is harder to differentiate, indicating a gradual transition into discernable states of recovery. B) Predictions based solely on changes in activations do not exceed chance levels (40%). C) Changes in FC predict changes in HR within participants (R^2=.075, p<.001). To account for baseline differences, HR is mean-centered within each participant and standardized for visualization. D) Successful prediction of changes in HR does not only recover differences between stress and non-stress conditions, but also predicts HR changes within stress recovery (b=.06, p < .001), acute stress (b=.018, p=.022), but not *PreStress* (b= 0.017, p=.067) phases. E) Comparing inter-individual differences in stress-induced changes (*Stress-PreStress)*, derived from the observed and the predicted HR changes of each block, showed a significant correlation (r=.18, p=.012). F) Observed and predicted stress-induced changes in HR were also correlated (r=.15, p=.042) in stress recovery (*PostStress - PreStress*), indicating that inter-individual differences in the stress-induced HR changes can also be recovered. G) The purple cluster ("salience") contributed most to the prediction of stress states (Δaccuracy = 15%), while the green ("DMN") and blue ("cross-clique") cluster added 6% and 7% to the overall accuracy, respectively. In contrast, the yellow ("limbic") cluster only added 1% accuracy

Dynamic connectivity changes predict negative affectivity

To map differences in dynamic network reconfigurations to psychological constructs, we derived questionnaire-based dimensions reflecting individual responses to stress and psychopathology using NNMF. We included single-item responses assessing state and trait factors including depressive symptoms (BDI), trait anxiety (TAI) as well as stress coping, intolerance of uncertainty (IoU), and resilience. The most parsimonious solution revealed five well-interpretable dimensions (Fig. 5A, Table S9). Two dimensions captured stress-resilient phenotypes (resilience:self-instruction; resilience:social/cognitive coping) that highly weighted items from the resilience questionnaire and corresponding subscales of the coping questionnaire. In contrast, two dimensions captured maladaptive stress phenotypes (3:intolerance of uncertainty, 5:avoidance/distraction) that highly weighted IoU and corresponding coping subscales. The fourth dimension (negative affectivity) highly weighted depressive symptoms and TAI items of the ‘depression’ factor (Fig. 5C;22). Individual scores on the five dimensions of negative affectivity and stress reactivity correlated differentially with the subjective response to psycho-social stress (Figure/Table S10).

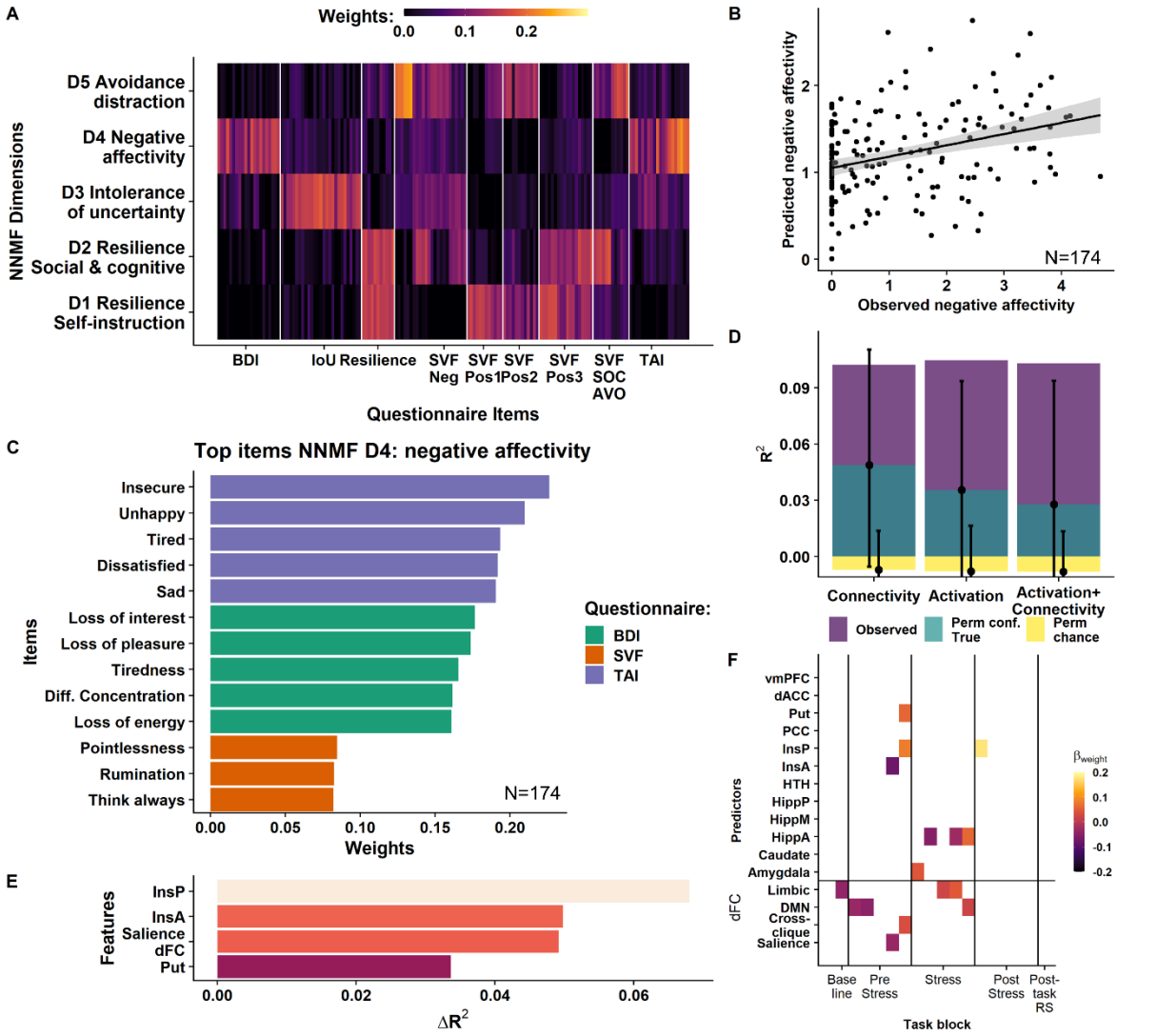

Figure 5: Block-wise changes in functional connectivity (FC) within the four stress-related subnetworks predict negative affectivity. A) Non-negative matrix factorization (NNMF) revealed 5 dimensions of individual stress responsivity that capture resilient and susceptible phenotypes. B) A model including stress-induced spatio-temporal FC and activation changes predicts negative affectivity. Predicted and observed values of negative affectivity were significantly correlated (r=.33, p_{perm}=.030) and the model explained 11% variance. C) Weights of representative items contributing to the negative affectivity NNMF dimension. Shown are the top five items from the three questionnaires contributing most items to the dimension. D) Adding stress-induced changes in activation and FC improves the prediction of negative affectivity compared to permutations of only the response variable (chance level, yellow) or the response variable plus the confounding variables age, sex, average framewise displacement, medication status, and pre-task cortisol response correspondingly (confound baseline, turquoise). Error bars depict 95% percentiles. E) The most important features contributing to the prediction include activation changes in the anterior and posterior insula, the putamen, as well as FC changes in the salience network cluster (criterion: ΔBIC ≥ 6). The ΔR^2 reflects how much predictive accuracy is lost when leaving out all timepoints of the feature. Models excluding those features have a higher BIC compared to the complete model indicating worse fit without these features. F) Standardized weights from the combined prediction model including stress-induced changes in activation and FC. Retained weights in ≥80% of outer cross-validation folds add to the prediction beyond confounding variables (age, sex, average framewise displacement, medication status, and pre-task cortisol response). DMN = default mode network, BDI = Beck depression inventory, TAI = trait anxiety inventory, IoU = intolerance of uncertainty, SVF = coping questionnaire (Stressverarbeitungsfragebogen), SOC = social support, AVO = avoidance.

Next, we evaluated whether these inter-individual differences in stress adaptation are predicted by stress-induced changes in activation and FC using elastic net with nested cross-validation. Individual block-wise changes in activation and FC combined predicted negative affectivity considerably better than confounding variables alone (ΔR^2=.075; p_{perm}=.030, Fig. 5B,D). The most important features were insula and putamen activation (*PreStress* and *Post-Stress*) and SN cluster FC (*PreStress*; ΔR^2>.049 if dropped, ΔBIC≥6). In addition, negative affectivity was predicted by activation of anterior hippocampus during *Stress* and lower FC in DMN and limbic clusters during *PreStress* as well as higher FC during *Stress* (Fig. 5E-F). Reduced models using only block-wise changes in activation (ΔR^2=.069; p_{perm}=.034) and FC (ΔR^2=.053; p_{perm}=.068) were comparable in accuracy to the full model, albeit with a nominally lower predictive performance (and non-significant vs. the confounder model for FC alone). Stress-induced changes in activation also predicted resilience:self-instruction (ΔR^2=.091; p=.01, Figure S11) while FC changes did not predict other psychological dimensions of stress adaptation.

Since negative affectivity predominantly reflected BDI and TAI items, we used the same algorithm to predict questionnaire scores. Trait anxiety (N=195) was best predicted by stress-induced changes in activations and FC (combined: ΔR^2=.10; p_{perm}=.004; activation: ΔR^2=.09; p_{perm}=.004, FC: ΔR^2=.068; p_{perm}=.009) while neither BDI (N=196), nor the presence of a mood or anxiety disorder were significantly predicted (Figure S10-11). Likewise, neither baseline FC nor FC changes differed between groups using univariate tests (ps_{FDR} > .36).

4. Discussion

Impaired stress regulation is common across mental disorders and mapping individual symptoms onto stress-induced brain network reconfigurations may help increase our pathomechanistic understanding of disorders. Here, we characterized dynamic changes in activation and FC across three phases of a stress task in participants with and without mood and anxiety disorders. First, we showed that dynamic stress-induced FC changes, but not activation changes, predict the momentary stress phase. Second, we showed that spatio-temporal brain response profiles (activation+FC) predicted inter-individual differences in negative affectivity, a well-established transdiagnostic marker of heightened stress susceptibility. Third, in line with recent preclinical findings showing that the insula orchestrates bodily responses to fear (50), activation of the insula and reduced FC in the SN cluster were among the most important features predicting negative affectivity, providing a link of the SN to stress states and psychopathology dimensions. This highlights that stress-related signaling dynamics (51–53) help un-

ravel signatures indicative of a key psychopathology dimension of affective disorders, potentially reflecting a negatively biased expectation (54,55). Taken together, we provide a quantitative mapping of dynamic stress-induced brain responses that reflect psychological differences in affective processing which may incur risk for mood and anxiety disorders. Our results highlight the large potential of novel analysis techniques that capitalize on the rich individual information in spatio-temporal brain response profiles to stress, supporting the idea that mood and anxiety disorders are best understood as disorders arising from differential network dynamics.

Predictive modeling of acute spatio-temporal stress signatures showed that dynamic network reconfigurations within the SN cluster reflect both stress states and psychopathological risk factors, echoing previous insights concerning neural signaling dynamics between stress-related regions (30,56–59). Specifically, increasing FC of the SN and decreasing FC of the DMN mirror previous findings (30,56,59) indicating increased arousal and vigilant processing of relevant stimuli (56). Notably, both effects persisted or even increased during stress recovery, supporting traces of increased amygdalar FC up to an hour after acute stress (60–62). Relatedly, stress onset led to a pronounced decrease in cross-clique FC particularly between the posterior insula and hippocampus, which may reflect a shift to exteroceptive processing and a delayed strengthening of interoceptive retrospection about events (63,64). Furthermore, block-wise FC predicted HR changes supporting the role of the central autonomic network (65,66), including vmPFC, ACC, amygdala, hypothalamus, and insula (67,68) in modulating cardiovascular reactivity (50).

At a mechanistic level, our findings uncover processes linking altered stress-induced brain function to individual symptoms of psychopathology. By combining dynamic stress-induced changes in activation and FC in a large transdiagnostic sample, we derived robust markers of individual stress reactivity and predicted a dimension of maladaptive stress responses: negative affectivity (69,70). Specifically, our results suggest that network-based reconfigurations, particularly in the insula/SN cluster, reflect negative affectivity, suggesting an association with negatively biased expectations (71) and physiological adaptations (50). In addition, altered stress-induced DMN-related FC has been reported in cross-diagnostic samples (31) and a reduction in FC might indicate an anticipatory response. Likewise, stress-induced changes in limbic and SN activation (e.g., striatum, amygdala, insula) have been associated with trait anxiety (29) and corresponding FC changes with mood and anxiety disorders (72–74). Neurobiologically-inspired treatments such as TMS target comparable networks to elicit therapeutic responses (75) and present-centered psychotherapy normalizes cortico-limbic processing in stress-related disorders (76). Our findings are also in line with recent preclinical work,

demonstrating that cortico-limbic connectivity during social interaction is related to stress-susceptibility (77). Recently, Hultman et al. showed that trait-like susceptibility for MDD is reflected in spatio-temporal signatures to threatening social interactions in limbic and hippocampal regions that are not predictive of the MDD phenotype (78), dissociating vulnerability and present MDD phenotypes (79,80). Our findings support the relevance of unique stress-related network dynamics for translational research as diagnostic and therapeutic target.

While previous studies highlighted characteristic changes in activations (15,16,81–83), most case-control studies are relatively small and cannot resolve dimensional aspects of psychological stress susceptibility. This may add to the limited convergence of findings (31,84–86). Similarly, our conventional analyses comparing group-level activation failed to identify differential signatures of stress, despite a comparably large sample (18,87). Therefore, our study adds to the growing concern about heterogeneity within diagnosis categories that may impede investigations of pathomechanisms (88,89). Moreover, it emphasizes that operationalizations of stress reactivity focusing on average activation might miss important spatio-temporal dynamics that are linked to psychopathology. In line with recent work on 'connectomic fingerprints', individual changes in stress-induced FC showed much higher accuracy in predicting stress states, compared to changes in activation. The best prediction of psychopathology was achieved by a combined activation+FC model demonstrating the potential of hierarchical models for improved individual predictions (90,91), especially during tasks (90,92–94). Since the most important individual features were related to insula activation and SN FC (which also recovered stress states best), our results support the notion that mental disorders are best conceptualized as network disorders (32). In other words, adaptive responses to stressors can potentially be tracked more faithfully in dynamic stress-induced perturbations (95–97) that help uncover unique information about mental processes (98,99).

Although our study provides an innovative approach to bridge the gap between acute stress reactivity and psychological responsivity, its limitations need to be addressed in future work. First, to ensure robust inferences, we aggregated FC within data-driven clusters to balance model complexity with the number of participants. Likewise, we only included a subset of nodes that have previously been associated with stress and psychopathology. Larger studies will be able to further extend the set of regions or avoid clustering to provide more nuanced insights. Second, it is conceivable that stress-induced changes on timescales that are not modeled with our approach (i.e., events) could improve the prediction. Third, to establish robustness, replication of spatio-temporal signatures of negative affectivity in an independent dataset is necessary. Likewise, whether dynamic FC changes generalize to other stress tasks remains to be shown and is important for a better understanding of stress-related disorders. Correspondingly, other dimensions of psychopathology might more strongly relate to stress

recovery (100). Finally, while previous work has shown that negative affectivity is associated with mood and anxiety disorders, our association between short-term stress-induced FC changes and this psychopathological trait cannot address the question of a causal link.

Collectively, our results emphasize that characterizing the neural response across stress phases by modeling individual signatures in a hierarchical model improves the prediction of changes within participants and between participants. Crucially, since individual signatures predicted the dimension negative affectivity, but not the presence of mood and anxiety disorders, our study highlights the need for transdiagnostic approaches to better understand the multifaceted psychopathological profiles within broad disorder categories. Therefore, our results provide a potential novel stress endophenotype to guide future translational research in mood and anxiety disorders.

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EBB, PGS and the BeCome working group were responsible for the study concept and design. MC and PGS validated the paradigm and procedure. AK and NBK conceived the method and AK performed the data analysis. AK wrote the first draft of the manuscript and NBK contributed to the writing. All authors contributed to the interpretation of findings, provided critical revision of the manuscript for important intellectual content and approved the final version for publication.

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Supplementary Information

Spatio-temporal dynamics of stress-induced network reconfigurations reflect negative affectivity

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Assessment of subjective stress experience (BSKE scales):

The BSKE (*Befindlichkeitsskalierung durch Kategorien und Eigenschaftswörter*, Janke, 1994) scales are a short version of the more extensive "*Eigenschaftswörterliste*" (EWL, (Janke and Debus, 1978), a scale developed to assess current emotional state across positive and negative dimensions. This reduced scale consists of 15 items (emotions / states) relevant for anxiety that have been previously used to assess stress reactivity (Elbau et al., 2018; Ising et al., 2008; Kühnel et al., 2020) and comparable to the PANAS or state anxiety questionnaire that are also used in stress research (Kuhn et al., 2021; Shilton et al., 2017) assesses different emotions and feelings that might be affects by stress such as agitation, anxiety, anger, or sensitivity. Participants were asked to rate their current state/feeling ("I feel …") on 6-point scale ranging from 1 ("not at all / gar nicht") to 6 ("very strongly / sehr stark"). We calculated sum scores including the items activity, wakefulness, self-certainty, focus, and relaxed state of mind for positive affect and including the items internal and external agitation, anxiety, sadness, anger, dysphoria, sensitivity as well as three items assessing somatic changes for negative affect.

Procedure:

On the day, participants arrived at the scanner at approximately 10 am. Upon arrival, the first saliva sample was taken to measure basal cortisol levels and an intravenous catheter was placed for blood sampling in a subsample (N=73). After that, participants were familiarized with the task and the response options. Electrodes were placed on the palm of the left hand for the measurement of skin conductance and on the back for electrocardiography. A pulse oximeter was placed on the fingertip to measure heart rate. Before entering the scanner, we took another saliva sample. The fMRI session started with a T2-weighted high-resolution image for spatial normalization, followed by an emotional face matching task and a pre-stress resting state. Subsequently, participants completed the psychosocial stress task. At the end participants rated their subjective state again and another saliva sample was taken. After a 30min break outside of the scanner a last resting state fMRI was acquired followed by another saliva sample and subjective state ratings.

Paradigm:

The psychosocial stress-task was the same as used and described in a previous publication (Kühnel et al., 2020). Participants had to solve mental arithmetic problems either in a control condition without time pressure and negative feedback or under stress with a time limit and negative feedback. Critically, the task had three phases, *PreStress*, *Stress*, and *PostStress*, each consisting of five 60 second blocks of arithmetic each followed by 40 second rest blocks (fixation cross). During an arithmetic block, participants were presented an arithmetic problem with a solution between 0 and 9. Arithmetic problems varied in their difficulty across three levels and difficulty was balanced across the three phases. The correct answer was chosen

using a response box allowing to navigate a two-button dial wheel system. After selecting the answer, the screen 'froze' for an anticipation phase (2.5 ± 1s, jittered) that was followed by the feedback ('correct', 'incorrect' or 'timeout', presented for 660ms). During *PreStress* and *Post-Stress*, participants had 10.5 seconds to solve the problem and respond and no further evaluative feedback or cues were given. Before *Stress*, participants were informed that answers are now 'recorded'. During stress, time to solve the arithmetic was generally limited to 4.5 seconds, and in part self-adaptive depending on the participant's preceding performance (i.e., response time was shortened if the participant performed well). Further, a time bar indicated how much time was left, inducing further time pressure, and a performance indicator showed that current performance was below group average ('in the red area'). Two instances of scripted negative verbal feedback in two rest periods informed the participants about their subpar performance and pushed them to work harder.

Heart rate measurement: Physiological recording and preprocessing

As described in Kühnel et al. (2020), we measured heart rate using photoplethysmography. Data was acquired with an MR compatible pulse oximeter (Nonin Medical Inc., Plymouth MN, USA) attached to the pulp of the left ring finger. PPG data, sampled at 5 kHz, was amplified using a MR compatible multi-channel BrainVision ExG AUX Box coupled with a BrainVision ExG MR Amplifier (Brain Products GmbH, Gilching, Germany) and recorded with BrainVision Recorder software 1.0. After down-sampling to 100 Hz, RR-intervals were detected using the Physionet Cardiovascular Signal toolbox (Vest et al., 2018). Success of detection of beat positions was evaluated by visual inspection. Measurements with insufficient data-quality leading to failed detection of beat positions were excluded (n= 27). Success of beat detection was rated by visually inspecting the detected beat positions. Crucially, the person rating the data was unaware of the patient status of each participant. Subsequent analysis of the heart rate was based on the derived RR-intervals and conducted with the RHRV package (Rodríguez-Liñares et al., 2008) for R. Further preprocessing involved the exclusion of implausible inter-beat-intervals (IBI). We filtered out IBIs shorter than 0.3 s and longer than 2.4s and excluded IBIs showing excessive deviations from the previous, following, or running average (50 beats) IBI. The threshold for excessive deviations was updated dynamically with the initial threshold set at 13% change from IBI to IBI (Vila et al., 1997).

Saliva cortisol measurement:

Cortisol concentrations were measured repeatedly before, during, and after the task in saliva and/or serum (Figure 1). Salivary cortisol was sampled directly at arrival before placement of the intravenous catheter for blood sampling in a subsample (T1), 20 minutes later before entering the MRI Scanner (T2) and directly after the stress paradigm (T6) and 30 minutes after the end (T8). After collection, all probes were centrifuged and stored at -80° C until further processing. Salivary cortisol concentrations were measured with electro-chemiluminescence-

assay (ECLIA) kit (Cobas®, Roche Diagnostics GmbH, Mannheim, Germany). The detection limit was 1090 pg/mL. The %CV (coefficient of variation) in saliva samples with varying concentrations was between 2.5% and 6.1% for intra-assay variability and between 3.6% und 11.8% for inter-assay variability. Five participants had to be excluded due to insufficient amount of saliva material at T6.

fMRI Imaging parameters:

The following scanner settings were used for acquisition of echo-planar images (EPI) for the imaging stress task: 40 oblique slices, oriented along the AC-PC plane, covering the whole brain, interleaved ascending acquisition order, TR= 2s, TE= 40ms, 64 × 64 matrix, field of view = 200 × 200 mm^2, voxel size = 3.5 × 3.5 × 3 mm^3. The EPI for the two resting state measurements (fixation cross, eyes open) were acquired with the following parameters: 42 oblique slices, oriented along the AC-PC plane, covering the whole brain, interleaved ascending acquisition order, TR= 2.5s, TE= 30ms, 96 × 96 matrix, field of view = 240 × 240 mm^2, voxel size = 3.5 × 3.5 × 3 mm^3. Additionally, the measurements included a structural high resolution T1 image and single spin-echo EPI volume with the same geometrical settings as the fMRI sequence, but a longer TR of 10 s and TE 0f 38.4 ms. This single EPI volume has the same geometric distortions as the fMRI images, as the k-space readout was identical. Yet, the image combines a higher signal-to-noise ratio and less susceptibility induced signal drop-out, and was used for normalization to correct for field distortions.

fMRI preprocessing and movement covariates:

We used the same preprocessing pipeline as reported in Kühnel et al (2020) for both the task and resting state fMRI data. First, data was slice-time corrected and realigned to the first image of the task to correct for head motion. For spatial normalization a single high-resolution spin-echo EPI image was segmented using the unified segmentation scheme. Extracted gray matter and white matter segments were used for DARTEL (Ashburner, 2007) normalization to MNI templates. Functional images were co-registered to the single EPI image and normalized by applying the DARTEL-derived transformation matrix. Data was interpolated with a resolution of 2x2x2 mm^3. The last step was the smoothing of the data with a 6x6x6 mm^3 full width at half maximum kernel. During the realignment, the six head motion-parameters were extracted for later use as nuisance covariates. Additionally, we extracted physiological noise components based on aCompCor (Behzadi et al., 2007). We extracted the voxel-wise timeseries of the normalized but unsmoothed functional data from thresholded ($p > .90$) white matter and cerebro-spinal fluid segments, performed PCA, and used the first five components of each segment as physiological noise covariates. Moreover, we calculated the average framewise displacement for all six head motion parameters (FD) and DVARS (spatial root mean square of the data after temporal differencing) for each task-block as well as for the complete task run for later use as a person-level confounding variable capturing interindividual differences in head motion. On the block level, those movement variables differed between task-phases.

Nonetheless, a prediction of the task-phase based on the average FD and DVARS of each task-block using the same support-vector machine algorithm as for the FC based data only reached an accuracy of 40% well below the accuracy of the FC based prediction and performed better in only 9 out of 221 participants (Figure S13). Moreover, individual predictive performance of the support vector machine based either on FD and DVARS or FC changes was only weakly correlated (r = .17). Crucially, individual dynamic FC (dFC) trajectories and movement covariates were only weakly correlated (rs between -0.03 and .08) and combining dynamic FC trajectories and movement features improved the prediction performance only slightly (70% dFC vs. 71% dFC+Movement). Similarly, changes in heart rate could be predicted by movement parameters although to a lesser extent compared to dynamic FC trajectories (R^2_{dFC} = .075 vs. $R^2_{Movement}$ = .05). Combining both sets of predictors improves prediction ($R^2_{dFC+Movement}$ = .09) suggesting that movement and dynamic FC trajectories contribute independent information. Since on the participant-level FD and DVARS were highly correlated (r = .89, p < .001) and neither was correlated with the outcomes of interest (i.e., psychometric dimensions of stress reactivity and diagnosis status) we only included FD as a confounding variable in the elastic-net prediction. Crucially, average FD was not 'selected' in the prediction models as a feature, further emphasizing that average FD did not affects successful prediction of negative affectivity or trait anxiety. In line with previous studies (Goldfarb et al., 2019) we would have excluded runs exceeding an average framewise displacement > 1.5 mm. However, all runs fulfilled this criterion and were included.

fMRI First-level design and similarity:

The first-level general linear models (GLM) were built using individual onsets and durations of all task-blocks extracted from the log files for each participant. The task was modelled with three regressors, each modeling the five arithmetic blocks (60s) from the conditions *PreStress*, *Stress* and *PostStress*, respectively. In addition, we included two regressors modeling individual motor responses and verbal feedback during the Stress phase. Nuisance regressors were the six movement parameters derived from realignment, their derivatives, and five physiological noise components extracted from white matter and cerebro-spinal fluid each. Data were high pass filtered with a cut-off of 256s. The contrasts of interest, Stress – *PreStress*, to assess acute psychsocial stress, and *PostStress* – *PreStress*, to assess effects of fast stress recovery, were estimated for each participant.

Definition of the predefined subnetwork / regions of interest:

For the analysis of block-wise changes in activation and functional connectivity, we predefined regions of interest (ROIs) based on showing changes in activation (Corr et al., 2020; Noack et al., 2019) or functional connectivity (Hermans et al., 2014; Oort et al., 2020; Zhang et al., 2019) in response to stress. To reduce computational complexity due to combinatorial explosion across a large network, we focused on regions that have been repeatedly associated with

mood and anxiety disorders (i.e., from the default mode network, salience network, and striatum, (Kaiser et al., 2015; Sharma et al., 2017)). We selected regions from the Shen (Shen et al., 2013) functional connectivity parcellation that performs well for predictive analyses, providing a good balance in terms of granularity and specificity (Finn et al., 2015). To determine parcels of the Shen atlas best reflecting the stress-related regions, we used functional (e.g., association with established networks, i.e., vmPFC, dACC, and PCC) and anatomical information (i.e., proportion of voxels belonging to a region in the Harvard-Oxford brain atlas). For smaller areas (Amygdala, Caudate, Putamen, Hippocampus subregions), we selected the Shen atlas parcel with the majority of voxels corresponding to anatomical ROIs of the Harvard-Oxford brain atlas. For larger structures, such as the posterior and anterior insula and midline structures (i.e., vmPFC, dACC, and PCC), we combined multiple parcels to cover complete regions. More specifically, for each (i.e., left and right) anterior and posterior insula, we averaged all voxels from the three and two best matching parcels, respectively (Table S7, Figure S2). Likewise, for the midline structures, we averaged over all voxels from neighboring left and right parcels (Table S7, Figure S2).

Concatenation of resting-state and task timeseries:

To assess task-induced functional connectivity changes referenced to a resting-state baseline we concatenated timeseries data from the psycho-social stress task and the two, flanking resting-states. Timeseries were linearly detrended (we did not include a quadratic trend to prevent excluding potential task effects with the same pattern induced by the task structure with non-stress phases flanking the acute stress), despiked, and denoised for each measurement separately so that the average gray scale values of each measurement was 0. To concatenate the task timeseries with the resting states, we matched the average gray scale values of the flanking resting-states with the average gray scale value of the rest baseline phases (fixation cross) during the *PreStress* condition for each region of interest. To this end, we calculated the average gray scale value (i.e., the measured raw intensity of the fMRI images) after detrending and denoising for each region of interest of the rest baseline phases (fixation cross) during the *PreStress* condition and then subtracted this offset from the complete task timeseries, so that the average intensity value during the rest baseline phases during *PreStress* was 0 and matched the average intensity values of the flanking resting-states.

Feature extraction for activation changes across task blocks:

To quantify changes in activation across task blocks, we extracted block-wise estimates from the same linear mixed-effects models we used for the dynamic changes in functional connectivity. Crucially, these models include regressors capturing task-induced changes in activation elicited by task structure (i.e., one regressor for each task block, one regressor for the motor response, and one regressor for the verbal feedback). Since we only estimated the upper triangle of the connectivity matrix, each region of interest was the target region in a different number of models (ranging from 20 to 1). For prediction we used an average across the 210

models based on their anatomical region and combined across all models predicting the same region and subsequently across left and right ROIs leading to 12 predictors (vmPFC, dACC, PCC, aIns, pIns, Caudate, Putamen, Amygdala, Hypothalamus, aHipp, mHipp, pHipp) for the stress phase prediction and 12x15 predictors (trajectories across time for all regions) for the prediction of interindividual differences.

Prediction of heart rate changes within conditions and interindividual differences:

To test whether the predictive performance was only driven by the differences between difference between the stress and non-stress conditions we applied linear-mixed effects models within conditions. Predicted and observed changes in heart rate were significantly associated in the *PostStress* (b = .06, p < .001) and to a lesser extent Stress condition (b = .018, p = .022) but not *PreStress* (b = .017, p = .068) task-blocks (Fig. 4D), indicating that especially FC-changes during stress recovery correspond to the recovery in the autonomous response. Moreover, interindividual differences in stress-induced heart rate changes (i.e., *Stress – PreStress*) were correlated (*Stress*: r=.18, p = .012, *PostStress*: r = .15, p = .043 Fig. 4E-F) when deriving them either from observed or predicted heart rate changes.

Prediction of interindividual differences based on average connectivity changes during conditions in the 4 clusters

In addition to the three prediction models based either on block-wise changes in dynamic functional connectivity (dFC), activation, or both, we explored a reduced model for dFC that aggregated block-wise changes within phases. We explored this model since dFC changes within phase were relatively stable. Consequently, the model included 4(clusters)*5(timepoints: Baseline resting state, PreStress, Stress, PostStress, PostStress resting state) features features. Notably, even with this reduced set of features, we successfully predicted negative affectivity (ΔR^2 = .053, *p* = .036; Figure S13) and trait anxiety (ΔR^2 = .066, *p* = .010). Thus, R^2 was similar compared to using complete dFC trajectories ($\Delta R^2_{negaffectivity}$ = .053, ΔR^2_{TAI} = .068), indicating that aggregation within one task phase does retain most predictive information for psychopathology.

General Psychopathology factor (P-factor):

In recent years a general psychopathology factor (p-factor) has become more popular to assess the overall strength of psychopathology for each individual across the complete spectrum of disorders (Caspi et al., 2014). Since p factors derived using factor analytic approaches on single symptoms have been shown to correlate highly with simple additive operationalizations of the p-factor (i.e., adding the number of symptoms / diagnoses, (Fried et al., 2021)), we derived a p-factor score by adding all subthreshold (1) and full diagnoses (2) within the last 12 months derived from the CIDI interview. While this p-factor was correlated with the positive

and negative subjective response to the stressor as well as the non-negative matrix factorization dimensions negative affectivity and intolerance of uncertainty (Fig. S8), we could not predict the p-factor from stress-induced brain responses or FC changes.

Figures

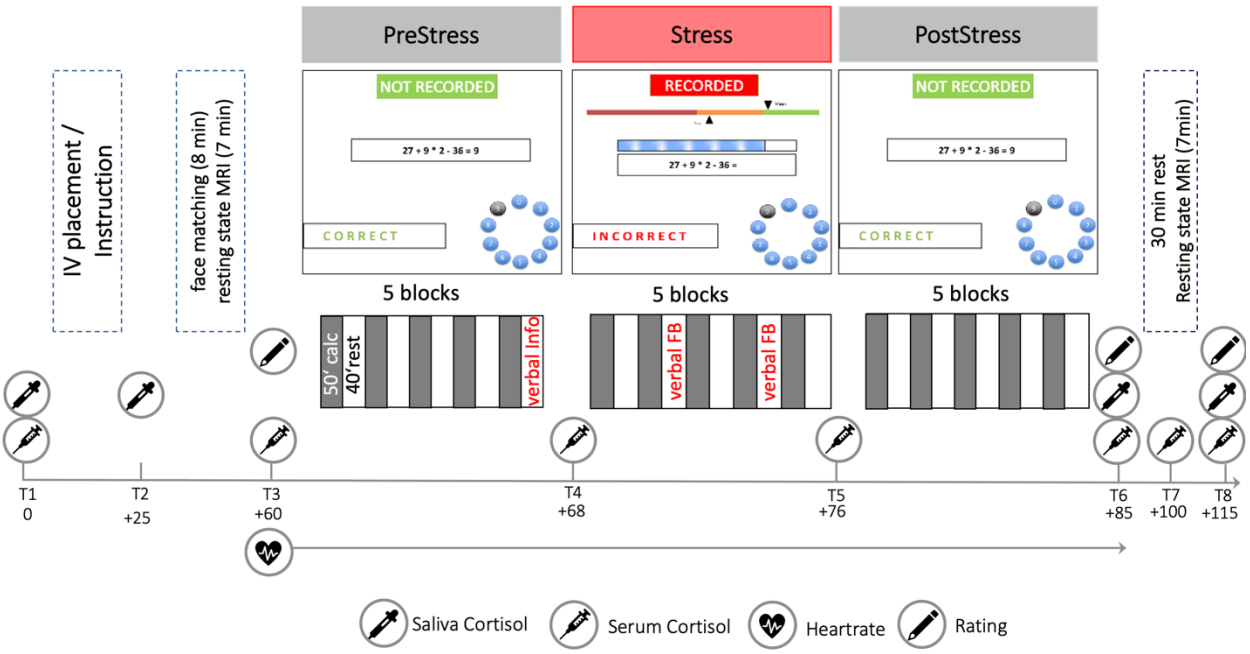

Figure S1: Detailed description of the psychosocial stress task (Kühnel et al., 2020). Before the stress phase, participants were informed about being recorded in the following trials. Additional aversive verbal feedback (verbal FB) about unsatisfactory performance was given in the 2nd and 4th rest period of the *Stress* condition. Saliva sampling was done in all participants (N=217) and in subsample of n=73 participants blood samples were taken to assess the cortisol response with higher temporal resolution.

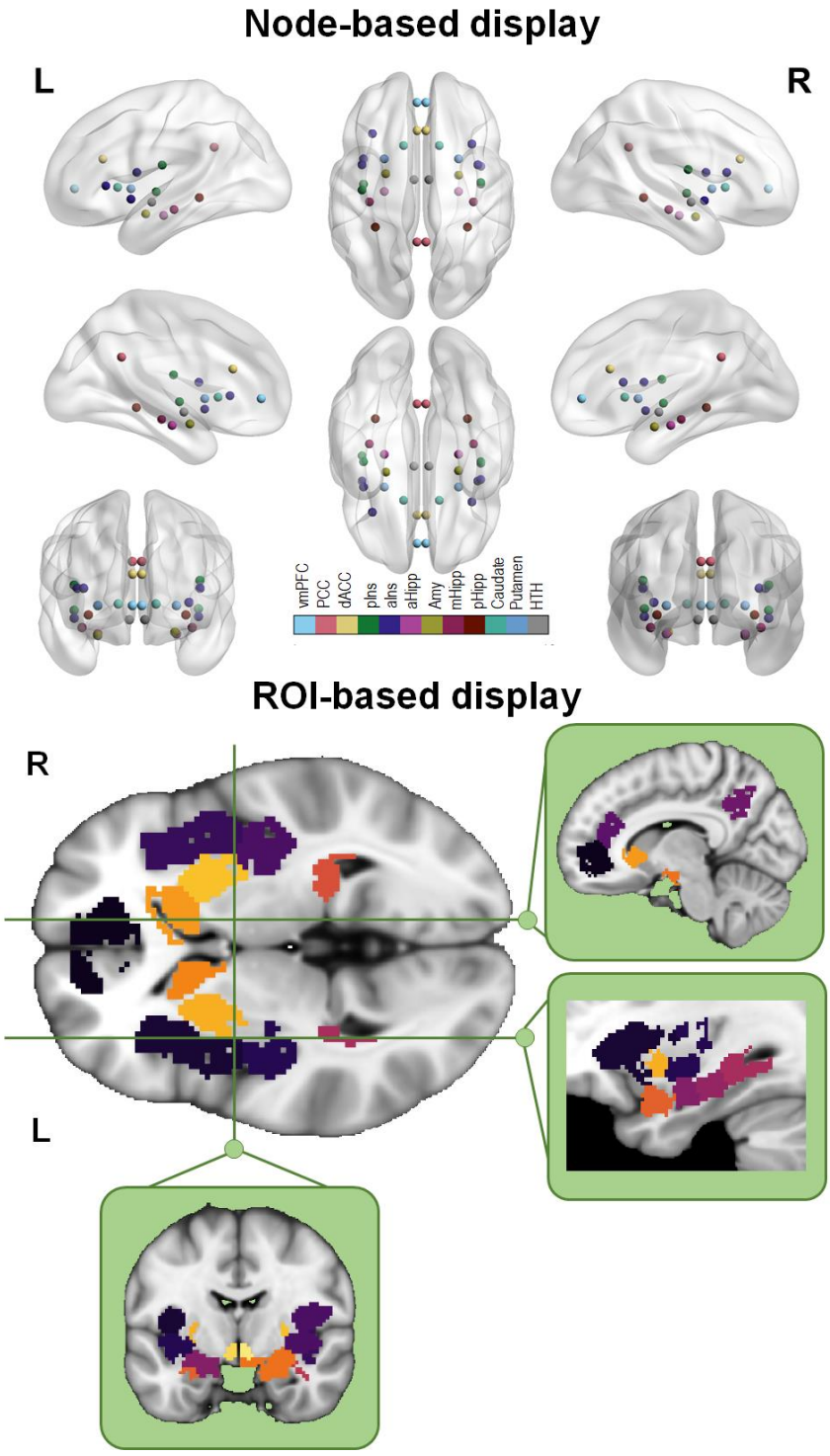

Figure S2: Stress-related regions of interest selected from the Shen functional connectivity atlas or Harvard Oxford atlas (Hypothalamus). In the upper part centroids of the parcels belonging to regions of interest are shown (same color for left and right regions). For example, the anterior insula (darkblue) contains three parcels. The lower panel shows the regions of interest as used for extraction. Each of the 21 ROIs has one corresponding color.

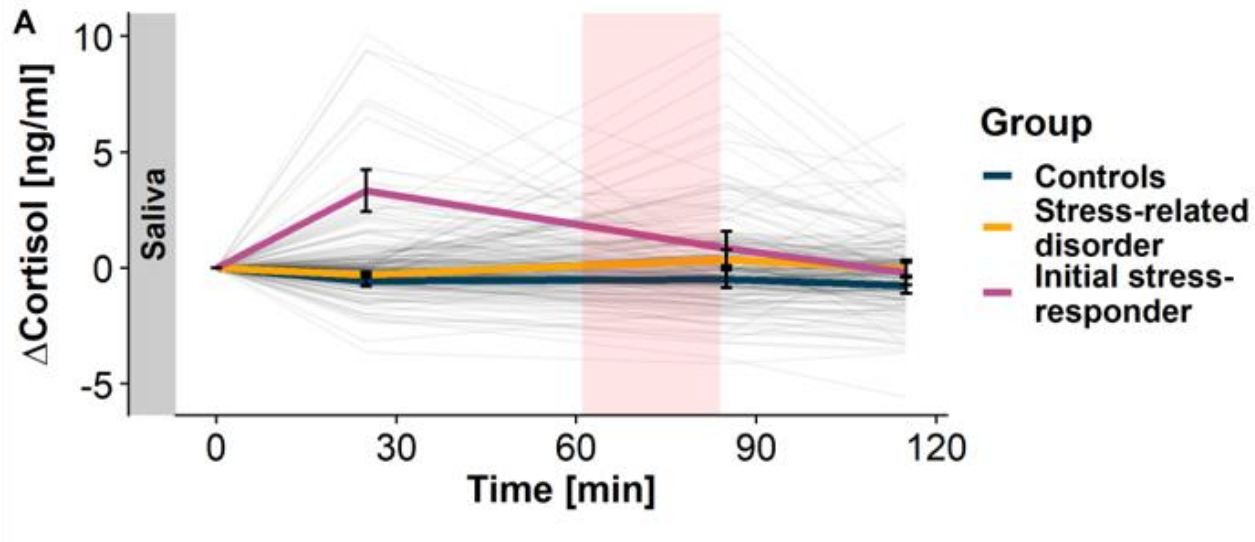

Figure S3: Trajectories of cortisol response differ between responders to the blood-drawing procedure in a subsample of 73 participants compared to participants without this initial response. The cortisol response was slightly albeit not significantly higher in participants with a mood- and/or anxiety disorder within the last 12-month (*b*=.24, *p*=.065) when excluding participants with a pre-task cortisol response.

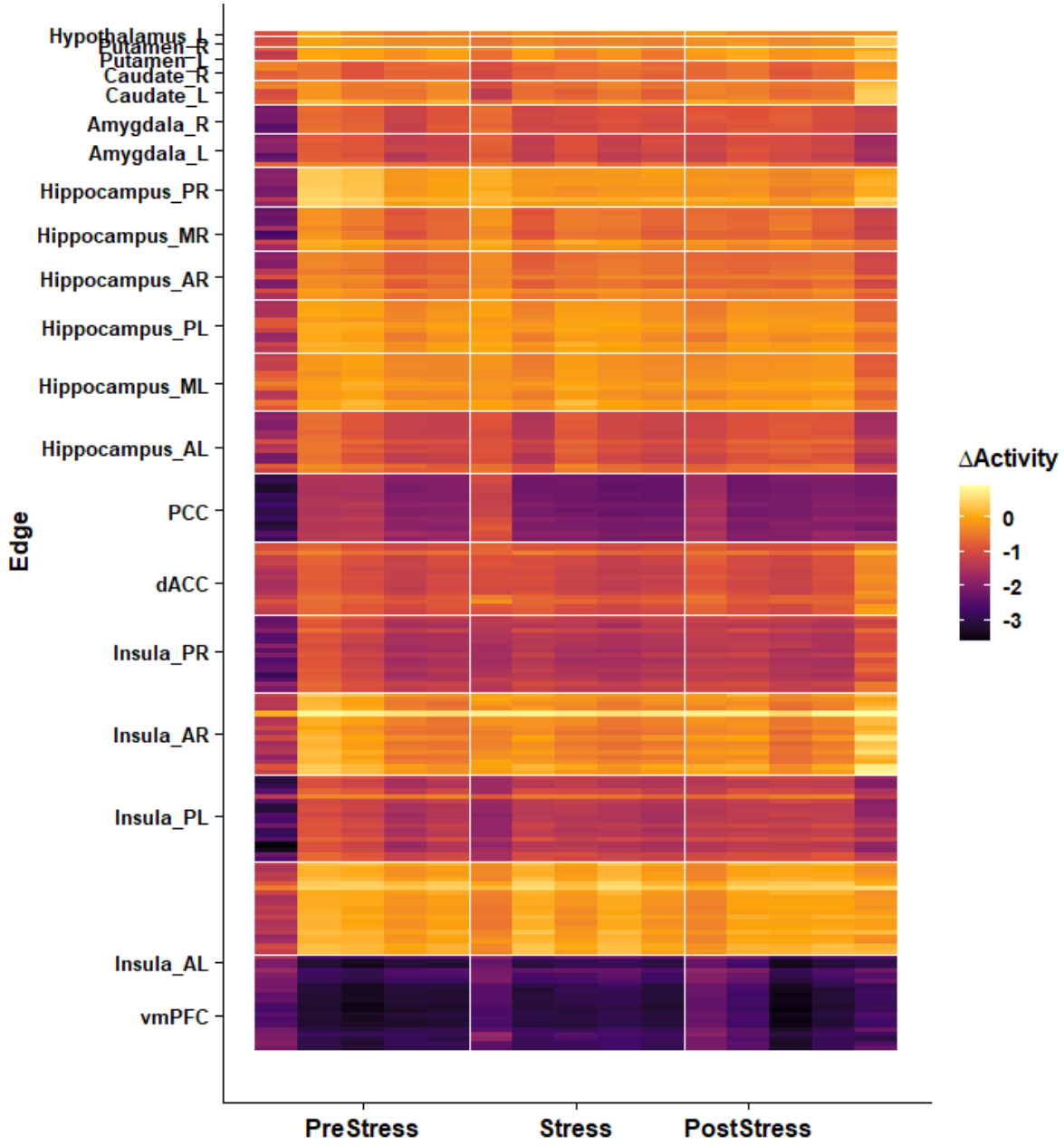

Figure S4. Changes in brain activation across task blocks. Response magnitude is similar across the different stress phases. Activation values (referenced against rest / baseline during *PreStress*) are derived from the hierarchical mixed-effects model for the functional connectivity changes in each edge as the models include task regressors for each task block. To improve computational efficiency, we only estimated the upper triangle of the connectivity matrix. Thus, the number of models with each region of interest as the target (i.e., predicted) region differs between ROIs. However, since all predictors were mean centered, the activation estimates were very similar and produced stable rank orders.

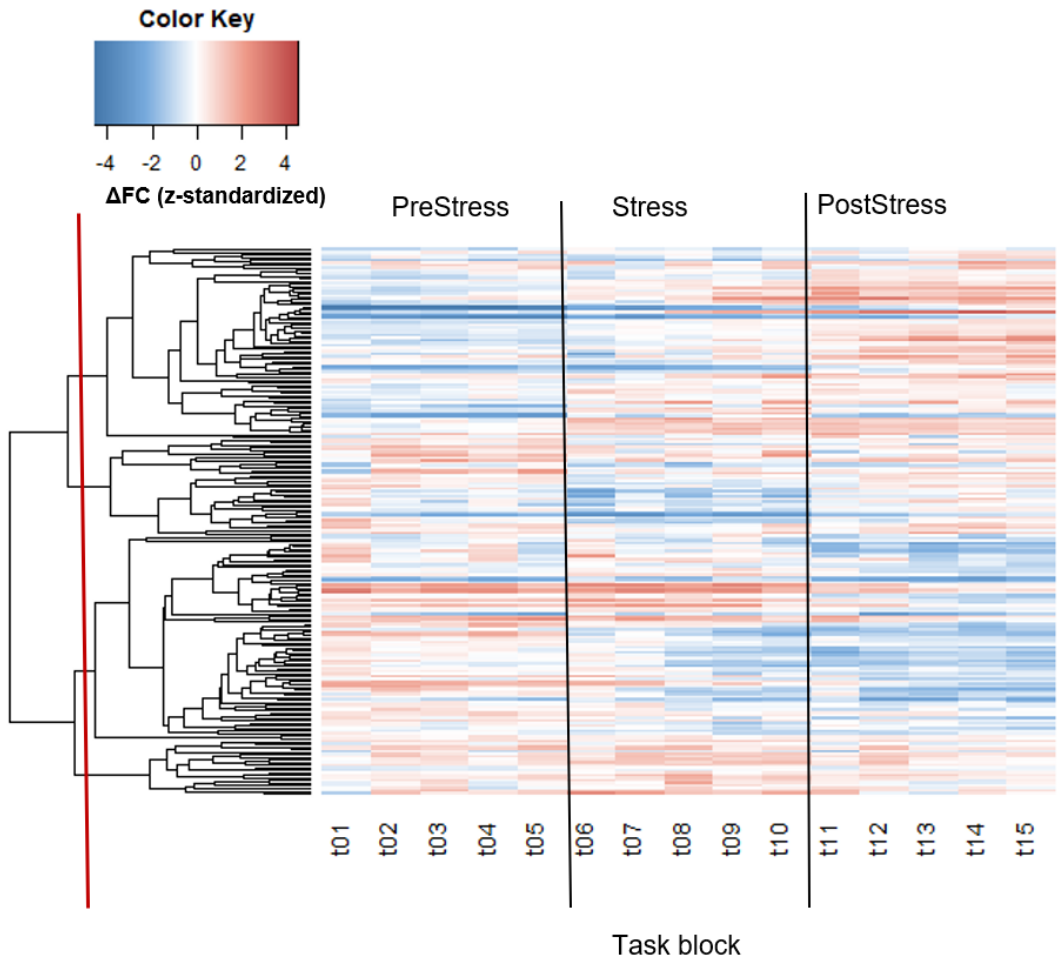

Figure S5: Dendrogram and ordered FC change matrix visualizing the hierarchical clustering solution. Choosing a more fine-grained resolution (i.e., more clusters) did not improve prediction of the intra- or inter-individual differences.

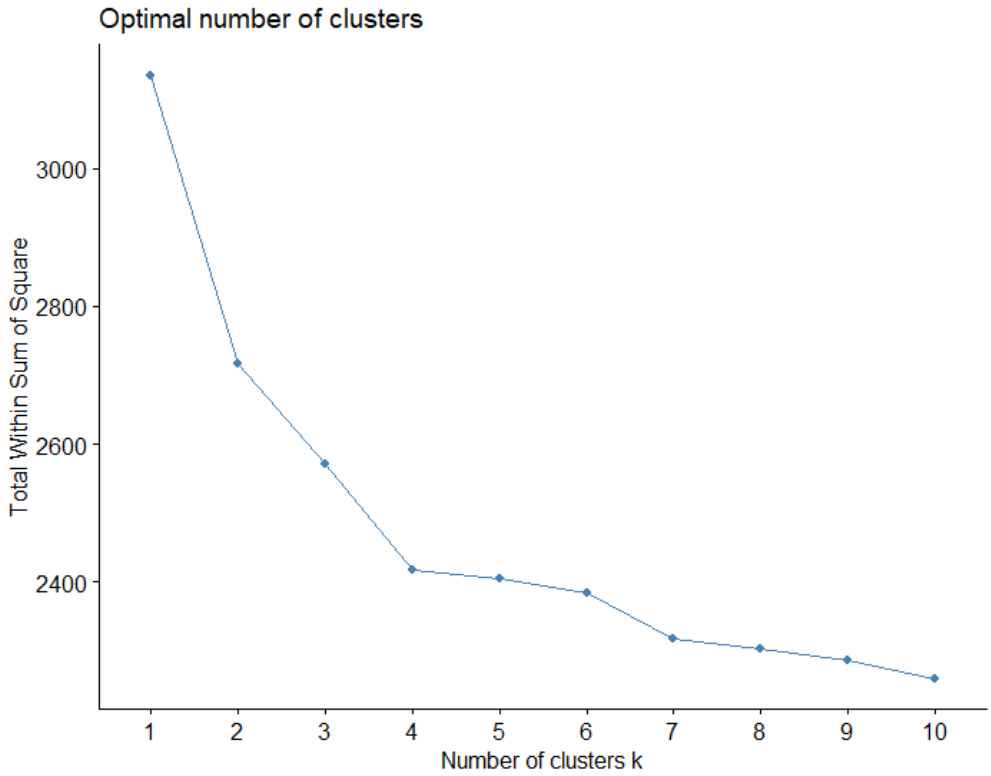

Figure S6: Scree plot for the total within cluster sum of squares (wss) for cluster solutions from k = 1-10. At 4 clusters the decrease in wss when adding additional clusters levels off.

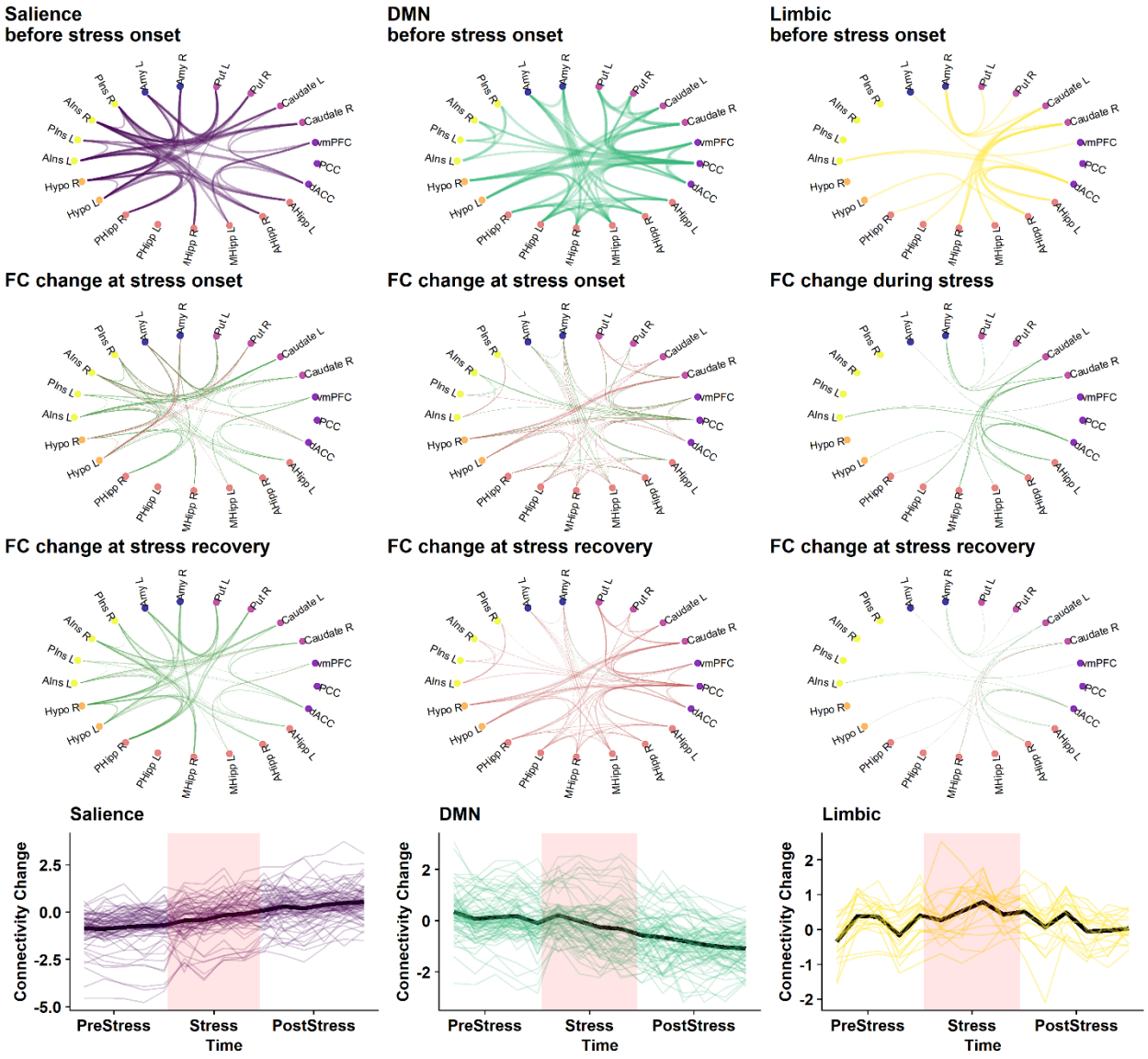

Figure S7: Circle plots for the three other subnetworks derived in the hierarchical clustering step with the corresponding average and single edge trajectories over time. The first row of circle plots (before stress onset) shows the functional connectivity (FC) change of each subnetwork compared to resting state FC. Line thickness corresponds to rescaled FC change. The second row shows stress-induced changes in FC compared to FC before stress onset (i.e., FC at stress onset (task-block 6) – FC at the beginning of the task (task-block 1). Line thickness corresponds to the rescaled magnitude of FC-change. Red lines show decreased FC and green lines increased FC. The third row shows the same difference but for the last task-block indicative of the recovery from stress. Animated circle plots showing change in FC strength with changing line thickness are available in the Supplementary material.

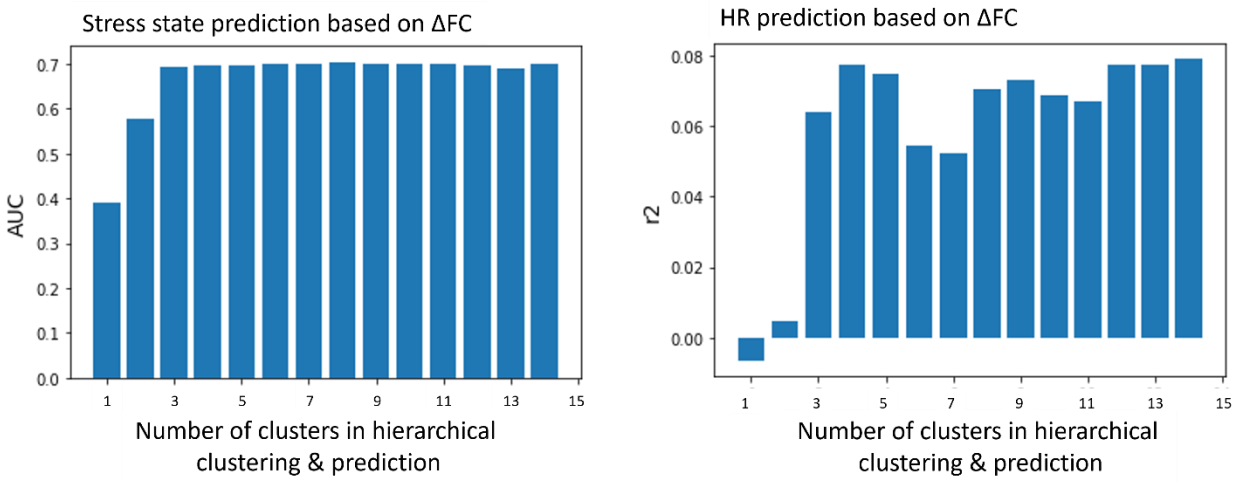

Figure S8: Predictive performance (nested cross-validation scores) for the intraindividual prediction of stress phase (AUC) and heart rate change (R2) across different cluster solutions in the hierarchical clustering step. Performance does not improve when adding more than four clusters. Models were trained using support vector machine or support vector regressions.

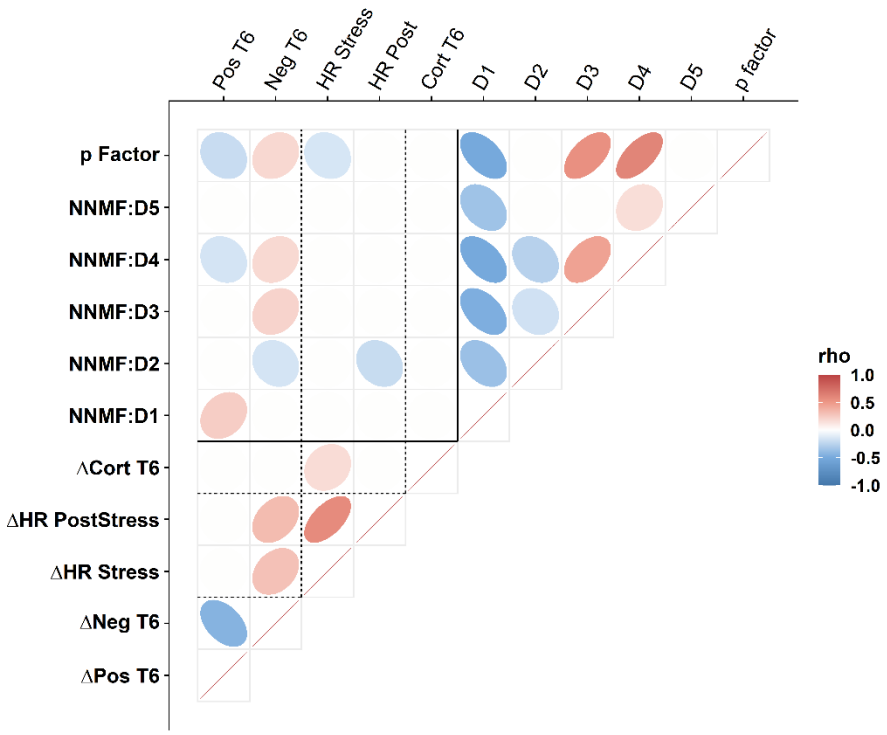

Figure S9: Correlation between the dimensions of symptoms of maladaptive stress reactivity derived using non-negative matrix factorization (NNMF) with autonomous, endocrine, and subjective stress reactivity to the psychosocial stress task. All correlations are partial correlations corrected for age, sex, and pre-task cortisol response (dummy coded yes/no). Only nominally significant correlations are shown (Supplementary Table S5). NNMF D1 = Resilience: Self-instruction, NNMF D2 = Resilience: Social support / cognitive, NNMF D3 = Intolerance of uncertainty, NNMF D4 = negative affectivity, NNMF D5 = Avoidance/Distraction, ΔCort T6 = Cortisol increase after the end of the task (T6) compared to baseline (T0), ΔHR *PostStress* = Difference in heart rate between task-block in the *PostStress* and *PreStress* condition, ΔHR Stress = Difference in heart rate between task-block in the *PostStress* and *PreStress* condition, ΔNeg T6 = Difference in state negative affect directly after the task (T6) compared to before the task (T3), ΔPos T6 = Difference in state positive affect directly after the task (T6) compared to before the task (T3).

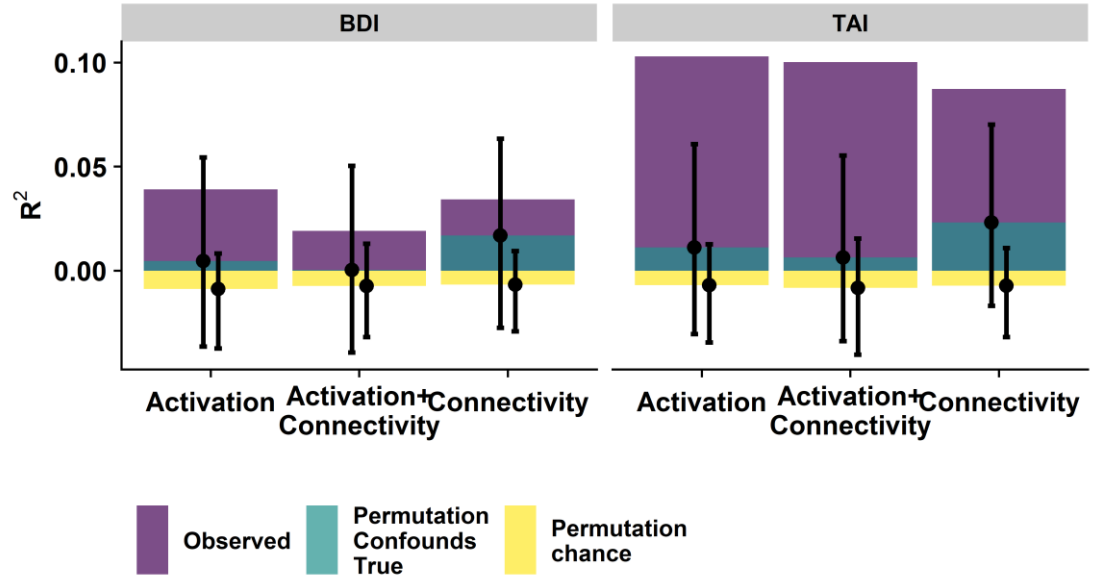

Figure S10: Trait anxiety (TAI) but not depressive symptoms (BDI) can be successfully predicted based on stress induced changes in functional connectivity and brain response and best when both are combined. Adding stress-induced changes in brain responses and FC improves the prediction of TAI compared to permutations of only the response variable (chance level, yellow) or the response variable and the confounding variables age, sex, average framewise displacement and pre-task cortisol response correspondingly (confound baseline, turquoise). Error bars depict 95% percentiles.

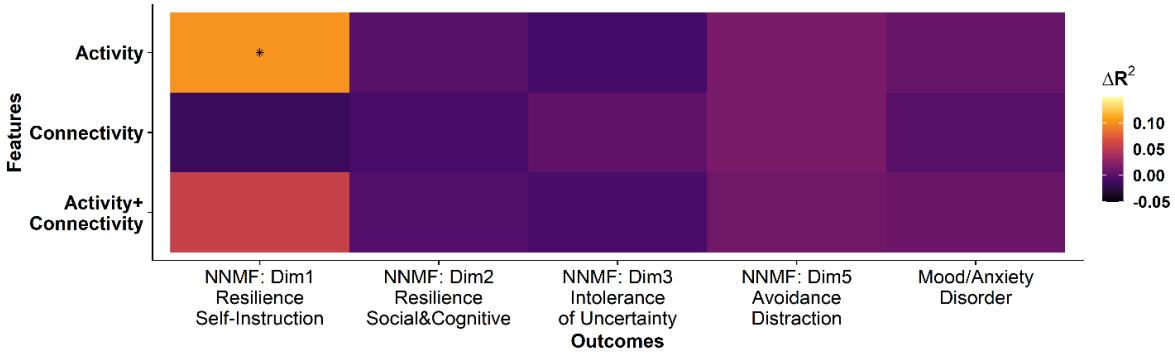

Figure S11: Predictive performance of the changes in FC or activation for the other dimensions of psychological stress reactivity and the presence of any mood or anxiety disorder in the last 12 months. Adding stress-induced changes in activation but not FC improves the prediction of Resilience: Self-instruction compared to permutations of the response variable and the confounding variables age, sex, average framewise displacement, medication status, and pre-task cortisol response correspondingly. Color indicates the increase in R2 compared to the prediction based on confounds. Asterisks indicate a one-sided p-value < .05.

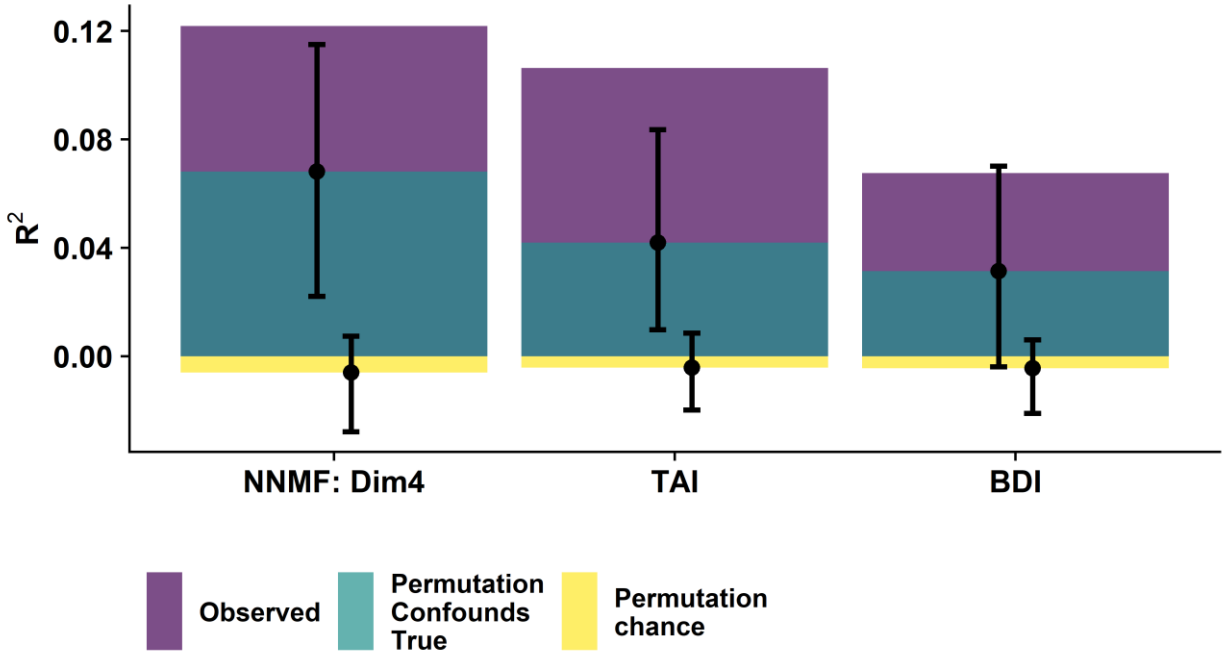

Figure S12: Predictive performance of the average changes in FC across each of the 5 task blocks for each condition (i.e., 4(clusters)*6(timepoints: resting baseline, *Pre-Stress, Stress, PostStress,* post-task resting state) features for negative affectivity, trait anxiety, and BDI. Adding stress-induced changes in FC significantly improves the prediction of negative affectivity (p=.036) and trait anxiety (p=.010) but not BDI (p=.053) compared to permutations of the response variable and the confounding variables age, sex, average framewise displacement, medication status, and pre-task cortisol response correspondingly.

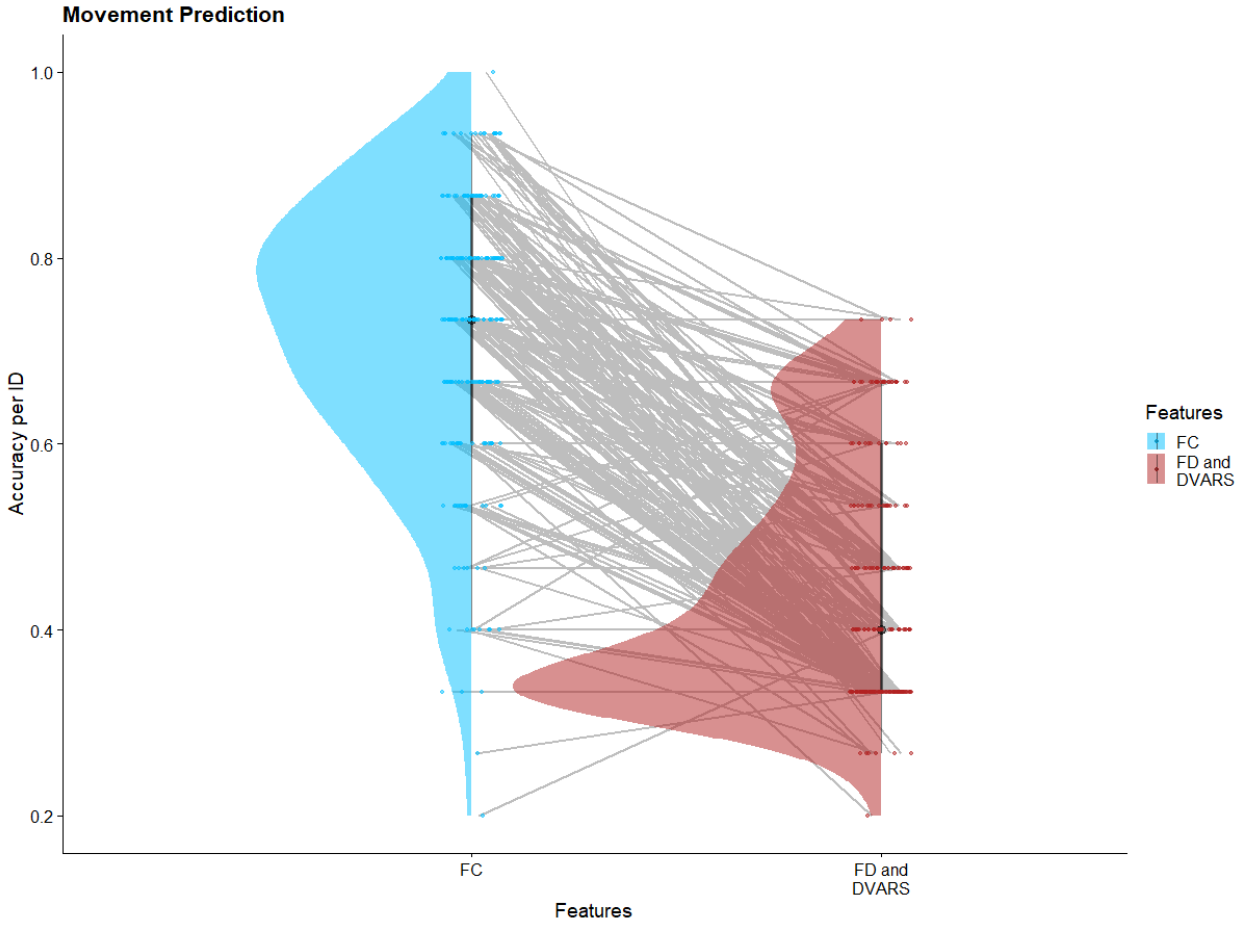

Figure S13: Prediction of the stress phase of a current task block is not driven by changes in head motion or image outliers. The accuracy of the prediction solely based on movement and DVARS estimates of each individual block only outperforms FC based prediction in 9 out of 221 individuals.

Tables

Table S1: Demographic and stress reactivity characteristics of sample and differences between participants with and without stress-related disorders within the last 12 months.

Variable	N	Overall, N = 217[1]	12-month healthy, N = 88[1]	Mood/Anxitey disorder, N = 129[1]	p-value[2]
AGE	217	35.1 (12.1)	33.3 (10.8)	36.3 (12.8)	0.13
SEX	217				0.8
Male		77 (35%)	32 (36%)	45 (35%)	
Female		140 (65%)	56 (64%)	84 (65%)	
Medication	217	9 (4%)	0 (0%)	9 (7%)	<0.001
Pre-task cortisol	217				<0.001
No		183 (84%)	63 (72%)	120 (93%)	
Yes		34 (16%)	25 (28%)	9 (7.0%)	
BDI	196	12.5 (12.7)	5.0 (7.5)	17.8 (13.0)	<0.001
TAI	195	43.2 (14.8)	33.1 (9.8)	50.6 (13.6)	<0.001
SVF					
DIS	182	12.9 (4.2)	13.6 (4.1)	12.4 (4.2)	0.11
SUBSA	182	9.9 (4.9)	10.3 (5.0)	9.7 (4.8)	0.5
FLT	182	10.7 (6.4)	8.6 (5.4)	12.2 (6.6)	<0.001
RUM	182	14.9 (6.2)	11.6 (5.8)	17.3 (5.4)	<0.001
PLD	182	9.0 (5.4)	12.0 (5.2)	6.9 (4.5)	<0.001
POS	182	14.5 (5.4)	16.1 (4.7)	13.4 (5.6)	0.001
REA	182	15.4 (4.2)	15.3 (3.8)	15.4 (4.5)	0.9
RES	182	9.5 (5.9)	6.9 (4.6)	11.4 (6.0)	<0.001
GUI	182	10.4 (4.3)	11.1 (4.3)	9.9 (4.1)	0.029
SEA	182	11.0 (5.8)	8.6 (5.0)	12.8 (5.7)	<0.001
SIT	182	15.5 (4.0)	14.9 (3.8)	16.0 (4.1)	0.038
SOC	182	13.9 (5.5)	14.1 (5.6)	13.8 (5.5)	0.6
AVO	182	12.9 (5.2)	12.4 (5.2)	13.3 (5.2)	0.2
POS1	182	9.7 (4.0)	11.6 (4.0)	8.4 (3.5)	<0.001
POS2	182	11.4 (3.9)	11.9 (3.9)	11.0 (3.9)	0.2

Variable	N	Overall, N = 217[1]	12-month healthy, N = 88[1]	Mood/Anxitey disorder, N = 129[1]	p-value[2]
POS3	182	15.2 (3.8)	15.4 (3.4)	15.0 (4.1)	0.4
NEG	182	11.6 (5.2)	8.9 (4.3)	13.4 (5.0)	<0.001
IOU	192	63.9 (23.7)	50.7 (17.5)	73.5 (23.0)	<0.001
Resilienz	192	60.6 (9.9)	65.2 (7.8)	57.3 (9.9)	<0.001

[1]Mean (SD); n (%), pre-task cortisol = cortisol response > .91 ng/ml at T1 (20 minutes after arrival) induced for example by the blood taking procedure in a subsample; BDI = Becks Depression inventory, TAI = trait anxiety inventory, SVF = stress coping questionnaire, DIS = distraction, SUBSA = substitutional satisfaction, FLT = flight tendency, RUM= rumination, PLD = playdown, POS = positive self-instruction, REA = reaction control, RES = resignation, GUI = guilt denial, SEA = self-accusation, SIT = situation control, SOC = need for social support, AVO = avoidance. POS1 – POS3 = stress-reducing strategies 1-3, NEG = stress-augmenting strategies, IOU = intolerance of uncertainty scale

[2]Wilcoxon rank sum test; Pearson's Chi-squared test

Table S2: Current and lifetime prevalence of psychiatric disorders identified using the CIDI in the present sample.

	12-months diagnosis N(%)	**Lifetime diagnosis N(%)**
Substance use disorders (F1)	10 (5%)	47 (21%)
Mood disorders (F3)	79 (36%)	87 (40%)
Anxiety-related disorders (F4)	119 (55%)	142 (68%)
Other disorders	10 (5%)	18 (8%)
No diagnoses	80 (37%)	53 (24%)
1 diagnosis	67 (31%)	65 (30%)
2 diagnoses	57 (26%)	66 (31%)
3 and more diagnoses	12 (5%)	32 (14%)

Note: Anxiety disorders (F4) include specific phobias. Mood and anxiety disorders in the last 12 months are defined as participants with a mood or anxiety-related disorder within the last 12 months excluding specific phobias. The control group includes all other participants that might still receive diagnoses from other axes (e.g. substance use disorder: smoking).

Table S3: Stress reactivity on the endocrine, autonomous, neural, and subjective level does not differ in participants reporting at least one stress-related disorder within the last 12 months.

Stress marker	N	β Mood/Anxiety Disorder (yes/no)	95% CI[1]	p-value
ΔCortisol (T6 – T1)	212	0.11	-0.18, 0.41	0.45
ΔNegative affect (T6)	216	1.0	-0.26, 2.2	0.12
ΔPositive affect (T6)	216	-0.32	-0.88, 0.24	0.26
ΔNegative affect (T8)	216	0.31	-0.52, 1.1	0.46
ΔPositive affect (T8)	216	-0.34	-0.90, 0.22	0.23
Heart rate ΔStress [bpm]	190	-0.73	-1.8, 0.32	0.17
Heart rate Δ*PostStress* [bpm]	190	-0.71	-1.5, 0.11	0.090

[1]CI = Confidence Interval. All coefficients are estimated using linear models that additionally include age, sex, and pre-task cortisol response as well as average log-transformed frame-wise displacement for neural similarity.

Table S4: Number of participants included across all analyses.

N	Subjective	Endocrine	Heart rate	Neural	NNMF
Subjective	216				
Endocrine	209	212			
Heart rate	189	185	190		
Neural (fMRI)	216	212	190	217	
NNMF	172	173	152	174	174

Note: Exclusion reasons: Endocrine (salivary cortisol) not enough material, Heart rate insufficient data quality; NNMF (Non-negative matrix factorization) missing questionnaire data (n=21 (BDI), n=22 (TAI), n=35 (Coping), n=25 (Resilience and intolerance of uncertainty)).

Table S5: Missing values for each variable by diagnosis status

Variable	12-month healthy, N = 88[1]	Mood/Anxitey disorder, N = 129[1]	p-value
BDI	6	15	.24
TAI	6	16	.18
Saliva Cortisol	3	2	.37
Heart rate	10	17	.69
Subjective stress response	0	1	-
Coping (SVF)	12	23	.41
Intolerance of Uncertainty	7	18	.17
Resilience	7	18	.17
NNMF	14	29	.18

Note: p-values were determined using Chi-Square tests. Exclusion reasons: Endocrine (salivary cortisol) not enough material, Heart rate insufficient data quality; NNMF=Non-negative matrix factorization missing questionnaire data, BDI=Becks depression inventory, TAI=trait anxiety inventory, SVF = Coping questionnaire.

Table S6: Missing values for each variable by age or sex

Variable	Male, N = 77[1]	Female, N = 140[1]	p-value	ΔAge [years]	p-value
BDI	6	15	.65	1.3	.63
TAI	6	16	.54	.7	.78
Saliva Cortisol	1	4	.79	13.2	.085
Heart rate	6	21	.18	1.4	.59
Subjective stress response	0	1	-	-	-
Coping (SVF)	12	23	.97	3.1	.18
Intolerance of Uncertainty	8	17	.86	1.5	.57
Resilience	8	17	.86	1.5	.57
NNMF	14	29	.96	3.3	.12

Note: p-values were determined using Chi-Square tests for SEX and t-tests for AGE. ΔAge reflects the mean difference in age between participants with missing data vs. available data. Exclusion reasons: Endocrine (salivary cortisol) not enough material, Heart rate insufficient data quality; NNMF=Non-negative matrix factorization missing questionnaire data, BDI=Becks depression inventory, TAI=trait anxiety inventory, SVF = Coping questionnaire.

Table S7: Regions of interest from the Shen functional connectivity atlas

Stress-related region of interest	**Region of interest in the Shen Atlas** (Index)
vmPFC	5 138
Anteriore Insula L	155 168 169
Posteriore Insula L	170 173
Anteriore Insula R	20 35 34
Anteriore Insula R	37 40
dACC	219 83
PCC	225 90
Hippocampus AL	231
Hippocampus ML	232
Hippocampus PL	230
Hippocampus AR	94
Hippocampus MR	95
Hippocampus PR	93
Amygdala L	228
Amygdala R	99
Caudate L	258
Caudate R	123
Putamen L	261
Putamen R	124
Hypothalamus L	148 (Harvard Oxford)
Hypothalamus R	147 (Harvard Oxford)

Table S8: Network labeling for each (i.e., labels for both regions of interest) edge sorted by cluster.

Cluster	ROI 1	ROI 2	Canonical network ROI 1	Canonical network ROI 2
1 (‚Salience‘)	vmPFC	Amygdala	DMN	Salience
1 (‚Salience‘)	vmPFC	Hippocampus	DMN	DMN
1 (‚Salience‘)	vmPFC	Hippocampus	DMN	DMN
1 (‚Salience‘)	vmPFC	Hippocampus	DMN	DMN
1 (‚Salience‘)	Insula	Amygdala	Salience	Salience
1 (‚Salience‘)	Insula	Amygdala	Salience	Salience
1 (‚Salience‘)	Insula	Caudate	Salience	limbic
1 (‚Salience‘)	Insula	Caudate	Salience	limbic
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Insula	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Insula	Insula	Salience	Salience
1 (‚Salience‘)	Insula	Putamen	Salience	limbic
1 (‚Salience‘)	Insula	Putamen	Salience	limbic
1 (‚Salience‘)	Insula	Caudate	Salience	limbic
1 (‚Salience‘)	Insula	Caudate	Salience	limbic
1 (‚Salience‘)	Insula	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Insula	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Insula	Amygdala	Salience	Salience
1 (‚Salience‘)	Insula	Amygdala	Salience	Salience
1 (‚Salience‘)	Insula	Caudate	Salience	limbic
1 (‚Salience‘)	Insula	Caudate	Salience	limbic
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Insula	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Insula	Insula	Salience	Salience
1 (‚Salience‘)	Insula	Putamen	Salience	limbic
1 (‚Salience‘)	Insula	Putamen	Salience	limbic
1 (‚Salience‘)	Insula	dACC	Salience	Salience
1 (‚Salience‘)	Insula	Amygdala	Salience	Salience
1 (‚Salience‘)	Insula	Caudate	Salience	limbic
1 (‚Salience‘)	Insula	Caudate	Salience	limbic
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hippocampus	Salience	DMN
1 (‚Salience‘)	Insula	Hypothalamus	Salience	Salience

Cluster	ROI 1	ROI 2	Canonical network ROI 1	Canonical network ROI 2
1 (‚Salience‘)	Insula	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Insula	Putamen	Salience	limbic
1 (‚Salience‘)	Insula	Putamen	Salience	limbic
1 (‚Salience‘)	Insula	dACC	Salience	Salience
1 (‚Salience‘)	dACC	Caudate	Salience	limbic
1 (‚Salience‘)	dACC	Caudate	Salience	limbic
1 (‚Salience‘)	dACC	Hippocampus	Salience	DMN
1 (‚Salience‘)	Hippocampus	Hypothalamus	DMN	Salience
1 (‚Salience‘)	Hippocampus	Hypothalamus	DMN	Salience
1 (‚Salience‘)	Hippocampus	Hypothalamus	DMN	Salience
1 (‚Salience‘)	Hippocampus	Hypothalamus	DMN	Salience
1 (‚Salience‘)	Hippocampus	Hypothalamus	DMN	Salience
1 (‚Salience‘)	Hippocampus	Amygdala	DMN	Salience
1 (‚Salience‘)	Hippocampus	Hypothalamus	DMN	Salience
1 (‚Salience‘)	Hippocampus	Hypothalamus	DMN	Salience
1 (‚Salience‘)	Hippocampus	Putamen	DMN	limbic
1 (‚Salience‘)	Hippocampus	Putamen	DMN	limbic
1 (‚Salience‘)	Amygdala	Caudate	Salience	limbic
1 (‚Salience‘)	Amygdala	Caudate	Salience	limbic
1 (‚Salience‘)	Amygdala	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Amygdala	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Amygdala	Putamen	Salience	limbic
1 (‚Salience‘)	Amygdala	Putamen	Salience	limbic
1 (‚Salience‘)	Amygdala	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Amygdala	Hypothalamus	Salience	Salience
1 (‚Salience‘)	Putamen	Hypothalamus	limbic	Salience
1 (‚Salience‘)	Putamen	Hypothalamus	limbic	Salience
1 (‚Salience‘)	Putamen	Hypothalamus	limbic	Salience
1 (‚Salience‘)	Putamen	Hypothalamus	limbic	Salience
1 (‚Salience‘)	Hypothalamus	Hypothalamus	Salience	Salience
2 (‚Cross-clique)‘	vmPFC	Amygdala	DMN	Salience
2 (‚Cross-clique)‘	vmPFC	Hippocampus	DMN	DMN
2 (‚Cross-clique)‘	vmPFC	Hippocampus	DMN	DMN
2 (‚Cross-clique)‘	vmPFC	Hippocampus	DMN	DMN
2 (‚Cross-clique)‘	vmPFC	Insula	DMN	Salience
2 (‚Cross-clique)‘	vmPFC	Insula	DMN	Salience
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Amygdala	Salience	Salience
2 (‚Cross-clique)‘	Insula	Amygdala	Salience	Salience
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN

Cluster	ROI 1	ROI 2	Canonical network ROI 1	Canonical network ROI 2
2 (‚Cross-clique)‘	Insula	Putamen	Salience	limbic
2 (‚Cross-clique)‘	Insula	Putamen	Salience	limbic
2 (‚Cross-clique)‘	Insula	dACC	Salience	Salience
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Amygdala	Salience	Salience
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Insula	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	dACC	Hippocampus	Salience	DMN
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Putamen	DMN	limbic
2 (‚Cross-clique)‘	Hippocampus	Amygdala	DMN	Salience
2 (‚Cross-clique)‘	Hippocampus	Caudate	DMN	limbic
3 (‚DMN‘)	vmPFC	Caudate	DMN	limbic
3 (‚DMN‘)	vmPFC	Caudate	DMN	limbic
3 (‚DMN‘)	vmPFC	Hypothalamus	DMN	Salience
3 (‚DMN‘)	vmPFC	Hypothalamus	DMN	Salience
3 (‚DMN‘)	vmPFC	Insula	DMN	Salience
3 (‚DMN‘)	vmPFC	PCC	DMN	DMN
3 (‚DMN‘)	vmPFC	Putamen	DMN	limbic
3 (‚DMN‘)	vmPFC	Putamen	DMN	limbic
3 (‚DMN‘)	vmPFC	dACC	DMN	Salience
3 (‚DMN‘)	Insula	Insula	Salience	Salience
3 (‚DMN‘)	Insula	Insula	Salience	Salience
3 (‚DMN‘)	Insula	PCC	Salience	DMN
3 (‚DMN‘)	Insula	Insula	Salience	Salience
3 (‚DMN‘)	Insula	Insula	Salience	Salience
3 (‚DMN‘)	Insula	PCC	Salience	DMN
3 (‚DMN‘)	Insula	PCC	Salience	DMN
3 (‚DMN‘)	Insula	PCC	Salience	DMN
3 (‚DMN‘)	dACC	Amygdala	Salience	Salience
3 (‚DMN‘)	dACC	Hypothalamus	Salience	Salience
3 (‚DMN‘)	dACC	Hypothalamus	Salience	Salience
3 (‚DMN‘)	dACC	PCC	Salience	DMN
3 (‚DMN‘)	dACC	Putamen	Salience	limbic
3 (‚DMN‘)	dACC	Putamen	Salience	limbic
3 (‚DMN‘)	PCC	Amygdala	DMN	Salience

Cluster	ROI 1	ROI 2	Canonical network ROI 1	Canonical network ROI 2
3 (‚DMN‘)	PCC	Amygdala	DMN	Salience
3 (‚DMN‘)	PCC	Caudate	DMN	limbic
3 (‚DMN‘)	PCC	Caudate	DMN	limbic
3 (‚DMN‘)	PCC	Hippocampus	DMN	DMN
3 (‚DMN‘)	PCC	Hippocampus	DMN	DMN
3 (‚DMN‘)	PCC	Hippocampus	DMN	DMN
3 (‚DMN‘)	PCC	Hippocampus	DMN	DMN
3 (‚DMN‘)	PCC	Hippocampus	DMN	DMN
3 (‚DMN‘)	PCC	Hippocampus	DMN	DMN
3 (‚DMN‘)	PCC	Hypothalamus	DMN	Salience
3 (‚DMN‘)	PCC	Hypothalamus	DMN	Salience
3 (‚DMN‘)	PCC	Putamen	DMN	limbic
3 (‚DMN‘)	PCC	Putamen	DMN	limbic
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hypothalamus	DMN	Salience
3 (‚DMN‘)	Hippocampus	Hypothalamus	DMN	Salience
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Caudate	DMN	limbic
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hypothalamus	DMN	Salience
3 (‚DMN‘)	Hippocampus	Hypothalamus	DMN	Salience
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Amygdala	DMN	Salience
3 (‚DMN‘)	Hippocampus	Hippocampus	DMN	DMN
3 (‚DMN‘)	Hippocampus	Caudate	DMN	limbic
3 (‚DMN‘)	Amygdala	Amygdala	Salience	Salience
3 (‚DMN‘)	Caudate	Caudate	limbic	limbic

Cluster	ROI 1	ROI 2	Canonical network ROI 1	Canonical network ROI 2
3 (‚DMN‘)	Caudate	Hypothalamus	limbic	Salience
3 (‚DMN‘)	Caudate	Hypothalamus	limbic	Salience
3 (‚DMN‘)	Caudate	Putamen	limbic	limbic
3 (‚DMN‘)	Caudate	Putamen	limbic	limbic
3 (‚DMN‘)	Caudate	Hypothalamus	limbic	Salience
3 (‚DMN‘)	Caudate	Hypothalamus	limbic	Salience
3 (‚DMN‘)	Caudate	Putamen	limbic	limbic
3 (‚DMN‘)	Caudate	Putamen	limbic	limbic
3 (‚DMN‘)	Putamen	Putamen	limbic	limbic
4 (‚limbic‘)	vmPFC	Insula	DMN	Salience
4 (‚limbic‘)	Insula	dACC	Salience	Salience
4 (‚limbic‘)	dACC	Amygdala	Salience	Salience
4 (‚limbic‘)	dACC	Hippocampus	Salience	DMN
4 (‚limbic‘)	dACC	Hippocampus	Salience	DMN
4 (‚limbic‘)	dACC	Hippocampus	Salience	DMN
4 (‚limbic‘)	dACC	Hippocampus	Salience	DMN
4 (‚limbic‘)	Hippocampus	Caudate	DMN	limbic
4 (‚limbic‘)	Hippocampus	Caudate	DMN	limbic
4 (‚limbic‘)	Hippocampus	Caudate	DMN	limbic
4 (‚limbic‘)	Hippocampus	Caudate	DMN	limbic
4 (‚limbic‘)	Hippocampus	Caudate	DMN	limbic
4 (‚limbic‘)	Hippocampus	Caudate	DMN	limbic
4 (‚limbic‘)	Hippocampus	Caudate	DMN	limbic
4 (‚limbic‘)	Hippocampus	Hypothalamus	DMN	Salience
4 (‚limbic‘)	Hippocampus	Caudate	DMN	limbic
4 (‚limbic‘)	Hippocampus	Caudate	DMN	limbic
4 (‚limbic‘)	Amygdala	Caudate	Salience	limbic
4 (‚limbic‘)	Amygdala	Caudate	Salience	limbic
4 (‚limbic‘)	Amygdala	Putamen	Salience	limbic
4 (‚limbic‘)	Amygdala	Putamen	Salience	limbic

Table S9: List of items included in the non-negative matrix factorization. Each item is assigned to the dimension with the highest weight. Item descriptions are shortened from the original item text

Dim	Questionnaire	Item	Item	D1	D2	D3	D4	D5
1	Resilience	3	Interest in things	**0.145**	0.132	0.058	0.004	0.086
1	Resilience	4	Like oneself	**0.169**	0.137	0	0	0.059
1	Resilience	6	Determined	**0.168**	0.158	0	0.024	0.022
1	Resilience	7	Stay interested	**0.149**	0.135	0.016	0	0.094
1	Resilience	9	Multiple perspectives	**0.154**	0.149	0.018	0.053	0.059
1	SVF	1	Focus on something	**0.136**	0.063	0.021	0	0.116
1	SVF	2	Tell myself: stay focused	**0.122**	0.1	0.022	0.035	0.03
1	SVF	5	Tell myself: I have done nothing wrong	**0.133**	0.037	0	0.037	0.07
1	SVF	10	Tell myself: persist	**0.174**	0.117	0.006	0.038	0.005
1	SVF	12	Deal faster than others	**0.146**	0.053	0	0.002	0
1	SVF	21	Tell myself: No regrests	**0.145**	0	0	0.043	0.095
1	SVF	26	I think, don't give up	**0.156**	0.116	0.003	0.032	0
1	SVF	30	Less sensitive than others	**0.164**	0.015	0.005	0	0
1	SVF	35	Tell myself: Not my fault	**0.122**	0.011	0	0.047	0.085
1	SVF	36	Tell myself: Others would struggle more	**0.128**	0.004	0.006	0	0.022
1	SVF	38	Tell myself: Don't give up	**0.155**	0.115	0.023	0.026	0
1	SVF	44	Think, not my responsibility	**0.095**	0.005	0.002	0.035	0.094
1	SVF	45	Tell myself: don't get discouraged	**0.17**	0.104	0	0.015	0.003
1	SVF	48	Try to keep composure	**0.152**	0.121	0.027	0.05	0.047
1	SVF	52	Better selfcontrol	**0.151**	0.038	0.012	0	0.02
1	SVF	55	Think about possible solutions	**0.169**	0.133	0.021	0.009	0
1	SVF	56	Think, not my fault	**0.126**	0	0	0.034	0.101
1	SVF	58	Stay in control	**0.132**	0.12	0.034	0.044	0.061
1	SVF	62	Tell myself: I can do it	**0.173**	0.128	0	0.032	0
1	SVF	63	Relax faster than others	**0.162**	0.039	0	0	0
1	SVF	70	Think it's not me	**0.111**	0	0	0.038	0.104
1	SVF	71	Tell myself: don't lose control	**0.136**	0.092	0.022	0.059	0.038
1	SVF	73	Take things easier than others	**0.155**	0.035	0	0	0
2	Resilience	1	Follow plans	0.159	**0.16**	0.013	0.059	0.039
2	Resilience	2	I can do anything	0.159	**0.164**	0.02	0.042	0.051
2	Resilience	5	I can solve multiple problems	0.138	**0.168**	0	0.025	0.046
2	Resilience	8	Find something to laugh about	0.149	**0.162**	0.033	0	0.074
2	Resilience	10	Overcome challenges	0.14	**0.144**	0.025	0.052	0.029

Dim	Questionnaire	Item	Item	D1	D2	D3	D4	D5
2	Resilience	11	I have the energy for essentials	0.15	**0.178**	0.017	0	0.02
2	SVF	3	Support from someone	0.058	**0.139**	0.031	0	0.087
2	SVF	8	Think about my behavior	0.073	**0.123**	0.063	0.05	0.067
2	SVF	13	Focus on details	0.091	**0.168**	0.032	0.08	0
2	SVF	15	Ask for advice	0.053	**0.153**	0.031	0	0.103
2	SVF	17	Think about the problem again and again	0.02	**0.148**	0.104	0.071	0.068
2	SVF	19	Regret	0	**0.104**	0.097	0.025	0.038
2	SVF	20	Tell myself: Keep it together	0.091	**0.118**	0.032	0.044	0.036
2	SVF	27	Talk to someone	0.068	**0.164**	0.05	0	0.069
2	SVF	29	Take action to solve the issue	0.138	**0.143**	0.014	0.047	0.009
2	SVF	31	Deep thinking about the problem	0.002	**0.143**	0.088	0.082	0.074
2	SVF	34	Fight agains nervousness	0.09	**0.103**	0.051	0.027	0.073
2	SVF	37	self-reproach	0	**0.125**	0.116	0.033	0.038
2	SVF	42	Ask for help	0.057	**0.143**	0.02	0	0.093
2	SVF	43	Make a plan	0.132	**0.144**	0.041	0.028	0
2	SVF	47	Rumination	0.007	**0.133**	0.077	0.075	0.116
2	SVF	50	Work	0.068	**0.091**	0.02	0.021	0.03
2	SVF	51	Tell myself: It was my fault	0	**0.096**	0.084	0.028	0.059
2	SVF	57	Ask for other opinion	0.079	**0.172**	0.04	0	0.065
2	SVF	60	Play through in your mind	0.009	**0.16**	0.101	0.064	0.071
2	SVF	61	Make avtive changes	0.129	**0.141**	0.01	0.044	0.004
2	SVF	67	My own fault	0	**0.119**	0.1	0.039	0.024
2	SVF	68	Talk to someone	0.074	**0.183**	0.031	0	0.062
2	SVF	69	Stays in thoughts	0	**0.115**	0.088	0.072	0.109
2	SVF	76	Understand reasons	0.094	**0.176**	0.054	0.039	0.019
3	IOU	1	Uncertainty stops me from having a strong opinion	0.008	0.031	**0.151**	0.035	0.016
3	IOU	2	Uncertainty is disorganized	0.033	0	**0.044**	0.041	0.011
3	IOU	3	Uncertainty is intolerable	0.039	0	**0.125**	0.063	0
3	IOU	4	It's unfair that there are not guarantees	0.008	0	**0.124**	0.042	0.046
3	IOU	5	Can't relax if I don't know what happens tomorrow	0.018	0	**0.139**	0.015	0.057
3	IOU	6	Uncertainty make me uneasy, stressed	0.012	0.04	**0.163**	0.058	0.063

Dim	Questionnaire	Item	Item	D1	D2	D3	D4	D5
3	IOU	7	Unforseen events upset me	0	0.028	**0.142**	0.055	0.052
3	IOU	8	Frustrating to not have all information	0.046	0.043	**0.157**	0.037	0.03
3	IOU	9	Uncertainty keeps from living a full life	0	0.017	**0.16**	0.067	0.007
3	IOU	10	Look ahead to avoid surprises	0.063	0.016	**0.159**	0.041	0
3	IOU	11	Small unforseen event can spoil everything	0.023	0.014	**0.154**	0.036	0
3	IOU	12	Uncertainty paralysis me	0	0.008	**0.173**	0.048	0.04
3	IOU	13	Being uncertain meas I am not first rate	0.002	0.004	**0.175**	0.022	0
3	IOU	14	I can't go forward when uncertain	0.006	0.001	**0.19**	0.026	0.024
3	IOU	15	I can't function well when uncertain	0.01	0.049	**0.15**	0.027	0.055
3	IOU	16	Unlike me others eem to know where they go	0	0.027	**0.173**	0.018	0.003
3	IOU	17	Uncertainty makes me vulnerable, unhappy, sad	0	0.049	**0.16**	0.05	0.026
3	IOU	18	Want to know what the future brings	0.046	0.006	**0.168**	0	0.015
3	IOU	19	Can't stand surprises	0	0	**0.098**	0.016	0.043
3	IOU	20	Small doubts stop me	0	0	**0.158**	0.038	0.046
3	IOU	21	Organize everything in advance	0.053	0.013	**0.16**	0	0.031
3	IOU	22	Uncertainty means lack of confidence	0.004	0.053	**0.179**	0.035	0
3	IOU	23	Unfair others seem sure about their future	0	0	**0.123**	0.007	0.038
3	IOU	24	Uncertainty keeps me from sleeping	0	0.067	**0.107**	0.071	0
3	IOU	25	Leave uncertain situations	0.003	0	**0.135**	0.036	0.023
3	IOU	26	Ambiguities in Life stress me	0.015	0.044	**0.151**	0.072	0.004
3	IOU	27	I can't stand being undecided	0.021	0.023	**0.163**	0.037	0.012
3	TAI	5	Decide slowly	0.007	0	**0.092**	0.065	0.054
3	TAI	9	To many thoughts	0	0.051	**0.12**	0.063	0.065
3	TAI	14	Worrying	0	0.043	**0.097**	0.058	0.072
3	SVF	7	Asky my self: Did I do something wrong	0	0.09	**0.109**	0.037	0.093
3	SVF	24	self-dissatisfaction	0.001	0.104	**0.112**	0.056	0.073
4	BDI	1	Sadness	0	0	0.001	**0.148**	0
4	BDI	2	Hopelessness	0	0	0.036	**0.115**	0.017
4	BDI	3	feelings of failure	0	0	0.086	**0.098**	0.011

Dim	Questionnaire	Item	Item	D1	D2	D3	D4	D5
4	BDI	4	loss of pleasure	0.005	0	0.015	**0.174**	0
4	BDI	5	feelings of guilt	0	0.025	0.044	**0.106**	0
4	BDI	6	feelings of punishment	0	0	0.047	**0.061**	0.03
4	BDI	7	rejection of self	0	0.001	0.063	**0.105**	0
4	BDI	8	self reproach	0	0.015	0.091	**0.099**	0
4	BDI	9	thoughts of suicide	0	0	0	**0.096**	0.032
4	BDI	10	to cry	0	0.011	0.023	**0.152**	0
4	BDI	11	restlessness	0	0.021	0.019	**0.073**	0.017
4	BDI	12	loss of interest	0.004	0	0.003	**0.177**	0.014
4	BDI	13	inability to decide	0	0	0.076	**0.139**	0.026
4	BDI	14	worthlessness	0	0.004	0.065	**0.12**	0
4	BDI	15	loss of energy	0	0.003	0.003	**0.161**	0.036
4	BDI	16	sleeping habits	0.028	0.072	0.004	**0.116**	0
4	BDI	17	irritability	0	0.005	0	**0.145**	0.009
4	BDI	18	appetite	0.021	0.002	0	**0.122**	0.006
4	BDI	19	trouble concentrating	0	0.009	0.023	**0.162**	0.012
4	BDI	20	tiredness/exhaustion	0.005	0.005	0.016	**0.166**	0.007
4	BDI	21	sexual interest	0	0	0	**0.146**	0.033
4	TAI	2	tired quickly	0.014	0.065	0.043	**0.14**	0.028
4	TAI	3	crying	0	0.009	0.041	**0.126**	0.014
4	TAI	4	worse than others	0.005	0	0.048	**0.164**	0.027
4	TAI	8	drowning in troubles	0	0.011	0.072	**0.123**	0.041
4	TAI	11	take everything like a bullet	0	0.033	0.095	**0.127**	0.034
4	TAI	12	lack of self-confidence	0	0.063	0.106	**0.109**	0.041
4	TAI	15	dejected	0.005	0.017	0.032	**0.191**	0.013
4	TAI	17	unimportant thoughts burden	0	0.042	0.078	**0.086**	0.035
4	TAI	19	take dissapointments too strong	0	0.035	0.092	**0.104**	0.083
4	TAI	20	currently nervous	0	0.021	0.091	**0.132**	0.057
4	TAI	1	unglücklich	0.038	0.036	0.052	**0.174**	0.032
4	TAI	6	tired	0.036	0.062	0.054	**0.194**	0.003
4	TAI	7	on edge	0.013	0.039	0.07	**0.169**	0.019
4	TAI	10	sad	0.021	0.032	0.048	**0.21**	0.018
4	TAI	13	insecure	0.022	0.025	0.026	**0.226**	0.038
4	TAI	16	unhappy	0.022	0.002	0.066	**0.192**	0.022
4	TAI	18	unbalanced	0.011	0.026	0.069	**0.187**	0.029
5	SVF	4	feel helpless	0	0.053	0.103	0.056	**0.127**
5	SVF	6	think of nothing	0.015	0.091	0.091	0.082	**0.1**
5	SVF	9	flee	0	0	0.067	0.045	**0.192**
5	SVF	11	avoid such situations	0.033	0.063	0.065	0.019	**0.134**
5	SVF	14	other occupation	0.091	0.045	0.024	0	**0.146**
5	SVF	16	good food	0.091	0.01	0.046	0	**0.119**
5	SVF	18	think, if possible leave	0.015	0	0.063	0.05	**0.203**
5	SVF	22	in future I will withdraw immediately	0.023	0.015	0.058	0.028	**0.157**

Dim	Questionnaire	Item	Item	D1	D2	D3	D4	D5
5	SVF	23	give up quickly	0	0	0.09	0.041	**0.132**
5	SVF	25	nice TV program	0.054	0.01	0.041	0.005	**0.124**
5	SVF	28	thoughts of running away	0	0	0.052	0.07	**0.199**
5	SVF	32	distraction	0.104	0.057	0.03	0.001	**0.145**
5	SVF	33	avoid situation in future	0.029	0.045	0.061	0.019	**0.176**
5	SVF	39	do not know how to combat it	0	0.036	0.079	0.054	**0.117**
5	SVF	40	treat yourself	0.133	0.026	0.007	0	**0.133**
5	SVF	41	want to end situation as quickly as possible	0.024	0.031	0.06	0.032	**0.225**
5	SVF	46	do not want to experience situation in future	0.053	0.096	0.057	0.031	**0.165**
5	SVF	49	hopeless	0	0.014	0.097	0.072	**0.128**
5	SVF	53	buy old wish	0.048	0.001	0.026	0	**0.11**
5	SVF	54	find everything pointless	0	0.025	0.076	0.085	**0.111**
5	SVF	59	withdraw from situation	0.026	0	0.053	0.031	**0.228**
5	SVF	64	mind to avoid in future	0.069	0.075	0.062	0.005	**0.142**
5	SVF	65	look for joy	0.132	0.034	0.017	0	**0.147**
5	SVF	66	divert attention	0.111	0.041	0.024	0.019	**0.136**
5	SVF	72	fullfill old wish	0.065	0	0.005	0	**0.12**
5	SVF	74	distraction	0.114	0.049	0.032	0	**0.125**
5	SVF	75	Resignation	0	0.01	0.081	0.057	**0.123**
5	SVF	77	think, how situation can be avoided	0.055	0.053	0.051	0.012	**0.194**
5	SVF	78	just walk away	0	0	0.05	0.06	**0.24**

Note: BDI = Becks Depression inventory, TAI = trait anxiety inventory, SVF = stress coping questionnaire, IOU = intolerance of uncertainty scale

Table S10: Partial correlations (corrected for age, sex, and pre-task cortisol) between symptoms of maladaptive stress reactivity derived by non-negative matrix factorization (NNMF) and endocrine, autonomous, and subjective responses to the psychosocial stress task.

	ΔPos T6	ΔNeg T6	ΔHR Stress	ΔHR Post	ΔCort T6	NNMF D1	NNMF D2	NNMF D3	NNMF D4
ΔPos T6	.	x	x	x	x	x	x	x	x
ΔNeg T6	-.44**	.	x	x	x	x	x	x	x
ΔHR Stress	-.14	.30**	.	x	x	x	x	x	x
ΔHR Post	-.10	.33**	.58**	.	x	x	x	x	x
ΔCort T6	-.07	.08	.17*	-.07	.	x	x	x	x
NNMF D1	.24**	-.11	.03	.-01	.02	.	x	x	x
NNMF D2	.02	-.15*	-.09	-.20*	.01	-.37**	.	x	x
NNMF D3	-.13	.21*	.05	.15	-.01	-.47**	-.17*	.	x
NNMF D4	-.16*	.19*	-.11	.01	-.05	-.51**	-.26**	.45**	.
NNMF D5	-.04	.05	.03	.09	-.09	-.35**	-.08	.12	.16

Note: * $p_{(uncorrected)} < .05$, ** $p_{(uncorrected)} < .001$, NNMF D1 = Resilience: Self-instruction, NNMF D2 = Resilience: Social support / cognitive, NNMF D3 = Intolerance of uncertainty, NNMF D4 = negative affectivity, NNMF D5 = Avoidance/Distraction, ΔCort T6 = Cortisol increase after the end of the task (T6) compared to baseline (T0), ΔHR *PostStress* = Difference in heart rate between task-block in the *PostStress* and *PreStress* condition, ΔHR Stress = Difference in heart rate between task-block in the *PostStress* and *PreStress* condition, ΔNeg T6 = Difference in state negative affect directly after the task (T6) compared to before the task (T3), ΔPos T6 = Difference in state positive affect directly after the task (T6) compared to before the task (T3).

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