The effects of acute stress, noradrenaline and cortisol on social and economic decision making

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SUMMARY

In our lives we encounter stressful situations on a daily basis. Our body reacts to such circumstances with a specific pattern of biological changes primarily characterized by the release of two substances: noradrenaline and cortisol. The former is released almost instantaneously and subsides about 10 minutes after the end of the acute stressor, whereas the latter takes longer to increase, is more sustained with effects evidenced for several hours. Though these two substances function according to different temporal profiles they interact and shape behaviour in a concerted fashion. The isolated as well as combined effect of these stress neuromodulators is the essential theme of this thesis.

Not only do we encounter stressful situations every day, but in some of these situations we are required to make decisions that have consequences for us and for those around us. In the present thesis, it will be discussed how acute stress and its associated underlying biological processes shape the way we make financial and social decisions. We will also investigate whether it impacts our ability of careful deliberation.

In the first experiment it will be demonstrated that pharmacologically increasing noradrenaline and cortisol levels alters the way we value losses by decreasing loss aversion, a behavioural regularity that makes us weigh losses more than gains of the same amount. More specifically, it will be shown that the two substances combined reduce loss aversion compared to either substance alone.

In the second experiment it will be shown that increased exogenous cortisol levels result in a shift from deliberative to intuitive thinking evidenced by reduced performance in a cognitive reflection test. These findings bear witness to the fact that in times of acute stress we have a tendency to jump to quick conclusions at the expense of careful deliberation.

In the third and fourth experiments we investigated whether stress impacts our tendency to be generous to individuals in our social environment with a varying degree of

closeness to us. In our third experiment we opted for a behavioural induction of acute stress and found that this resulted in increased levels of generosity towards close others.

In the fourth experiment we found that increased levels of exogenously administered cortisol also had the same effect as behaviourally induced acute stress. Lastly, we propose a model for acute stress effects on social decisions according to which stress neither necessarily lead to fight-or-flight or tend-and-befriend reactions, but can be associated with both, depending on situational characteristics and timing.

Overall, we demonstrate that acute stress and its biological markers cortisol and noradrenaline exert notable effects on the way we make economic and social decisions and the way we reason, thereby highlighting the importance of taking into consideration our biological and psychological state when making important choices.

CHAPTER 1

Old brains with new challenges

What does an encounter with a ferocious lion and a giving a presentation in front of a large panel of experts at a scientific conference have in common? Though many of us would struggle to find similarities between these two events at first sight, there is one particular way in which they are almost identical: both give rise to intense, acute stress in most of us. How we deal with such situations is the main topic of the present thesis. In particular, we will investigate how acute stress and its biological markers affect the way we make certain types of decisions.

The term “stress” was first defined by Hans Selye, an endocrinologist of Hungarian origin who defined it as a “nonspecific response of the body to any demand made upon it” (Selye, 1936). Stress is a pervasive part of human life and its diverse effects on our physiology and behavior have been documented in decades of research. Though we are still far from understanding the full extent of how stress affects our brains, bodies and behavior, some fundamental findings have already been well established.

Upon encountering a stressor our bodies react with a specific pattern of biological changes. Our sympathetic nervous system is activated almost instantaneously preparing us to either fight back or flee (Cannon, 1932). This fight-or-flight reaction happens fast and subsides rapidly after cessation of the stressor. In most instances, this reaction is accompanied by a second wave of physiological changes brought about by the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the release of glucocorticoids such as cortisol

(CORT, Joels & Baram, 2009). This process helps us further to cope with the stressful event. In comparison to fight-or-flight, the activation of the HPA-axis starts later and takes much longer to subside, exerting an effect on brain function for several hours. Thus it not only plays an important role in the acute stress response but also in subsequent homeostatic regulatory processes (Joels & Baram, 2009).

Though these functions evolved in our ancestors to respond to threats of a primarily physical nature, these very same systems are activated in response to modern day stressors as well. When we give a public speech, go for a job interview or have a difficult meeting at work, our body reacts to these events biologically in the same way that it would have reacted to a lion trying to attack our ancestors while hunting for food. As present day stressors are almost always of an intellectual rather than physical nature, researchers have been interested in finding out how our "old" brains deal with these new challenges. It is now well established that acute stress significantly affects our cognition (McEwen & Sapolsky, 1995) and also changes the way we make decisions (Buchanan & Preston, 2014; Porcelli & Delgado, 2017; Starcke & Brand, 2012).

As our decisions often have important consequences for us as well as those around us, it is crucial to understand what impact stress has on them. Research presented in this thesis contributes to this understanding by demonstrating that acute stress and its biological markers change the way we value losses and gains in economic decisions and thus have important financial implications in our lives. Furthermore, it will be shown, that stress can impact how generous we are to people around us. Perhaps somewhat counterintuitively we find that stress can, in certain cases, make us more prosocial. This is particularly important as it provides a more optimistic alternative to the traditionally held association between stress and antisocial tendencies (Susman, 2006). Lastly, we will show that cortisol, one of the main stress hormones can make us prone to quickly jump to conclusions at the expense of careful,

deliberate consideration thereby raising awareness to the fact that decisions we reach under stress may be more susceptible to errors and biases.

The physiology of stress

To understand how stress affects our behavior we must first understand the physiological changes it causes in our bodies in more detail. As I mentioned above, the stress response is characterized by the coordinated activation of two distinct systems, *the Sympatho-Adrenomedullary System (SAM)*, and the *HPA Axis* (Ulrich-Lai & Herman, 2009).

Sympatho-Adrenomedullary System and activation of the sympathetic nervous system (SNS)

Almost immediately upon encountering a stressor the SNS is activated, resulting in the release of catecholamines including noradrenaline (NA) and adrenaline. While noradrenaline is primarily released from the locus coeruleus (LC), adrenaline is foremost produced in the adrenal medulla from where it rapidly reaches the bloodstream (Jones & Bright, 2001). Increased levels of these catecholamines can bring about almost instantaneous physiological changes such as increased heart and respiration rate, heightened blood flow to the muscles and brain, peripheral vasoconstriction, inhibition of the digestive system, pupil dilation and bladder relaxation. Through the release of vasopressin urine formation is stopped in order to maintain maximum blood volume (Jones & Bright, 2001). All of these physiological changes are concentrated towards enabling the organism to mobilize resources to respond adequately to imminent physical threat and form the basis of the "fight-or-flight" reaction (Cannon, 1932). Through its projections to various parts of the brain the locus coeruleus norepinephrine (LC-NE) system also affects cognition, motivation, arousal and activation of the HPA axis (Benarroch, 2009). The sympathetic activation is relatively short lived as it can subside within

about 10 minutes after the cessation of a stressor (Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009; Kirschbaum, Pirke, & Hellhammer, 1993).

The hypothalamic-pituitary-adrenal (HPA) axis

The second wave of the stress response is orchestrated by the HPA axis, whose activation occurs later and is longer lasting than that of the SAM and SNS. Activation of the HPA axis originates in the paraventricular nucleus of the hypothalamus, which, if activated releases corticotropin releasing factor (CRF), which acts on the pituitary gland and causes it to produce adrenocorticotrophic hormone (ACTH). Through blood circulation ACTH arrives at its intended target, the adrenal cortex located in the kidneys, and facilitates the release of the glucocorticoid hormone cortisol in humans (Stephens, 2012), among others. Rapid cortisol responses to acute stressors develop fully 20-30 minutes after stress onset, and usually subside again after about one hour (Hermans, Henckens, Joels, & Fernandez, 2014). Thereafter genomic effects of cortisol begin to develop whose primary contribution is thought to be restoring homeostasis. Genomic glucocorticoid effects can last for several hours after the stressful event (Hermans et al., 2014).

Two systems in synergy

A fundamental characteristic of the stress response is that the distinct stress systems do not affect bodily functions in isolation, but they dynamically interact and shape biological changes and behavior in synchrony (Joels & Baram, 2009; Jones & Bright, 2001). For instance the two systems act together to mobilize the body's energy resources to respond to threat: while activation of the SAM and SNS enable the organism to respond vigorously to threat, these functions require energy. One of the main functions of cortisol is precisely to

release the body's energy reserves by releasing glycogen and preventing further storage of glucose. Furthermore, stress mediators also impact brain function in an orchestrated, coordinated way brought about by the spatial and temporal overlap of their action profiles, as well as the direct interactions between them (Joels & Baram, 2009). As an example of spatial overlap, it has been demonstrated that receptors for different stress mediators are often simultaneously expressed in certain brain regions that play a key role in the stress response, such as the basolateral amygdala, prefrontal cortex and the hippocampus, enabling a refined neuronal response to stress (Joels & Baram, 2009). In contrast to the traditionally held view that different stress modulators exert their action at distinct temporal profiles, it has now been shown that most modulators play minor additional parts in the temporal profiles of others, enabling an integrated, finely tuned response to stressors of different duration and nature (Joels & Baram, 2009). In addition to the temporal and spatial overlap, direct interactions between stress mediators and other neurotransmitters also exist (Joels & Baram, 2009). For instance an interaction between the stress mediator CRH, opioids and glutamate facilitate a shift to a low ratio of phasic to tonic firing of noradrenergic neurons in the LC, which increases arousal and scanning of the environment enabling the organism to respond to stress in an adequate manner (Valentino & Van Bockstaele, 2008). These examples show that interaction between different stress mediators, other neurotransmitters as well as a temporal and spatial overlap between different stress systems is a hallmark of the stress response. This motive will emerge repeatedly throughout this dissertation as it is one of the key catalysts of the findings presented here.

The effects of acute stress on large scale brain networks

Focus in neuroscientific research has increasingly been shifting towards identifying large scale brain networks that show systematic connections related to certain types of cognitive

tasks (Pessoa, 2014) in contrast to the previously popular approach focusing on the brain's discrete, modular organization (Barrett & Satpute, 2013). Observations from imaging studies have now confirmed that organization into large scale brain networks is a fundamental characteristic of the human brain (Barrett & Satpute, 2013).

In the following section I will specifically discuss two such networks, the salience (SN) and executive control (EC) networks (Hermans et al., 2014; Seeley et al., 2007). These two systems are of particular relevance for the present thesis, as evidence has shown that acute stress impacts brain function and behavior by altering the balance of activation between these two systems.

The salience network

The term 'salience network' was first used by Seeley et al. (2007) in their seminal paper, where the authors identified a distinct paralimbic-limbic network of regions that are critical for detecting behaviorally relevant stimuli, and have important functions related to perception, emotion, motivation and interpersonal experience (Uddin, 2017). The salience network is comprised of brain regions such as the amygdala, dorsal anterior cingulate cortex (dACC), hypothalamus, anterior insula, thalamus, inferotemporal/temporoparietal regions, striatum, brainstem and midbrain nuclei (Hermans et al., 2014; Uddin, 2017). Increased coactivation in areas that comprise the SN is associated with a wide range of salient information, including threats and rewards.

Research findings show that activation in the SN is upregulated in times of acute stress. For instance, van Marle, Hermans, Qin, & Fernandez (2009) reported heightened sensitivity to emotionally valenced stimuli after stress in the amygdala, a central structure of the SN, concurrent with the concept of hypervigilance. In line with this there is evidence of greater activation in ventral affective areas including the amygdala after acute stress

associated with preferential processing of emotionally relevant information at the expense of executive working memory performance (Oei et al., 2012). Hermans et al. (2014) reviewed diverse findings on the effects of acute stress on the salience network confirming that sympathetic arousal and increased cortisol levels are associated with heightened activity in part or the whole of the SN (for a comprehensive review see Hermans et al., 2014).

Along the same lines, Hermans et al. (2011) demonstrated that the entire salience network had increased activation and functional connectivity in response to aversive stimulation and that noradrenaline had a causal neuromodulatory role in this effect. The authors drew parallels between their findings and theories of LC function (Benarroch, 2009). Accordingly, stress related activation of LC shifts neuronal firing to a tonic mode associated with hypervigilance and distractibility, and thus prepares the organism to attend to unexpected threatening stimuli. Furthermore, through diverse LC projections (amongst others, to regions that form part of the SN) stress-induced increases in NA activity can impair top-down attentional control, enhance vigilance and thus promote an adaptive stress response. Interestingly, Hermans et al. (2011) did not find any evidence that administration of a cortisol synthesis blocker had any effect, thereby concluding that cortisol elevations are not necessary for the stress induced facilitation of the SN. This was interpreted in the context of new evidence about the fear-reducing properties of cortisol (Soravia et al., 2006), which implicate this hormone primarily in the downregulation of stress responses. However, other studies show that cortisol has a facilitatory effect on noradrenalie induced hypervigilance in the amygdala if the two are released in synchrony, while this effect is reversed if the timing of the two are not synchronized (Joels, Fernandez, & Roozendaal, 2011). These findings bear witness to the complex, intricate interactions that take place between noradrenaline and cortisol and give rise to the presumption that the two substances in isolation may have differential effects on brain function and behavior than they do in combination and that their effects are strongly dependent on the temporal characteristics of activation. However, to date,

studies systematically investigating the isolated and concomitant effect of the two major stress neuromodulators on behaviour have been scarce. Addressing this issue will be a recurrent feature in the research presented in this thesis.

In addition to regions associated with the processing of emotionally valent stimuli such as the amygdala, the SN also includes reward related areas, such as the striatum and ventral tegmental area (Delgado, 2007). As stress is known to alter SN functioning, in addition to increasing the salience of threats, stress may also change the way we respond to rewards. This is particularly true because stress, in addition to increasing CORT and NA, is also known to potentiate dopamine (DA) release (Pruessner, Champagne, Meaney, & Dagher, 2004; Scott, Heitzeg, Koeppe, Stohler, & Zubieta, 2006; Suridjan et al., 2012; Ungless, Argilli, & Bonci, 2010), the main neurotransmitter involved in the processing of rewards. Thus, in stressful situations the role of the SN is to integrate information related to the salience of negatively valenced information and the salience of potential rewards (Pessoa, 2014).

Due to the complex and dynamic nature of the stress response it is hardly surprising that the findings on how stress affects reward processing are inconsistent. While many publications report that stress reduces the sensitivity to rewards (Berghorst, Bogdan, Frank, & Pizzagalli, 2013; Porcelli, Lewis, & Delgado, 2012), others find that stress enhances reward responsiveness both in animals (Chaijale, Snyder, Arner, Curstis, & Valentino, 2015) and humans (see Mather & Lighthall, 2012) for a review).

The discrepancy in findings is likely due to the multitude of modulating factors. For instance, a comprehensive review from Vaessen, Hernaus, Myin-Germeys, & van Amelsvoort (2015) found that while physiological stress, such as pain, consistently increased striatal DA release, psychological stress lead primarily to DA increase in the medial prefrontal cortex. Furthermore, other factors such as the stage of reward processing (anticipatory or consummatory stage; Kumar et al., 2014) personality traits (Suridjan et al., 2012), early life

parental care (Pruessner et al., 2004) may be some of the many factors that modulate how stress impacts dopamine release in the brain. Additionally, it has been shown that stress induced reductions in activity in reward related regions such as the nucleus accumbens (NAcc) were counteracted by high levels of cortisol, further highlighting the complicated nature of stress effects on reward processing in particular and on the salience network in general (Oei, Both, van Heemst, & van der Grond, 2014).

Overall, what determines whether stress shifts focus towards the salience of threats, or whether it enhances or reduces the saliency of rewards is not yet well understood. The SN is a complicated network of systems that is capable of integrating emotional and motivational information from different channels, whose function likely depends on a complex interplay with other brain systems such as the LC-NE system, and between different hormones and neurotransmitters, as well as situational demands, individual differences and task characteristics. **In the study presented in Chapter 2 we used a pharmacological manipulation to test whether the stress neuromodulators NA and CORT shift focus towards the saliency of threats (losses), or rewards (gains).**

The executive control network

The EC network is associated with several higher-order cognitive functions, such as flexible decision making, goal-directed behavior, working memory processes, response inhibition and selective attention (Diamond, 2013). Its exact anatomical composition is the subject of some debate (Alvarez & Emory, 2006), but most research findings agree that it primarily encompasses prefrontal and parietal areas (Hermans et al., 2014; Koenigs, Barbey, Postle, & Grafman, 2009; Seeley et al., 2007).

Evidence from neuroimaging studies shows that the EC is downregulated in times of acute stress: reduced activation in the dorsolateral prefrontal cortex (DLPFC) in a working

memory task was found after acute stress induction (Qin, Hermans, van Marle, Luo, & Fernandez, 2009). These findings were supported by those of Dolcos & McCarthy (2006), who showed that emotional distractors during a working memory task caused a relative downregulation of the DLPFC and lateral parietal cortex compared to emotional processing regions. Looking specifically at reward responsiveness, it has been shown that acute stress induced a significant decrease in reward-related responses in the medial prefrontal cortex, while ventral striatal responses were not affected (Ossewarde et al., 2011). These findings offer evidence that reward-seeking and habitual behaviors after stress may be due to decreased prefrontal cortex (PFC) dependent cognitive control, as relative deactivation in prefrontal regions may lead to ventral striatal dominance after stress. This finding is also corroborated in clinical research findings showing that acute stress can negatively affect drug addiction through altered reward responsiveness (Saal, Dong, Bonci, & Malenka, 2003), and that acute, chronic and early life stress can all be detrimental to drug use (Sinha, 2009).

The suppression of the executive control network is caused primarily by the action and interaction of stress levels of glucocorticoids and catecholamines such as noradrenaline. This is supported by evidence from pharmacological studies on humans which showed that the administration of hydrocortisone and yohimbine (an alpha-2 adrenoreceptor antagonist) suppressed PFC activity, which was more pronounced when the two drugs were administered in combination than in isolation (Schwabe, Tegenthoff, Höffken, & Wolf, 2012; van Stegeren, Roozendaal, Kindt, Wolf, & Joels, 2010).

Acute stress and the balance of the two systems

Taken together it is clear that acute stress impacts both the SN and EC, albeit likely in opposite directions. The complexity and sophistication of stress effects on the brain are also well demonstrated by Arnsten (2000) in his intriguing review showing that the same

neurochemicals can have completely opposite effects on prefrontal versus subcortical structures. While stress levels of NA engage low affinity alpha-1 noradrenergic receptors in the PFC and reduce its function, the same stress induced NA acting on alpha1 receptors in subcortical limbic regions has an enhancing effect. Additionally, the catecholamine induced impairment of the PFC is further facilitated by glucocorticoids (Barsegyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010). The "neurochemical switch" (Arnsten, 2000) from executive functioning to the dominance of subcortical salience network regions is likely to be adaptive in situations of threat that necessitate fast and more vigilant responses to unexpected environmental stimuli. However, the downregulation of higher-order cognition and goal-directed behavior coupled with heightened vigilance may be maladaptive in some modern day stressful situations. For instance, with the "neurochemical switch" set to vigilance, we are likely to find it difficult to concentrate on a math exam while ignoring irrelevant noises from outside the classroom. **Furthermore, the lack of executive control and the change in balance between the two systems may make us susceptible to errors in reasoning by making us more prone to jump to quick conclusions at the expense of careful deliberation, as will be demonstrated in the experiment detailed in Chapter 3.**

A matter of time

As detailed above, acute stress is associated with a fast, coordinated response orchestrated by the combined action of catecholamines and glucocorticoids. Neurobiological changes shortly after stress onset downregulate prefrontal, executive functions and upregulate the salience network favoring vigilance and a rapid, adaptive response to acute threat. However, while it may be advantageous in the short run, the acute stress response is disadvantageous if it persists over a longer period of time. Thus, our bodies need to restore homeostasis once the acute threat subsides. Research evidence suggests that glucocorticoids

play an important role in this process as well. More specifically, genomic glucocorticoid effects are thought to reverse rapid, non-genomic effects that occur in the immediate aftermath of stress by upregulation of the executive network and downregulation of the salience network (Hermans et al., 2014). Several research findings support this notion. Henckens, van Wingen, Joels, & Fernandez (2010) showed that administration of hydrocortisone reduced amygdala activity in response to emotional faces 75 and 285 minutes before the task. Additionally after 285 minutes increased connectivity between amygdala and PFC was observed, which facilitated responses to neutral faces, but suppressed activity in response to emotional faces. Along the same lines Henckens, van Wingen, Joels, & Fernandez (2012) found that hydrocortisone administration approximately 4,5 hours before an MRI scan caused reduced positive coupling between the amygdala and regions associated with the initial stress reaction such as the LC, hypothalamus and hippocampus, as well as reduced negative coupling with executive control areas, providing evidence of neural processes that run counter to those occurring during acute stress and supports the theory that corticosteroids can help decouple the amygdala from the rest of the brain, thus limiting its influence. This is in contrast to the increased functional coupling between amygdala and dACC, anterior insula and the LC in the immediate aftermath of stress (van Marle, Hermans, Qin, & Fernandez, 2010). Henckens et al. (2010) investigated the time-dependency of glucocorticoid effects on working memory processing and found that hydrocortisone administration 240 minutes prior to a working memory task increased performance and neural activity in the dorsolateral prefrontal cortex, whereas administration 30 minutes prior to the task had no effect. It is worth noting, that the time frames used in different studies investigating the time-dependent effects of glucocorticoids vary significantly. This is likely due to the fact that the exact time frame of genomic and non-genomic glucocorticoid action is not yet well understood.

Particularly little is known about how time-dependent stress effects shape decision making. While rapid, non-genomic glucocorticoid action coupled with noradrenergic activation in the immediate aftermath of stress may favor a more instinctive response, genomic cortisol may exaggerate the influence of cognitive control and strategic thinking above and beyond no-stress levels, thus leading to behavioral effects opposite to those immediately after stress. This dynamic pattern has indeed started to emerge from some research findings (Bendahan et al., 2017; Vinkers et al., 2013). Although these results are a promising first step towards understanding the time-dependency of stress effects on behavior, much research is needed to elucidate the detailed workings of these dynamic processes. Understanding how the time course of biological stress reactions might shape decisions is important, as it would allow us to determine the 'optimal' timepoint to make decisions after encountering a stressful situation to facilitate favorable outcomes. **The time-dependency of stress effects on social decisions is the core question addressed in our experiment presented in Chapter 4.**

Decision making

So far I have mostly discussed how stress impacts our brain function and biology. In the following section I will detail how these biological changes translate into behavioral outcomes. More precisely, I will discuss how stress effects the way we make decisions. In particular I will focus on two types, monetary decisions involving risk and uncertainty, as well as social decisions.

Value based decision making

When we make decisions, we often decide between different options based on their subjective values. That is, we compute which choice alternative has the highest value to us and choose accordingly. Such value based decision making is universal in nature, and is one of the focal points of study in the discipline of neuroeconomics (Glimcher, Camerer, Fehr, & Poldrack, 2009).

In order to understand how a value based decision is made (Rangel, Camerer, & Montague, 2008) we can take a simple example such as deciding whether or not to purchase a steak or a salad for dinner at the end of a long working day. In the first step this involves the identification of internal states (such as the level of our hunger), external states (such as how far we have to travel to the salad bar and the steak restaurant) and consider potential courses of action (such as buying the steak or the salad). The second step is valuation, where we must assign values to each of the choice options to help us predict how much benefit we will receive from each alternative. In this step we would consider how rewarding we would find eating a tasty steak compared to a likely less tasty salad and weight this up against the potential negative consequences such as weight gain and increase in cholesterol levels after the steak versus likely no adverse health effects of the salad. Third, we would select an action, after comparing the calculated subjective values of each option, and choose the best alternative. Finally, after the decision has been made, our brain should be able to judge whether the outcome was as desired as predicted and learn from the experience to guide future decisions. This last step of feedback based learning is crucial to optimal decision making, as it enables goal-directed behaviour leading to advantageous outcomes that are flexible in response to changes in the environment (Rangel et al., 2008). Thus, we may choose to eat steak for a few days, but upon realizing that this leads to us gaining weight, we would learn

from this negative outcome, which would decrease the subjective value of eating the steak and we would be able to switch to salad the next day.

However, such goal-directed behavior and feedback based learning is not the only way we make decisions. Instead, value based decisions may also be dominated by habitual systems. Habit learning is described by the formation of a stimulus (S)-response (R) association that is reflexive and independent of the evaluation of consequences. In this case, we as decision makers, would have difficulty in adjusting our behavior in response to changes in the environment or circumstances (such as realizing that we have now become overweight). Thus, once we have learned to associate the end of the working day (S) with eating a large steak (R), we would continue choosing the steak, even if we have become overweight, because we would be unable to learn from the undesirable outcome of weight gain to downgrade our valuation of steak. Causing a switch from goal-directed to habitual behaviors is one of the ways stress can impair our decision making (Schwabe, Tegenthoff, Höffken, & Wolf, 2010; Schwabe et al., 2012; Schwabe & Wolf, 2011). Accordingly, under acute stress we may have significant difficulty in choosing the salad, even if we have become overweight or are already satiated. Of course goal-directed and habitual learning systems are only two of many frameworks that impact the way we make value-based decisions. However, their importance is notable and they are particularly relevant for the present thesis. In the next section I will discuss a special case of value-based decisions: decisions involving risk.

Risky decision making

In many situations, we need to make choices between options that have uncertain outcomes. Investing in the stock market, choosing our course of study while considering whether it would lead to a lucrative job in the future or knowing whether we would be happy with our chosen life partner are all examples of such situations. Decisions involving

uncertainty are usually categorized into those under ambiguity, where the probabilities of choice options are completely unknown, or choice under risk, where known probabilities are associated with each option. An example of risky decision making would be a choice between winning 10 euros with a probability of 0.1, or winning 2 euros with a probability of 0.8, while an example of ambiguity would be deciding whether or not to take another card in game of Black Jack.

A research paradigm often used to examine risky decision making is the game of dice task (GDT, Brand et al., 2002), in which participants are asked to select between different options associated with either high probabilities of low payoffs, or low probabilities with high payoffs. Other paradigms investigating risky decision making involve lotteries, where the choice options usually include the potential to win and lose certain amounts with known probabilities.

Stress effects on risk taking have already been demonstrated in research. Starcke, Wolf, Markowitsch, & Brand (2008) reported increased risk taking in the GDT in response to anticipatory acute stress and the individual cortisol response was negatively related to GDT performance. Similar findings were reported by Pabst, Brand, & Wolf, (2013b) as well. Buckert, Schwieren, Kudielka, & Fiebach (2014) also found that individuals with a robust cortisol response to acute stress showed more risky decision making, particularly where gains were involved. Cueva et al.(2015) and Coates & Herbert (2008) also highlighted the important role of endogenous cortisol levels in risk taking and Robertson, Immink, & Marino (2016) presented evidence that exogenous cortisol administration resulted in increased risk taking in men. Research evidence has also identified gender as a moderating factor in stress effects on risky decision making. Preston (2007); van den Bos, Harteveld, & Stoop (2009) and Lighthall, Mather, & Gorlick (2009) all found more risk seeking for men, and demonstrated that CORT elevations after stress were positively correlated with risk seeking (van den Bos et al., 2009). In contrast, females were found to be either more risk avoidant (Lighthall et al., 2009;

Preston, 2007) or there was an inverse relationship between CORT elevations and risk seeking in women, with moderate elevations causing risk aversion and higher elevations risk seeking (van den Bos et al., 2009). It is important to stress that that these results are not altered by whether or not risk seeking is advantageous in the task used. While Lighthall et al. (2009) employed the Balloon analogue risk task, where a moderate level of risk seeking is advantageous both Preston (2007) and van den Bos et al.(2009) used the Iowa Gambling Task (IGT, Bechara, Damasio, Damasio, & Anderson, 1994), where risk seeking is disadvantageous.

Another interesting motive emerging from the stress and risky decision making literature is that stress effects may also be moderated by whether or not decisions are made about gains or losses. For instance, Pabst et al. (2013b) found that while stress did not alter risk taking for gains, it decreased risk seeking for losses. In contrast, Porcelli & Delgado (2009) found increased risk taking for losses and decreased risk taking for gains, and Buckert et al. (2014) found that risk seeking after stress only increased and was only related to cortisol responses for gains. It is clear from the discrepancies between these findings that a more systematic investigation is needed to understand how stress affects risky choices about losses and gains. One reason for the observed ambiguity in findings is that most tasks that have been used in research so far are unable to systematically differentiate between risk aversion and loss aversion, thus observed risk attitudes may be confounded by individual attitudes to loss.

Loss aversion refers to a common phenomenon according to which the prospect of a certain loss has more weight in our decision than the prospect of a gain of the same value (Kahneman & Tversky, 1979). For example, the distress we would feel after losing 100 Euros would feel stronger than the delight we would derive from winning the same amount. It has been suggested, that the pain experienced from losing is about twice as powerful as the pleasure of gaining, thus, individuals are more willing to take risks to avoid losses than they are to obtain gains (Kahneman, Knetsch, & Thaler, 1990). It is also known that individual

differences in loss aversion exist (Boyce, Wood, & Ferguson, 2016), thus it is plausible that individual loss aversion attitudes moderate stress effects on risk taking, however the majority of decision making paradigms used do not control for this potential confound. To make up for this gap in the literature, we decided to investigate the effects of stress on risk and loss aversion in a paradigm (Sokol-Hessner et al., 2009; Wang, Filiba, & Camerer, 2010) that is designed to dissociate between loss and risk attitudes**. As research results already showed that cortisol elevations drive stress effects on risk aversion we opted for a pharmacological manipulation of cortisol levels. Given the evidence on the interaction between NA and CORT in modulating brain function, we additionally decided to include a pharmacological NA manipulation and a combined NA + CORT condition to investigate how the two neuromodulators impact risk and loss aversion in isolation as well as in combination (Chapter 2).**

Stress and social decisions

Humans are social beings. We live in large scale societies and engage in a multitude of social interactions every day. Therefore, when we make decisions, their outcomes often not only have consequences for us, but also for those around us.

While traditional economic theory assumes that individuals are primarily egoistic, place the highest priority on maximizing their own material gain and have little regard for others, there is abundant evidence that humans frequently consider the wellbeing of others when making decisions. On the one hand, we often decide in ways that are not in line with our own best interests (see for example decision biases and other fallacies, eg. Kahneman, Knetsch, & Thaler, 1991) , and on the other hand we are often willing incur costs to help others (Silk & House, 2011). Some of us take prosociality to such remarkable levels, that we are even willing to donate our organs to random strangers (Kalenscher, 2017; Vekaria,

Brethel-Haruwitz, Cardinale, Stoycos, & Marsh, 2017). Though such extreme altruism is rare, almost all of us engage in moderate levels of prosocial behaviour, such as sharing of resources or dividing labour, from time to time (Fehr & Fischbacher, 2003). Although certain schools of thinking deem prosociality difficult to reconcile with evolutionary theories such as natural selection as it reduces individual fitness, the adaptive advantage of certain forms of prosocial behavior (such as improvement of group fitness and its contribution to the functioning of healthy large-scale societies) is obvious. Nonetheless the existence of pure altruism and indeed the definition of altruism itself is still subject of intense philosophical and psychological debate (Wilson, 2015).

Theories have developed that are able to account for certain motivations for prosocial behavior. For instance, according to the theory of kin selection individuals behave altruistically towards genetic relatives even at a cost to themselves in order to increase collective reproductive success and thus promote inclusive fitness (Hamilton, 1963). Theories of reciprocal altruism assume that prosocial acts are motivated by a tit-for-tat strategy, according to which an individual is willing to engage in altruistic behavior towards a beneficiary under the assumption that this altruistic act would be reciprocated, should needs be reversed at a later time (Trivers, 1971). The idea of reciprocal altruism predicts that we should be particularly prosocial towards those, from whom reciprocity could be expected, such as socially or proximally close individuals. These two theories are not mutually exclusive and by no means account for prosocial motivations in their entirety. In fact, there is a multitude of other factors that may explain why we are prosocial. Examples from animal research have identified factors such as allomaternal care (care for the young by group members other than the mother) as a driving force behind prosocial behavior (Burkart et al., 2014). Yet other theories, such as parochial altruism (Bernhard, Fischbacher, & Fehr, 2006) also aim to account for instances where prosociality towards ingroup members coupled with

hostility towards outgroups results in increased group fitness and thus a stronger opposition to competitive outgroups.

Behavioral economics research investigates prosocial behavior with the help of economic games (Brañas-Garza, Espín, Herrmann, Kujal, & Nagel, 2016). One of which, the Dictator Game (DG; Kahneman, Knetsch, & Thaler, 1986), is central to two of the experiments described in the present thesis. In this game an individual (the dictator) decides how much of a certain monetary endowment he is willing to donate to a beneficiary. As the beneficiary has no leverage on the dictator because he cannot punish unfair treatment, if the decision maker is purely selfish, he should decide to donate nothing, thus keeping the entire endowment to himself without any negative consequences. However, it has been reliably demonstrated that individuals normally decide to donate money in the DG. Although this behavior may be difficult to reconcile with traditional economic theory, it makes perfect sense if one considers the collective as well as individual adaptive benefits of such actions.

Neuroimaging studies have shown that donations in the DG are positively associated with brain activation related to cognitive control (Zheng & Zhu, 2013). This would suggest that the uncontrolled, instinctive action is egoistic, and cognitive control is needed to modulate the bias to be egoistic by increasing the subjective value of other regarding actions. However, other studies have identified the opposite pattern: Yamagishi et al. (2016) claimed in a large-scale study that the cortical thickness of the DLPFC and strategic thinking ability were negatively correlated with prosocial decisions in the DG, suggesting that the instinctive response is prosocial. Opposing results from these different studies may be reconciled by taking into consideration the social distance between DG interaction partners. Accordingly, if the social distance between dictator and beneficiary is large, the instinctive response may be egoistic, and cognitive control may need to be exercised to become more prosocial. In contrast, if the two parties are socially close, the dictator may show an instinctive tendency towards prosociality, with little need for the modulatory impact of cognitive control. Research

from our team corroborates this hypothesis, by showing that brain activation concurrent to resolving a conflict between egoistic and selfish motives increases as a function of social distance between dictator and beneficiary (Strombach et al., 2015).

Overall, most research findings agree that donations in the DG in particular and prosocial behavior in general, are influenced by cognitive control mechanisms as well as processes associated with automatic, instinctive responses, which are likely to be controlled by prefrontal and limbic regions respectively. The balance of activation within these regions may modulate the value one places on other-regarding as opposed to selfish reward. As we know that prefrontal cognitive control regions are downregulated during stress, whereas limbic regions (see salience network in Chapter 1) are upregulated, it is tempting to hypothesize, that if stress indeed exaggerated instinctive responses, it should increase prosocial behavior if the dictator and beneficiary were socially close, and would show the opposite pattern if the decision maker and beneficiary were socially distant. Understanding how stress and social distance interact in shaping prosocial decisions is essential, as it could help stressed decision makers avoid potential pitfalls, such as neglecting helping behavior towards strangers, which may lead to decreased charitable giving. Furthermore, if stress does increase prosocial behavior selectively to socially close and decreases to socially distant others, this may lead to preference for legislation that undervalues the maintenance of a strong social security system, and promotes parochial altruism which fosters racism and is detrimental to society as a whole. From an academic perspective, this insight would also help to reconcile contradictory research findings where DG donations to anonymous beneficiaries decreased under stress (Vinkers et al., 2013), while donations to known others increased (von Dawans, Fischbacher, Kirschbaum, Fehr, & Heinrichs, 2012). **In our experiments described in Chapters 4 and 5 we set out to investigate how acute stress and social distance interact in shaping giving in the Dictator Game**.

Tend and befriend or fight or flight

Another intriguing angle to consider in the context of stress and social behavior is the tend-and-befriend reaction. The idea that individuals may become more prosocial and affiliate in connection with stress is relatively novel and stands in stark contrast to the canonical fight-or-flight reaction (Cannon, 1932), according to which humans as well as animals respond to threat with either aggression or withdrawal. The theory of tend-and-befriend finds its origins in a seminal paper by Taylor and colleagues (Taylor et al., 2000) who described it as a primarily female stress response, aimed at protecting the offspring (tending) and seeking help from the social group (befriending) in times of threat. It is thought to have an adaptive evolutionary advantage as it promotes the survival of offspring, has a facilitatory effect on allomaternal care and provides a buffer against the negative effects of stress. Initially it was thought that while females respond to stress with a tend-and-befriend reaction, men primarily resort to fight-or-flight. However, research evidence now suggests that in certain situations men show similar tendencies (Berger, Heinrichs, von Dawans, Way, & Chen, 2016). Interestingly social affiliation is not only beneficial as a coping mechanism after stress, but it can lead to attenuated stress responses before or during a stressful event (Häusser & Mojzisch, 2012). What factors determine whether a situation leads to fight-or-flight or tend and befriend is not yet well known. Indeed the very idea of a tend-and-befriend reaction is controversial, as many research findings still corroborate the view that stress (both chronic and in early life) leads to increased antisocial behavior (Bendahan et al., 2017; Sandi & Haller, 2015).

We set out to test this in our paper reported in Chapter 5 and put forward the theory that stress may not exclusively foster either fight-or-flight or tend-and-befriend tendencies, but may do either, depending on the time that has passed since stress onset. More specifically, while the catecholamine surge immediately after stress may foster a

fight-or-flight reaction, the emergence of non-genomic glucocorticoid effects may shift behavior towards tend-and-befriend as a form of coping.

Stress induction in laboratory conditions

Systemic and processive stressors

Stress researchers have developed a multitude of ways to induce stress in laboratory conditions. Though most of these procedures are aimed at mimicking naturally occurring stress, they differ in many key characteristics. Generally, they can be allocated to two main categories: processive and systemic stressors. The former is associated with a certain situation that is appraised by participants as stressful, such as a public speaking task and thus requires the engagement of the limbic system (Porcelli & Delgado, 2017), while the latter involves physiological stressors such as pain, and is mediated primarily by the brainstem (Porcelli & Delgado, 2017; Starcke & Brand, 2016). Some examples of systemic stressors are the cold pressor test (CPT, Hines & Brown, 1936), where participants have to complete the painful task of placing their hand in ice cold water for a certain period of time. Another example of a systemic stressor would be receiving or being threatened with an impending electric shock (Clark et al., 2012). Processive stressors mostly involve some form of social evaluation and many of them involve elements of unpredictability and uncontrollability (Dickerson & Kemeny, 2004; Koolhaas et al., 2011). The most widely used processive stressor is the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), in which participants are subjected to a public speaking task in the form of a job interview followed by a difficult mental arithmetic task performed in front of a panel of judges while being videotaped. Several different versions of this task exist, including a version for groups (von Dawans, Kirschbaum, & Heinrichs, 2011), and one for children (Buske-Kirschbaum et al., 1997). Some stress induction

procedures encompass both processive and systemic elements, such as the socially evaluated cold pressor task (SECPT, Schwabe, Haddad, & Schachinger, 2008), where individuals are videotaped and observed by the experimenter while immersing their hand in ice cold water, as in the original version of the CPT. The Maastricht Acute Stress Test (MAST; Smeets et al., 2012) combines the most stressful features of the CPT and the TSST. Here participants are required to repeatedly immerse their hand into cold water for durations unknown to the participants and also perform mental arithmetic calculations similar to the TSST while being videotaped and given negative feedback by the experimenter in case of mistakes. Thus, elements of uncontrollability, unpredictability and social evaluation were combined with the physically stressful element of pain to provide a comprehensive and effective method. In addition to systemic and procedural features laboratory stressors also differ significantly in duration, with some only lasting about 3 minutes (CPT), while others such as the group TSST take up to 20 minutes to complete (Starcke & Brand, 2016).

The duration and type of stress are important determinants of the type of stress response they evoke. While most stressors activate the SAM system and thus result in noradrenergic activation, not all stress procedures activate the HPA-Axis to reliably increase glucocorticoid levels (Dickerson & Kemeny, 2004). Thus, depending on the research question being asked it is important to consider which stress induction procedure is most appropriate. Should HPA-Axis activation be desired, it is advisable to use a procedure such as the TSST, or SECPT, which include elements of social evaluation as well as some systemic stressors (in case of the SECPT). Alternatively, should the element of social evaluation be undesirable but HPA-Axis activation is required, stressors such as the Mannheim Multicomponent Stress Test (MMST; Kolotylova et al., 2010) may be used. Considering the timeline of stress reactions, it is noteworthy to consider that while activation of the SAM system is almost immediate, its effects return to baseline in about 10 minutes after stress offset (Kirschbaum et al., 1993), whereas peak cortisol levels are usually not reached until about 20 minutes after stress onset

(Dickerson & Kemeny, 2004), and return to baseline within about 60 minutes after stress[1], at which point genomic cortisol responses begin to develop (Hermans et al., 2014). In the research featured in Chapter 4 we were interested in investigating the combined effects of noradrenergic and glucocorticoid activation on social decision making. Thus we opted for the group version of the TSST, as this procedure has been shown to result in robust cortisol responses, and its temporal features allow for a time window of activation where both CORT and NA should be at high enough concentrations to exert an effect. Crucially, we opted for behavioral task that was less than 10 minutes in duration to fit within the time period before sympathetic activation returns to baseline after stress offset.

Pharmacological manipulations

In addition to inducing stress using processive and systemic stressors, the main stress biomarkers cortisol and noradrenaline can also be manipulated pharmacologically in order to investigate the direct, causal effects of the two hormones on behavior. There are several substances that can be used to induce changes in cortisol and noradrenaline. For cortisol the most commonly used method is administration of hydrocortisone, a corticosteroid hormone receptor agonist (e.g. Schwabe et al., 2012), while noradrenergic activation is often manipulated using yohimbine or proplanolol (Oei, Tollenaar, Elzinga, & Spinhoven, 2010) and less frequently through the administration of metroprolol (O'Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999), guanfacine as well as atomoxetine (Montes, Stopper, & Floresco, 2015).

Yohimbine is a substance extracted from the central African Pausynistalia yohimbe tree. While its main action is to boost NA release it has commercially been used as a dietary supplement to treat sexual function disorders (Andersson, 2001). It acts as a potent alpha-2

[1] Though the exact timing of genomic cortisol effects is still the subject of debate with some findings placing this at an even later point after stress, see above.

adrenergic receptor antagonist, while it also has moderate to weak antagonistic effects on alpha-1 adrenergic receptors and some dopamine as well as serotonin receptors, with the exception of 5HT 1A, where it acts as a partial agonist (Millan et al., 2000). Proplanolol, on the other hand, blocks the action of adrenaline and noradrenaline at beta-adrenergic receptors. Results from animal studies also show that proplanolol can be considered as a weak, indirect alpha-1 adrenoreceptor agonist, as the blockade of beta-adrenergic receptors means that synaptic norepinephrine is only able to activate alpha-adrenoreceptors (Tuross & Patrick, 1986). Furthermore, proplanolol is also known to be an agonist of some serotonin receptors (Davids & Lesch, 1996; Hoyer et al., 1994; Schmuck, Ullmer, Kalkman, Probst, & Lubbert, 1996).

In research on the effects of stress on cognition the administration of hydrocortisone, proplanolol and yohimbine is widespread. For instance, proplanolol has been found to reverse the negative effects of stress on cognitive flexibility (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007), and has been used to investigate the effects of stress on declarative memory in humans (Maheu, Joober, & Lupien, 2005) as well as on memory for emotional events (Cahill, Prins, Weber, & McGaugh, 1994). Yohimbine has been used in animal studies investigating impulsive choice (Schippers, Schetters, De Vries, & Pattij, 2016), it has been shown to impair the ability to adjust to decision biases by altering negative feedback sensitivity in rats (Montes et al., 2015) and lead to impaired flexibility in decision making (Schwager, Haack, & Taha, 2014). In human studies yohimbine has been used in combination with hydrocortisone to investigate the effects of noradrenergic and glucocorticoid activation on habitual and goal-directed behavior (Schwabe et al., 2010, 2012) and memory systems (Schwabe & Wolf, 2013; van Stegeren et al., 2010). One important issue to consider is that most studies that use pharmacological manipulation of stress hormones usually focus on either NA or CORT, rarely both. Though combined designs have started to emerge in recent years, there is very little decision making literature with such features. We aimed to address

this issue in the research projects presented here, thus we opted for oral administration of yohimbine, hydrocortisone, both substances or placebo to our participants. We opted to use yohimbine as opposed to proplanolol, as we wanted to increase NA activation rather than decrease it. Our design allowed us to investigate how the two substances impact decisions when administered in isolation, and crucially how the two substances interact. This last point is important, as on the one hand it allows for a more realistic pharmacological manipulation given that naturally occurring stress is usually associated with the combined activation of both systems[2]. Furthermore, given the large body of evidence about the intricate interconnectedness of the stress reaction (Hermans et al., 2014) it is to be expected that CORT and NA together exert a differential effect on behavior than each substance alone.

Measuring stress

Irrespective of whether stress is induced using processive or systemic stressors or pharmacological methods, it is essential to measure participants' reaction to the manipulation to ascertain whether it had been successful. When measuring stress reactions, the first possibility is to measure subjective feelings of stress and changes in negative and positive mood. There is a multitude of instruments designed for this purpose. One of the most commonly used is the Positive and Negative Affect Scale (Watson, Clark, & Tellegen, 1988), where participants have to indicate their mood on a scale consisting of 10 positive and 10 negative mood items. A similar scale is the Profile of Mood States Scale (POMS; Spielberger, 1972)) which measures several mood dimensions including tension/anxiety, hostility/anger, vigor/ activity, fatigue/inertia, depression/dejection, confusion/bewilderment. Yet another commonly used instrument is the state version of the State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), which is widely used in research and

[2] But see Limitations in the Discussion

clinical settings to assess individual levels of anxiety both on a state and on a trait level, each consisting of 20 items. Though these forms are comprehensive and relatively easy to administer, they can take several minutes to complete. Therefore researchers have to consider their appropriateness in situations where measurements need to happen fast. The need for quick measurements is often the case during stress induction, as the manipulations themselves are usually short in duration, and the noradrenergic effects subside relatively quickly after the end of the stressor. Thus it may be ill-advised to use lengthy scales to assess the effectiveness of the induction. Instead, short and concise measuring instruments such as Visual Analogue Scales (VAS; (Lesage, Berjot, & Deschamps, 2012) may be more appropriate. These scales can be adjusted to measure feelings of stress as opposed to mood, and therefore provide a simple, quick and direct snapshot on participants' stress levels. Usually measurements of subjective feelings of stress are done at baseline and after the stress manipulation, however it is prudent to also include a measurement in the middle of the stress induction procedure to capture real-time changes, as feelings of stress may quickly subside once participants are aware the procedure had ended.

Though subjective measurements of stress are useful, they by no means provide a sufficient manipulation check. Firstly, they are subject to confounds such as social desirability effects, and secondly they reveal nothing about the biological processes that underlie the stress reaction. Thus, they are almost always used in combination with several measures designed to assess the physiological stress response. As detailed above, stress usually results in the activation of the SAM system and associated noradrenergic activation, as well as heightened levels of glucocorticoids. To measure sympathetic activation commonly used measures are electrodermal activity, cardiovascular activity and blood pressure (Mendes, 2009). Furthermore, saliva samples can be taken and analyzed for concentrations of the enzyme alpha-amylase (sAA; Nater & Rohleder, 2009). A study directly investigating the effects of noradrenergic activation on sAA concentrations reported that participants who

received yohimbine had elevated levels of sAA (Ehlert, Erni, Hebisch, & Nater, 2006) indicating that sAA is an adequate marker of sympathetic and parasympathetic stimulation caused by noradrenergic input from the central nervous system. However, confidence in sAA as a measure of sympathetic activation is not unanimous (Nater & Rohleder, 2009). This is due to a number of contradictory findings about its correlation with plasma catecholamine levels after exposure to psychological and physiological stress. Though most studies report a positive correlation (e.g. Rohleder, Nater, Wolf, Ehlert, & Kirschbaum, 2004), some found no relationship between sAA levels and plasma epinephrine and norepinephrine levels (Nater et al., 2006). Overall, despite the controversy sAA is thought to be an appropriate NA activation marker and is thus widely used in stress research, including the research presented in this thesis.

Cortisol concentrations can be measured in blood, urine or saliva. Of these three, saliva sampling may be the most practical of the three due to ease of measurement. An important thing to consider in psychobiological research is that the relationship between salivary and serum cortisol levels do not have a linear relationship in response to challenge (Hellhammer, Wüst, & Kudielka, 2009).

Both increases in NA and CORT follow distinct temporal profiles with NA increasing rapidly but the increase is short lived, while CORT reaches its peak concentrations later but remains high much longer. To capture this intricate temporal dynamic repeated measurements throughout the experiment are required. These can be best achieved using quick and non-invasive methods such as saliva sampling.

Though both subjective feelings of stress and biological changes can be measured, not all experimental manipulations affect both. For instance, pharmacological manipulations of CORT and NA often do not elicit the same subjective stress response as stressors such as the TSST or SECPT. Specifically considering yohimbine and hydrocortisone administration, while the former has been associated with feelings of anxiety and has even been shown to

lead to panic attacks in some people (Charney, Woods, Goodman, & Heninger, 1987), the latter usually does not lead to increased feelings of stress. These results highlight the importance of thorough manipulation checks not only including subjective but also objective physiological measures.

Although the methods above are appropriate for measuring hormonal reactions to acute stressors, measuring cortisol may also be required for other purposes. For instance, long term exposure to cortisol may need to be assessed in connection with a number of disorders such as Cushing syndrome, metabolic syndrome and several psychiatric disorders such as PTSD and depression. Alongside existing measures such as cortisol awakening response (Wilhelm, Born, Kudielka, Schlotz, & Wüst, 2007) and diurnal profiling of cortisol levels, a new and promising method has emerged in recent years for this purpose. Evidence suggests, that scalp hair analysis may result in a reliable and accurate measure of long-term cortisol exposure, which may even be superior to existing methods, as it is less susceptible to day-to-day and situational variability than existing profiling methods from urine, blood or saliva samples (Manenschijn, Koper, Lamberts, & van Rossum, 2011; Sauve, Koren, Walsh, Tokmakejian, & Van Uum, 2007; Stalder & Kirschbaum, 2012).

One particular case where long-term cortisol exposure has attracted much research interest is chronic stress, which will be the topic of the next section.

Chronic stress

Although the present dissertation is focused on the effects of acute stress on our decision making, it is important to briefly discuss the concept of chronic stress, as the two are closely related and chronic stress can come about as a result of recurrent exposure to periods of acute stress. So far I have described in detail what biological changes take place in our bodies when we encounter an acute stressor. Accordingly, it should by now be clear to the reader that a

temporary activation of the HPA-Axis is almost always a basic feature of the acute stress response. Though the physiological and behavioral response to stress is generally viewed as favorable, e.g., because it facilitates behaviors that help coping with the stressor, frequent activation of the stress system is problematic as it can wreak havoc on our bodies and wellbeing. Our reaction to acute stress developed during evolution to help us deal with infrequent threats of a primarily physical nature (Jones & Bright, 2001). However, our chronically stressful modern lives require our stress systems to become active much more often than it had originally been intended by evolution (Jones & Bright, 2001). As a result, chronic stress results in the dysregulation of the HPA-Axis, long term changes in cortisol levels and associated adverse health effects. Intuitively one would assume that chronic exposure to stressors would likely result in hypercortisolism (Kirschbaum et al., 1995; Schaeffer & Baum, 1984). However, it has now become evident that stress related disorders can also lead to hypocortisolism (Heim, Ehlert, & Hellhammer, 2000). This latter hypothesis has its roots in research on posttraumatic stress disorder (PTSD), which has been reliably associated with decreased cortisol levels (Yehuda, 2001), but now evidence exists that hypocortisolism is also a common feature in chronically stressed individuals such as parents of terminally ill children (Miller, Cohen, & Ritchey, 2002) and victims of domestic violence (Seedat, Stein, Kennedy, & Hauger, 2003).

To reconcile the discrepancies in research findings on cortisol levels and chronic stress Miller, Chen, & Zhou (2007) published a meta-analysis to investigate what factors determine whether chronic stress leads to decreases or increases in HPA-activity. The authors proposed that the nature of the stressor and characteristics of the person exposed to it are essential determining factors. Firstly, it was reported, that there is an inverse relationship between HPA activity and time since stress onset. In other words, the more time that passed since the stress first occurred, the lower an individual's cortisol measures including morning cortisol, daily

volume, adrenocorticotropic hormone (ACTH) and post-dextomethasone cortisol[3]. By contrast, when chronic stressors are still active in a person's life, levels of daily cortisol output are significantly higher. This finding is particularly intriguing, because it parallels the time-dependent characteristics of the acute stress response described in earlier sections. Accordingly, stress first activates the HPA-axis resulting in increased levels of cortisol, however after cessation of the stressor HPA activity sinks to below normal levels and can even stay that way for extended periods of time. This is similar to how acute stress results in quick, non-genomic cortisol effects that exert their influence in the immediate aftermath of stress, followed by genomic cortisol effects several hours later aimed at restoring homeostasis (Joels & Baram, 2009).

Research evidence also suggests that different types of stressors result in different HPA activity over time. In particular, traumatic events, physical stress and stress that is uncontrollable result in a high and flat diurnal rhythm characterized by lower than normal morning cortisol response followed by higher than normal secretion throughout the day. In contrast, stressors threatening the social self, such as divorce or stressors that are potentially controllable present with higher than normal cortisol levels throughout the day. Though intriguing, these results are only preliminary, as in many cases different types of stressors overlap. Therefore, more systematic research and longitudinal designs are needed to solidify these findings. Miller et al. (2007) also found evidence showing that emotions elicited by stress determine how they impact the HPA axis. More specifically, situations that elicit the feelings of shame were associated with higher cortisol levels later in the day, whereas feelings of loss elicited a flattened diurnal pattern. A further, robust finding presented was related to double dissociation between depression and PTSD in connection with chronic stress. Notably, individuals who developed major depression in connection with chronic stress had significantly higher cortisol after the dexamethasone suppression test than individuals under

[3] The dextomethasone suppression test is a widely used method to test adrenal gland function and cortisol levels

chronic stress without depression. In contrast, individuals under chronic stress who also suffer from PTSD showed the opposite pattern of results, namely significantly lower levels of cortisol (both following dexamethasone suppression test and lower daily output of cortisol) than chronic stress sufferers without PTSD.

Overall, findings related to chronic stress further highlight the intricate nature of how our bodies react to adversity. Understanding both acute, as well as chronic stress is essential as both have pronounced and often negative effects on our lives. Chronic stress is known to result in a multitude of health problems, including damaged immunity, obesity, bone tissue disorders, and psychiatric conditions such as major depression or chronic anxiety among others (McEwen, 2004). The acute stress response is thought to be generally adaptive, but it is also known to alter our cognition and memory processes, and it may alter the way we think and cloud our judgement without our awareness. How stress changes our decisions and ability to reflect are the questions at the essence of the present thesis. In the following chapters I will demonstrate research showing that stress changes the way we view losses and gains, alters our attitude towards others and impairs our ability to override impulsive errors in simple reasoning tasks.

CONFIRMATION OF CONTRIBUTION

Chapters 2 – 5 of the dissertation feature manuscripts that had been published in peer reviewed scientific journals, where I acted as first or shared first author. In each publication I had significant roles in planning the experiments, supervising and carrying out data collection, undertaking statistical analyses as well as writing the manuscript.

The contribution I made to these manuscripts is also confirmed by my supervisor Marijn van Wingerden indicated by his statement and signature:

I, Marijn van Wingerden, confirm that Zsofia Margittai contributed to the manuscripts featured in this dissertation as detailed above.

Düsseldorf,

_____

Marijn van Wingerden

A complete list of the manuscripts, which have been copied from their published versions are as follows:

Chapter 2:

Margittai, Z., Nave, G., Van Wingerden, M., Schnitzler, A., Schwabe, L., & Kalenscher, T. (2018). Combined Effects of Glucocorticoid and Noradrenergic Activity on Loss Aversion. *Neuropsychopharmacology*, *43*(2), 334–341.

Chapter 3:

Margittai, Z., Nave, G., Strombach, T., van Wingerden, M., Schwabe, L., & T, K. (2016). Exogenous cortisol causes a shift from deliberative to intuitive thinking. *Psychoneuroendocrinology*, *64*, 131–135.

Chapter 4:

Margittai, Z., Strombach, T., van Wingerden, M., Joëls, M., Schwabe, L., & Kalenscher, T. (2015). A friend in need: Time-dependent effects of stress on social discounting in men. *Hormones and Behavior*, *73*, 75–82.

Chapter 5:

Margittai, Z., van Wingerden, M Schnitzler, A., Joëls, M., & Kalenscher, T. (2018). Dissociable roles of glucocorticoid and noradrenergic activation on social discounting. *Psychoneuroendocrinology*, *90*, 22–28.

CHAPTER 2

Combined Effects of Glucocorticoid and Noradrenergic Activity on Loss Aversion

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Combined Effects of Glucocorticoid and Noradrenergic Activity on Loss Aversion

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Loss aversion is a well-known behavioral regularity in financial decision making, describing humans' tendency to overweigh losses compared to gains of the same amount. Recent research indicates that stress and associated hormonal changes affect loss aversion, yet the underlying neuroendocrine mechanisms are still poorly understood. Here, we investigated the causal influence of two major stress neuromodulators, cortisol and noradrenaline, on loss aversion during financial decision making. In a double-blind, placebo-controlled between-subject design, we orally administered either the α2-adrenergic antagonist yohimbine (increasing noradrenergic stimulation), hydrocortisone, both substances, or a placebo to healthy young men. We tested the treatments' influence on a financial decision-making task measuring loss aversion and risk attitude. We found that both drugs combined, relative to either drug by itself, reduced loss aversion in the absence of an effect on risk attitude or choice consistency. Our data suggest that concurrent glucocorticoid and noradrenergic activity prompts an alignment of reward- with loss-sensitivity, and thus diminishes loss aversion. Our results have implications for the understanding of the susceptibility to biases in decision making.
Neuropsychopharmacology (2018) **43,** 334–341; doi:10.1038/npp.2017.75; published online 10 May 2017

INTRODUCTION

Most people would prefer to avoid losing 5 EUR than to win 5 EUR. This phenomenon is called loss aversion, a well-known behavioral regularity in financial decision making, describing humans' tendency to overweigh losses compared to gains of the same amounts (Kahneman and Tversky, 1979). Accumulating evidence suggests that stress has an impact on loss aversion (Porcelli and Delgado, 2009; Putman *et al*, 2010; Takahashi *et al*, 2012; Pabst *et al*, 2013a; Chumbley *et al*, 2014; Sokol-Hessner *et al*, 2015), however, there is fundamental disagreement on the direction of the effects, and the underlying neuroendocrine mechanisms are largely unknown.

Organisms respond to acute stress with a rapid release of noradrenaline (NA) through the sympathetic nervous system and a slower release of glucocorticoids (mainly cortisol (CORT) in humans) as the end-product of the hypothalamic–pituitary–adrenal axis. The effects of CORT and NA on brain function shape cognition and behavior in a concerted, time-dependent fashion (Joels and Baram, 2009; Joëls *et al*, 2011; Schwabe *et al*, 2012), characterized by overlapping, non-genomic cortisol and catecholaminergic action shortly after stress onset, followed by genomic cortisol effects that develop several hours later and can have opposite effects on brain function to those in the immediate aftermath of stress (Hermans *et al*, 2014).

In the present experiment, we contrast two competing hypotheses on how CORT and NA influence loss aversion. Recent findings on the effect of stress hormone action on cognition and decision-making suggest that stress prompts the upregulation of a salience network in the brain, including insula, amygdala, and other limbic regions, while simultaneously suppressing higher cognitive prefrontal control networks (Hermans *et al*, 2011, 2014; Schwabe *et al*, 2012; Margittai *et al*, 2016), resulting in hypervigilance to potential losses. Activation of the salience network is boosted by catecholamines, such as noradrenaline, whose effects are further enhanced when combined with glucocorticoids such as cortisol (van Stegeren *et al*, 2008, 2010; Hermans *et al*, 2011, 2014). Importantly, two key regions of the salience network, the amygdala (De Martino *et al*, 2010; Sokol-Hessner *et al*, 2013; Gelskov *et al*, 2015), and insula (Canessa *et al*, 2013; Markett *et al*, 2016), have been associated with loss aversion, likely by mediating attention to potential losses. On the basis of this presumption, the 'salience of losses' hypothesis postulates that combined action of the stress-neuromodulators NA and CORT should amplify loss aversion by boosting loss-related neural

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functioning, and thus enhancing the salience of potential losses.

By contrast, CORT and NA are also known to impact reward processing (Pruessner *et al*, 2003; Starcke and Brand, 2012). For example, Mather and Lighthall (2012) proposed that stress can increase the salience of rewards, and enhance learning about positive choice outcomes while impairing learning about negative outcomes. In line with this presumption, several studies have reported that acute stress leads to increased reward sensitivity (Sinha, 2008; van den Bos *et al*, 2009; Putman *et al*, 2010) and decreased loss sensitivity in risky decision making (Pabst *et al*, 2013a, 2013b). In a recent meta-analysis, Starcke and Brand (2016) reported that stress affects decisions made under risk and ambiguity, particularly in situations where reward seeking is disadvantageous. Importantly, the direction of the stress effect on reward and loss sensitivity seems to depend on the concomitance of the stress-neuromodulators CORT and NA. While isolated exogenous administration of CORT (ie, in the absence of elevated NA) has been shown to reduce reward sensitivity and neural activation in reward-related regions (Montoya *et al*, 2014; Kinner *et al*, 2016), concurrent CORT and NA action is associated with enhanced reward sensitivity and ventral striatal activation, particularly at higher levels of cortisol elevations (Oei *et al*, 2014), as well as reduced anxiety and vigilance to threat (Vasa *et al*, 2009). On the basis of these findings the 'alignment hypothesis' suggests that when CORT and NA act concurrently, CORT may offset NA-induced vigilance to threats by amplifying reward sensitivity, presumably by stimulating dopaminergic release in the midbrain mesolimbic reward pathway, in particular the nucleus accumbens (Piazza and Moal, 1997; Marinelli and Piazza, 2002; Oei *et al*, 2014). Hence, the alignment hypothesis predicts that combined CORT and NA action results in an alignment of reward- with threat-susceptibility and, thus, ultimately, diminished loss aversion.

No study to date has delineated whether stress neuromodulators increase the salience of expected losses, as conjectured by the salience-of-losses hypothesis, or prompt an alignment of reward- with loss-sensitivity, as hypothesized by the alignment hypothesis. Importantly, these two theories make opposing predictions regarding the effects of stress neuromodulators on loss aversion. While the salience-of-losses hypothesis predicts linear, additive effects of CORT and NA on loss sensitivity, resulting in increased loss aversion, the alignment hypothesis predicts that CORT and NA in concert diminish loss aversion relative to either neuromodulator alone. To contrast these theoretical predictions, we pharmacologically manipulated CORT and NA in a double-blind, placebo-controlled experimental design and probed their combined and isolated causal effects on loss aversion.

MATERIALS AND METHODS

Participants

Ninety-two healthy, male participants took part in the experiment after prior eligibility screening. Individuals who reported the use of medication, psychiatric or medical treatment, acute or chronic illness, heavy smoking, drinking, regular drug use, or enrollment in Economics or Psychology study programs were excluded from participation. All participants were fluent German speakers, gave their informed consent and received financial compensation for their participation. The study was carried out in line with the Declaration of Helsinki and was approved by the medical ethics committee of the University Hospital Düsseldorf. Participants were asked to refrain from sexual activities 24 h before participation, not to smoke, eat, and drink anything other than water, and to avoid

Table 1 Demographic and Trait Control Measures

	Placebo	Yohimbine	Cortisol	YohCort	F (YOH)	*p*	F (CORT)	*p*	F (YOHCORT)	*p*
	M (SD)	*M* (SD)	*M* (SD)	*M* (SD)						
Age	26.62 (7.24)	22.85 (3.00)	25 (5.89)	24.29 (8.96)	2.40	0.125	0.004	0.950	1.12	0.294
BMI	22.96 (2.50)	22.62 (2.10)	22.90 (2.13)	22.96 (2.40)	0.08	0.773	0.08	0.774	0.17	0.680
Baseline cortisol	15.57 (13.90)	14.42 (9.31)	12.51 (6.39)	14.41 (8.65)	0.03	0.856	0.54	0.466	0.53	0.469
Baseline sAA	49.31 (25.50)	63.67 (64.11)	69.56 (84.11)	49.70 (40.46)	0.05	0.827	0.06	0.802	1.87	0.175
Baseline VAS	17.57 (15.96)	11.95 (12.33)	14.56 (12.50)	12.43 (13.89)	1.76	0.189	0.19	0.667	0.36	0.552
STAI	41.41 (11.29)	37.10 (6.04)	36.17 (9.84)	38.00 (9.25)	0.39	0.536	1.19	0.279	2.37	0.127
Empathy (SPF)	41.55 (6.13)	42.10 (7.46)	41.54 (4.27)	41.39 (6.78)	0.02	0.879	0.07	0.788	0.07	0.790
BIS-15	32.41 (7.93)	31.60 (4.75)	31.92 (6.84)	32.30 (5.64)	0.02	0.878	0.01	0.938	0.19	0.663
BIS	20.00 (4.42)	18.45 (3.72)	18.00 (3.19)	19.17 (3.46)	0.06	0.812	0.66	0.421	2.98	0.088
BAS	41.32 (4.02)	42.55 (4.01)	43.00 (3.84)	41.17 (4.64)	0.11	0.736	0.03	0.862	3.02	0.086
SDS-17	9.82 (3.67)	9.75 (2.99)	9.75 (2.91)	9.48 (2.83)	0.07	0.798	0.07	0.798	0.02	0.878
Risk taking	4.32 (0.72)	3.95 (1.10)	4.25 (1.03)	4.04 (1.36)	1.57	0.214	0.00	0.956	0.124	0.726
Chronotype	12.14 (3.52)	12.00 (3.32)	11.88 (3.15)	11.78 (3.68)	0.02	0.875	0.11	0.743	0.00	0.976

Abbreviations: BAS, Behavioral Approach Scale; BIS-15, Short version of the Barratt Impulsiveness Scale; BIS, Behavioral Inhibition Scale; BMI, body mass index; F (CORT), main effect of hydrocortisone; F (YOHCORT), yohimbine × hydrocortisone interaction; F (YOH), main effect of yohimbine; sAA, salivary alpha amylase; SDS-17, Social Desirability Scale; SPF, Saarbrücker Persönlichkeitsfragebogen (German version of the Interpersonal Reactivity Index); STAI, State Trait Anxiety Inventory; VAS, visual analog scale.

exercising 2 h before the experiment. These criteria were similar to those employed in prior studies, (eg Vinkers *et al*, 2013). Two participants were unable to complete the experimental tasks due to technical failure and were thus excluded from all analyses. One further participant was excluded because he exclusively selected the gamble option on all trials, irrespective of the payoff and risk contingencies. We used an exclusively male sample in order to avoid differential HPA-axis activation caused by the intake of oral contraceptives and variations in menstrual cycle (Kirschbaum *et al*, 1999). See Table 1 for demographic measures.

Trait Measures

In order to control for potential trait confounds between treatment groups, participants completed a number of online questionnaires several days before testing. We recorded trait anxiety (State Trait Anxiety Inventory-STAI, Spielberger *et al*, 1983), impulsivity (Barratt Impulsiveness Scale—BIS-15; Meule *et al*, 2011), reward and punishment sensitivity (BIS/BAS scale; Carver and White, 1994), social desirability (SDS-17; Ströber, 2001), general willingness to take risks, chronotype (short version of the Morningness-Eveningness Questionnaire; Randler, 2013), and empathy (Saarbrücker Persönlichkeitsfragebogen, Paulus, 2007, which is a German version of the Interpersonal Reactivity Index, Davis, 1980). See Table 1 for statistics.

Pharmacological Manipulation, Physiological and Subjective Stress Measures

In a double-blind, placebo-controlled experimental design, participants were randomly assigned to one of four experimental groups: (A) placebo ($N=24$), (B) placebo + yohimbine (20 mg, Cheplapharm, $N=21$), (C) placebo + hydrocortisone (20 mg, Jenapharm, $N=24$), (D) yohimbine + hydrocortisone (20 mg each, $N=23$). Dosage was in line with prior studies (Schwabe *et al*, 2010; van Stegeren *et al*, 2010). To assess the effectiveness of the treatment, saliva samples were collected at baseline and +30, +45, and +75 min after pill intake using Salivette devices (Sarstedt, Germany) and subsequently analyzed for cortisol and alpha-amylase (sAA, a marker of noradrenergic activity) concentrations. Samples were frozen and stored at −20 °C until analysis, and they were analyzed as reported by Rohleder *et al* (2004). In total, 15 of the 460 saliva samples used for analysis were compromised, missing data were excluded from the analysis. Subjective stress ratings were assessed using visual analog scales (VAS, 100 mm scale) at the same time points as the saliva samples.

Risk and Loss Aversion Task

The experimental task (Wang *et al*, 2010) was similar to that used by Sokol-Hessner *et al* (2009), Chumbley *et al* (2014) and Sokol-Hessner *et al* (2015). Participants made 40 binary choices between receiving amount (x) for sure and a lottery, where they had a 0.5 probability of either winning amount (y) or losing amount (z), Figure 1. The task used an adaptive design; thus, choice options were dynamically selected based on participants' prior answers, according to an informational criterion that optimized the estimation of individual

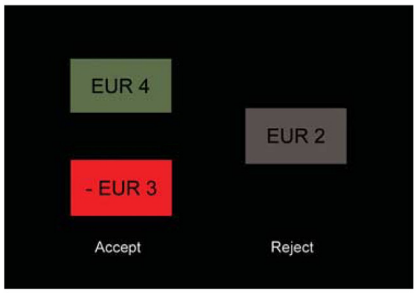

Figure 1 Example decision screen of the experimental task. Participants had to decide, whether they would like to gamble (in this example 50% chance of winning 4 Euros and 50% chance of losing 3 Euros), or choose the safe option (in this example, winning 2 Euros for sure).

parameters describing loss aversion (λ), and risk aversion (ρ). In line with Sokol-Hessner *et al* (2009, 2015), we used the prospect-theory (Kahneman and Tversky, 1979) inspired utility function $u(w+)=w^{\rho}$ to determine positive payoffs ($w+$), and $u(w-)=-\lambda(w)^{\rho}$ to determine negative payoffs ($w-$). Next, we fitted a softmax function (equation 1) to the data, such that the probability of choosing the risky lottery for a given utility function was:

$$p(\text{lottery}|\rho,\lambda,\mu)=\frac{1}{1+e^{-\mu\left(\frac{1}{2}u(x)+\frac{1}{2}u(z)-u(y)\right)}} \quad (1)$$

where the nuisance parameter (μ) assesses consistency in choice behavior. Note that $\lambda>1$ indicate loss aversion, $\lambda<1$ indicate loss seeking and $\lambda=1$ indicates loss neutrality. $\rho>1$ indicate risk aversion, $\rho<1$ indicate risk seeking and $\rho=1$ indicates risk neutrality. We log-transformed λ values for all analyses, a common approach (Sokol-Hessner *et al*, 2015) because the distribution of λ is positively skewed. The experiment was incentive compatible: upon completion of the session one of participants' choices was chosen at random, played, and paid out. Participants were aware of this before the commencement of the task.

Procedure

All experimental sessions took place in the afternoon between 14:00 and 18:00 hours in order to control for diurnal variations of cortisol levels. Upon arrival at the laboratory, participants were asked to give their informed consent and complete a number of baseline measures (Table 1). Thereafter participants consumed the drugs. After a waiting period of 45 min (Schwabe *et al*, 2010) participants were asked to start with the experimental tasks. The experiment included three separate tasks in a counter-balanced order: the present task and two unrelated tasks that were reported elsewhere (Margittai *et al*, 2016). The total duration of the three tasks was ~20 min.

Analyses of Trait and Baseline Measures, Pharmacological Manipulation Check and Analysis of Loss- and Risk Aversion Parameters

We analyzed trait and baseline measures using univariate analyses of variance (ANOVA) with the between-subject

factors noradrenergic activation (yohimbine *vs* placebo), and cortisol administration (hydrocortisone *vs* placebo). Analyses of the loss- and risk-aversion parameters were performed in a similar fashion.

As a confirmation of our pharmacological manipulation, we analyzed baseline-corrected changes in salivary cortisol and salivary alpha-amylase- and baseline-corrected changes in subjective feelings of stress using mixed ANOVAs (between-subject factor: noradrenergic activation (yohimbine *vs* placebo) and cortisol administration (hydrocortisone *vs* placebo), within subject factor: time point of measurement.

RESULTS

Trait and Baseline Measures

Our analyses showed no significant differences in baseline, demographic or trait measures between the groups (Table 1).

Manipulation Check

Salivary cortisol and alpha amylase. Salivary cortisol significantly increased in participants taking hydrocortisone; main effect of hydrocortisone on salivary cortisol: $F_{1,\ 78} = 100.24$, $p < 0.001$, $\eta_p^2 = 0.56$; time point × hydrocortisone interaction $F_{1.15,89.83} = 12.44$, $p < 0.001$, $\eta_p^2 = 0.14$. There was no significant effect of yohimbine on salivary cortisol ($F_{1,78} = 0.60$, $p = 0.440$, $\eta_p^2 = 0.01$) nor a cortisol × yohimbine interaction ($F_{1,78} = 0.42$, $p = 0.520$, $\eta_p^2 = 0.01$), indicating that yohimbine did not alter cortisol levels, Figure 2a. Conversely, sAA increased significantly after taking yohimbine: $F_{1,\ 83} = 16.84$, $p < 0.001$, $\eta_p^2 = 0.17$, time point × yohimbine interaction ($F_{1.52,126.14} = 4.68$, $p = 0.018$, $\eta_p^2 = 0.05$), but not after taking hydrocortisone: ($F_{1,83} = 0.14$, $p = 0.710$, $\eta_p^2 = 0.002$). There was no hydrocortisone × yohimbine interaction on sAA levels ($F_{1,83} = 0.06$, $p = 0.815$, $\eta_p^2 = 0.001$), indicating that hydrocortisone did not alter sAA levels, Figure 2b.

Subjective Stress Ratings

Baseline-corrected changes in subjective feelings of stress increased in participants who received yohimbine (main effect of yohimbine: $F_{1,85} = 5.75$, $p = 0.019$, $\eta_p^2 = 0.06$), in line with prior research (eg, Elman *et al*, 2012), but not in those who received cortisol (main effect of hydrocortisone: $F_{1,85} = 0.27$, $p = 0.61$, $\eta_p^2 = 0.003$). There was no interaction between the two substances on subjective feelings of stress, nor a time point × hydrocortisone interaction, nor a three way interaction between yohimbine, hydrocortisone, and time point of testing ($p > 0.141$). This is in line with existing results indicating that cortisol administration does not usually result in changes in subjective affect or mood (Schwabe *et al*, 2010, 2012).

Hydrocortisone and Yohimbine Jointly Reduce Loss Aversion but do not Affect Risk Attitude

To assess the influence of cortisol and noradrenaline on loss aversion and risk attitude, we analyzed individual loss aversion and risk attitude parameters using a 2 × 2 between-subjects ANOVA with the factors noradrenergic activation (yohimbine *vs* placebo) and cortisol administration (hydrocortisone *vs* placebo). This analysis revealed a significant interaction effect of noradrenergic and cortisol activation on the loss aversion parameter $\log(\lambda)$, ($F_{1,85} = 6.37$, $p = 0.013$, $\eta_p^2 = 0.07$, Figure 3b). Breaking down this interaction effect, an independent samples *t*-test revealed that hydrocortisone significantly reduced $\log(\lambda)$, but only when accompanied by yohimbine intake ($t(45) = 2.46$, $p = 0.018$, $d = 0.73$; Bonferroni–Holm corrected), and yohimbine decreased $\log(\lambda)$ depending on hydrocortisone availability ($t(41) = 2.35$, $p = 0.023$, $d = 0.76$; Bonferroni–Holm corrected, Figure 3b). Finally, loss aversion in individuals who received both drugs was significantly lower compared to all other participants ($t(87) = 2.41$, $p = 0.018$, $d = 0.34$). A similar analysis with the risk aversion parameter ρ or the consistency parameter μ as

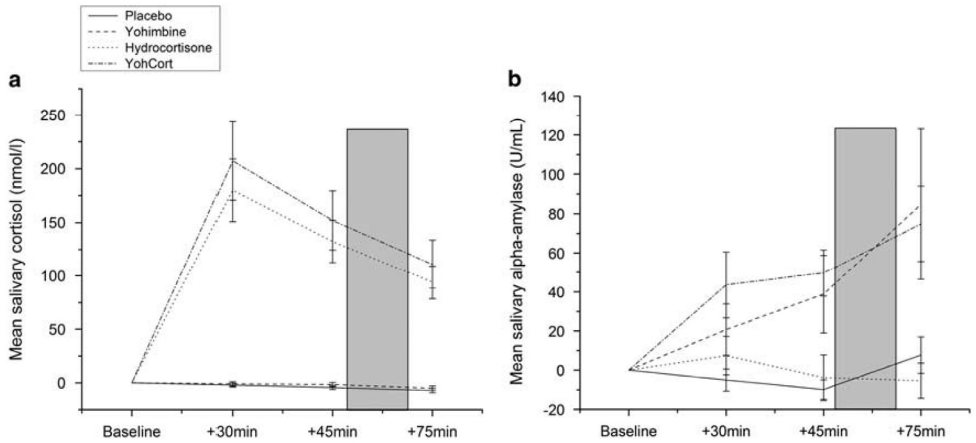

Figure 2 Baseline corrected increases in salivary cortisol and alpha amylase. (a) Salivary cortisol increased significantly ($p < 0.001$) over time after taking hydrocortisone in the hydrocortisone and yohimbine+cortisol (yohcort) groups. (b) Salivary alpha amylase also increased significantly ($p < 0.05$) over time after taking yohimbine in the yohimbine and yohcort groups. The gray bars indicate the time of behavioral testing. Error bars indicate ± 1 SEM.

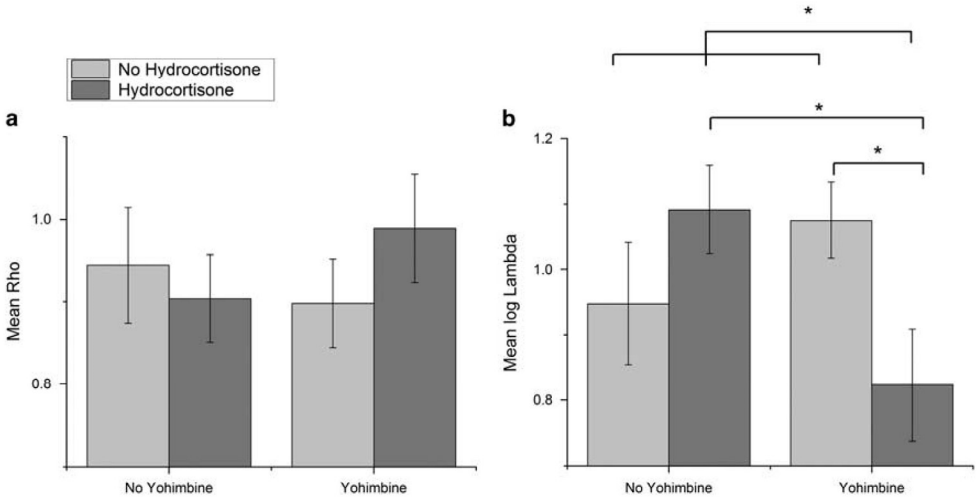

Figure 3 (a) Risk aversion parameters were not affected by the pharmacological manipulation. (b) The effects of hydrocortisone and yohimbine on loss aversion. Individuals who received yohimbine and hydrocortisone had reduced loss aversion compared to those who received either substance alone. Loss aversion in the yohimbine+hydrocortisone group was also lower compared with all other participants. Significant effects ($p < 0.05$) are indicated by an asterisk. Error bars indicate ± 1 SEM.

the dependent variables revealed no significant main or interaction effects of drugs (all $p > 0.286$, Figure 3a).

Treatment Expectancy

Following the experimental tasks, we asked participants to indicate whether they believed to have received placebo or an active substance during the experiment. The number of participants who believed to have been given placebo *vs* active substances did not significantly differ between the four treatment conditions ($\chi^2(3,\ N=89)=6.63,\ p=0.085$). To further rule out expectancy effects, a point biserial correlation revealed no significant relationship between belief about treatment (placebo *vs* active substance) and the loss aversion parameter ($r=-0.11,\ p=0.298$). Thus, belief about treatment is unlikely to have interfered with the results.

DISCUSSION

Stress is known to alter loss aversion (Porcelli and Delgado, 2009; Takahashi *et al*, 2012; Pabst *et al*, 2013a, 2013b; Chumbley *et al*, 2014), but the underlying neuroendocrine mechanisms have remained elusive so far. Here, we examined the causal effects of the exogenous manipulation of two stress neuromodulators, CORT, and NA, on loss aversion. We found that cortisol combined with noradrenergic stimulation diminished loss aversion relative to the action of either drug alone. By contrast, we found no drug effects on risk attitude or choice consistency measured in the same financial decision-making paradigm.

Our study provides evidence for a putative neuroendocrine mechanism underlying loss aversion. Our results are in disagreement with the predictions of the salience-of-losses theory according to which NA and CORT have additive effects on the salience of anticipated punishment and losses (Gullo and Stieger, 2011), and thus loss aversion. By contrast, our data support the alignment hypothesis according to which the combined action of NA and CORT decreases loss aversion, presumably through the alignment of reward- to punishment-susceptibility associated with the upregulation of reward-sensitivity (Piazza and Moal, 1997; Marinelli and Piazza, 2002; Oei *et al*, 2014). This conclusion is in line with a recent neuroimaging study showing that elevated cortisol was associated with increased activity in reward-processing regions such as the nucleus accumbens after behaviorally induced stress (Oei *et al*, 2014).

Through the systematic manipulation of both NA and CORT, which allowed us to disentangle the isolated and combined effects of these two stress neuromodulators on loss aversion, we were able to demonstrate that NA and CORT in concert, but not in isolation, prompt an alignment of reward- and punishment-sensitivity. Thus, our results contribute to resolving contradictions in previous results regarding the direction of the stress effect on loss aversion, and its precise neuroendocrine foundation, and hopes to pave the way towards a unified theory on the neuroendocrine mechanisms underlying decision making under risk.

While some studies (Putman *et al*, 2010; Takahashi *et al*, 2012; Chumbley *et al*, 2014; Sokol-Hessner *et al*, 2015) reported stress or stress neuromodulator action to be negatively correlated with loss aversion, others found a positive relationship (Rogers *et al*, 2004; Porcelli and Delgado, 2009; Sokol-Hessner *et al*, 2009). In addition, one study by Sokol-Hessner *et al* (2016) found no effects of the cold-pressor task on loss aversion. These studies either correlated arousal—an indirect manifestation of sympathetic activity—with loss aversion (Sokol-Hessner *et al*, 2009, 2013), reduced NA-activity via exogenous administration of beta-blockers (Rogers *et al*, 2004; Sokol-Hessner *et al*, 2015), correlated endogenous measures of long term CORT exposure (extracted from hair cells) with loss aversion

(Chumbley *et al*, 2014), or administered only CORT (Putman *et al*, 2010).

Overall, while all of the aforementioned studies focused on either CORT or NA alone, none of them controlled for the respective other stress neuromodulator, or systematically explored the interplay of NA and CORT on loss aversion. Consequently, given the neurohormonal interplay reported here, the influences of one hormone on loss aversion was likely modulated by the uncontrolled action of the other hormone, resulting in heterogeneous findings. In addition, procedural differences are also likely to account for some of the disparity between existing findings. More specifically, while some studies used a behavioral stress induction, eg, Porcelli and Delgado, 2009; Pabst *et al*, 2013a, 2013b; Sokol-Hessner *et al*, 2016, our primary focus was a pharmacological manipulation to investigate the causal effects of the two main stress mediators on loss aversion. The effects are thus not directly comparable, as pharmacological manipulations, such as the one used in the present experiment, have some differences from naturally occurring stress. For instance, they tend to result in supraphysiological levels of the neuromodulators compared to natural stress (Lupien *et al*, 1999), and do not bring about the affective response to threat in the same way that naturally occurring stress usually does. This point is important to keep in mind, as it has been reported in prior research that low elevations in cortisol may have a different, even opposite, effect on reward-sensitivity (Oei *et al*, 2014) than higher elevations. However, an advantage of a pharmacological design is that allows for precise, causal conclusions about the effects of cortisol and noradrenaline on behavior.

In line with the above, a review published by Porcelli and Delgado, 2017 also emphasizes the wide array of methodological and theoretical differences present in existing research that pose a challenge for the comparison of findings. In addition to not controlling systematically for both neuromodulators, the different stress induction procedures are likely to result in different elevations in neuromodulator levels, and the timing of the behavioral tasks in relation to stress onset may also explain some of the disparity between findings (Pabst *et al*, 2013b; Starcke and Brand, 2016).

Whereas our findings showed a striking interactive effect of our cortisol and noradrenergic action on loss aversion, the stress neuromodulator manipulation did not affect risk aversion (ρ). This is consistent with other reports (Chumbley *et al*, 2014; Sokol-Hessner *et al*, 2015), but in contrast to some prior findings that have shown that stress hormone actions, particularly cortisol, go along with sensitivity to risk (Coates and Herbert, 2008; Starcke and Brand, 2012; Kandasamy *et al*, 2014). However, while our task allowed disentangling loss from risk aversion and choice consistency (by using a prospect theory-driven adaptive design that maximized the information gained from each decision; Chumbley *et al*, 2014), other studies did not conceptually discriminate between these parameters with the same theoretical rigor. Our results replicate those of Chumbley *et al* (2014) and Sokol-Hessner *et al* (2015), who used the same task and structural model, and also found no relationship between endocrine stress markers and risk attitude, or choice consistency. These results suggest that stress-related neuromodulatory action might not have a general effect on risk attitude, but only on risky choices in which losses and gains are involved.

One limitation of our study is that we included only male participants in order to avoid an influence of hormonal variations due to the use of oral contraceptives or menstrual cycle phase that have been shown to affect cognition (Mather and Lighthall, 2012). There is evidence that males and females behave differently in economic decision making under stress (Croson and Gneezy, 2009). For example, women have been shown to become more risk averse and men more risk seeking under stress (Lighthall *et al*, 2009), and stress impacts reward-related decision processes differently for the two genders (Lighthall *et al*, 2012). Women have also shown to be more loss averse than men in certain situations (Rau, 2014). Future research should therefore investigate whether the results reported here generalize across genders.

In summary, we independently manipulated CORT and NA activity to disentangle their isolated and combined causal effects on decision-making. This is a crucial feature of our design because the two neuromodulators in combination affect cognition differently than they do in isolation (Joels and Baram, 2009; van Stegeren *et al*, 2010; Joëls *et al*, 2011; Schwabe *et al*, 2012; Vinkers *et al*, 2013). Our main finding, that combined action of CORT and NA diminished loss aversion relative to the action of either neuromodulator alone substantiates the body of research, and extends these findings to decision-making under risk. Further, our behavioral task allows disentangling loss aversion from risk attitude and choice consistency, while maximizing the informational gain from each participants' decision, and thus reducing measurement noise. An interesting expansion of the current findings would be to investigate the underlying neural activation during the decision making tasks using fMRI.

Our findings highlight the effect of combined NA and CORT action on loss aversion, and thus provide further insight into how acute stress, associated with concurrent NA and CORT activity, may lead to poor decision making. Increased hypersensitivity to reward paired with reduced sensitivity to punishment may result in heightened susceptibility to substance abuse (Lovallo, 2008). Thus, our findings have particular relevance to vulnerable populations such as drug users, problem gamblers, and other individuals suffering from addiction.

FUNDING AND DISCLOSURE

AS has been serving as a consultant for Medtronic Inc, Boston Scientific, St. Jude Medical, Grünenthal and has received lecture fees from Abbvie, Boston Scientific, St. Jude Medical, Medtronic Inc, UCB, MEDA Pharma, Teva Pharma, and GlaxoSmithKline. AS is a government employee and receives through his institution funding for his research from the German Research Council, the German Ministry of Education and Health, and the Gossweiler Foundation. TK's and ZM's work has been funded by the Deutsche Forschungsgemeinschaft (German Research Council, DFG-KA 2675/4-1 to TK). MVN received funding from the Volkswagen Stiftung 'Freigeist' initiative, AZ: 88216. LS and GN have no funding sources to declare.

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CHAPTER 3

Exogenous cortisol causes a shift from deliberative to intuitive thinking

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Short communication

Exogenous cortisol causes a shift from deliberative to intuitive thinking

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ABSTRACT

People often rely on intuitive judgments at the expense of deliberate reasoning, but what determines the dominance of intuition over deliberation is not well understood. Here, we employed a psychopharmacological approach to unravel the role of two major endocrine stress mediators, cortisol and noradrenaline, in cognitive reasoning. Healthy participants received placebo, cortisol (hydrocortisone) and/or yohimbine, a drug that increases noradrenergic stimulation, before performing the cognitive reflection test (CRT). We found that cortisol impaired performance in the CRT by biasing responses toward intuitive, but incorrect answers. Elevated stimulation of the noradrenergic system, however, had no effect. We interpret our results in the context of the dual systems theory of judgment and decision making. We propose that cortisol causes a shift from deliberate, reflective cognition toward automatic, reflexive information processing.

1. Introduction

Have you ever jumped to an intuitive conclusion that later turned out to be wrong? If yes, the cognitive process you went through is well captured by the dual process theory, which has become a central framework in human judgment and decision-making research in recent decades (Kahneman, 2011). The dual system theory postulates the existence of two modes of information processing: one that is fast, intuitive and automatic, and another that is slow, analytical and reflective (Kahneman, 2011). As strong reliance on automatic processing is prone to cognitive biases and often leads to disadvantageous outcomes (Kahneman, 2011; Toplak et al., 2011), it is essential to determine which factors intensify its dominance. Here, we propose that endocrine stress markers tilt the balance of the two systems toward dominance of automatic processing.

Acute stress is characterized by parallel hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system activation, and elevated levels of neuromodulators cortisol (CORT) and noradrenaline (NA). Glucocorticoids (both externally administered and endogenous) are known to affect cognition by interfering with frontal-lobe-dependent functions, such as cognitive control, working memory, and selective attention and thereby weaken individuals' ability to discriminate between relevant and irrelevant information (al'Absi et al., 2002; Lupien and Mcewen, 1997; Lupien et al., 2007). The simultaneous action of exogenously administered NA and CORT has been shown to induce a shift from goal-directed toward habitual behavior (Schwabe et al., 2012), and evidence suggests that behaviorally induced stress alters decision making (Margittai et al., 2015; Starcke and Brand, 2012) for example by increasing susceptibility to decision biases (Porcelli and Delgado, 2009). Some of the reported findings are consistent with a stress-hormone induced bias toward automatic processing, however, such a causal link cannot be made without the employment of a task specifically designed to assess automatic versus deliberate processing, combined with a precise pharmacological manipulation of the two main stress neuromodulators.

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Using orally administered hydrocortisone and/or yohimbine (a drug that increases noradrenergic stimulation), we tested the extent to which endocrine stress markers impaired performance in the cognitive reflection task (CRT, Frederick, 2005), a well-established paradigm designed to quantify one's capacity to suppress intuitive, incorrect responses to simple arithmetic problems in favor of deliberate reasoning (Alter et al., 2007; Johnson et al., 2012; Pinillos et al., 2011; Toplak et al., 2011). CRT scores have been shown to predict performance in various areas of decision making and cognitive functioning (Campitelli and Labollita, 2010; Cokely and Kelley, 2009; Frederick, 2005; Hoppe and Kusterer, 2011; Liberali et al., 2012; Oechssler et al., 2009; Toplak et al., 2011).

Since increased levels of CORT and NA interfere with prefrontal functions responsible for cognitive control, required for deliberate reasoning, and upregulate limbic and subcortical mechanisms, such as amygdalar and striatal function, they are likely to increase dominance of automatic processes (Hermans et al., 2014). Based on these findings we expected that increased levels of stress modulators would impair performance on the CRT by causing a shift away from deliberate, toward intuitive thinking.

2. Method

2.1. Participants

Eighty-three men participated in this experiment (age: $M = 24.33$, SD = 5.94; see SOM for eligibility criteria, demographic and control measures. The four experimental groups did not differ in demographic and control measures, see SOM. We used an exclusively male sample in order to avoid differential HPA-axis activation caused by the intake of oral contraceptives and variations in menstrual cycle (Kirschbaum et al., 1999), thus our results are not generalizable to both genders and further research should be carried out in a female sample to be able to compare findings. Participants gave their informed consent. The experiment was approved by the medical ethics committee of the University Hospital Düsseldorf, and was carried out in line with the declaration of Helsinki.

2.2. Procedure

In a double-blind, placebo controlled between subjects design, participants were randomly assigned to one of four experimental groups: placebo ($N = 22$), placebo + yohimbine (an alpha2-adrenoreceptor blocker that stimulates noradrenergic activity; 20 mg, Chephlapharm, $N = 20$), placebo + hydrocortisone (cortisol agonist, 20 mg, Jenapharm, $N = 20$), or yohimbine + hydrocortisone (20 mg each, $N = 21$). After pill intake and a waiting period of 45 min (Schwabe et al., 2013a, 2012, 2010a), participants completed the CRT and two unrelated tasks (see SOM).

The CRT contains three short mathematical questions:

(1) A bat and a ball cost €1.10. The bat costs €1.00 more than the ball. How much does the ball cost?
(2) If it takes 5 machines 5 min to make 5 widgets, how long would it take 100 machines to make 100 widgets?
(3) In a lake, there is a patch of lily pads. Every day, the patch doubles in size. If it takes 48 days for the patch to cover the entire lake, how long would it take for the patch to cover half of the lake?

To take the example of the first question, the intuitive answer here is €.10, but the correct answer, requiring suppression of intuitive responding is €.05. Low CRT scores thus indicate increased difficulty in suppressing intuitive, incorrect answers.

2.3. Saliva sampling and further stress measures

Saliva samples were collected twice at baseline, from which an average was calculated as participants' baseline measure, and +30, +45 and +75 min after pill intake using Salivette devices (Sarstedt, Germany). Samples were frozen and stored at −20 °C until analysis for concentrations of salivary cortisol and alpha-amylase (a marker of noradrenergic activity) as reported by Rohleder et al. (2004). Values for unusable samples (8 out of 415) were replaced with the mean of the appropriate experimental group. Results remain significant even after exclusion of participants with one or more missing saliva samples ($N = 5$). Blood pressure was measured and subjective feelings of stress were assessed using visual analogue scales (VAS, 100 mm scale) at the same timepoints as the saliva samples.

3. Results

3.1. Manipulation check of the drug administration

Salivary cortisol increased after taking hydrocortisone, as shown by a mixed ANOVA (within-subject factor: timepoint, between-subjects factors: hydrocortisone (yes/no) and yohimbine (yes/no); main effect of hydrocortisone: $F_{1,79} = 103.85$, $p < .001$, $\eta^2 = .56$; timepoint x hydrocortisone interaction $F_{1.87,147.58} = 42.62$, $p < .001$, $\eta^2 = .26$). Yohimbine had no effect on cortisol levels, and the two substances showed no interaction ($p > .213$ Fig. 1A).

Salivary alpha-amylase concentrations were analyzed similarly, revealing increased levels in those participants who received yohimbine compared to those who did not (main effect of yohimbine: $F_{1,79} = 8.31$, $p = .005$, $\eta^2 = .095$; yohimbine x time interaction $F_{1.92,151.53} = 6.48$, $p = .002$, $\eta^2 = .067$). Hydrocortisone had no effect on alpha-amylase levels, nor was there an interaction between the two substances (both $p > .563$ Fig. 1B).

3.2. Blood pressure measures

We measured blood pressure using Sanitas SBC-41 wrist monitors at the same timepoints as the saliva samples. Due to device malfunction measures from one participant could not be obtained. Three separate mixed ANOVAs for the systolic, diastolic and pulse measures (using the same factors as detailed in the ANOVAs under saliva samples) revealed a main effect of timepoint on pulse ($F_{2.45,190.95} = 2.91$, $p = .046$, $\eta^2 = .017$), indicating that pulse increased somewhat in all groups over the course of the experiment, however neither pulse nor blood pressure were affected by either yohimbine or hydrocortisone (all $p > .106$).

3.3. Subjective feelings of stress

We measured participants' subjective feelings of stress using VAS scales at the same timepoints as the saliva samples and blood pressures. A mixed ANOVA with the same factors as reported above revealed significantly increased levels of subjective feelings of stress over time in those who received yohimbine (timepoint x yohimbine interaction: $F_{2.52,198.83} = 4.96$, $p = .004$, $\eta^2 = .060$). There was no effect of hydrocortisone manipulation, nor an interaction between the two substances on subjective feelings of stress (all $p > .130$), which is in line with reports indicating that cortisol administration often does not cause changes in subjective affect or mood (Putman and Roelofs, 2011).

3.4. Cortisol causes a shift from deliberate to intuitive thinking

To test how cortisol and noradrenaline actions impact cognitive reflection in isolation and by interaction, we employed a 2×2 ANOVA with hydrocortisone (yes/no) and yohimbine (yes/no) as

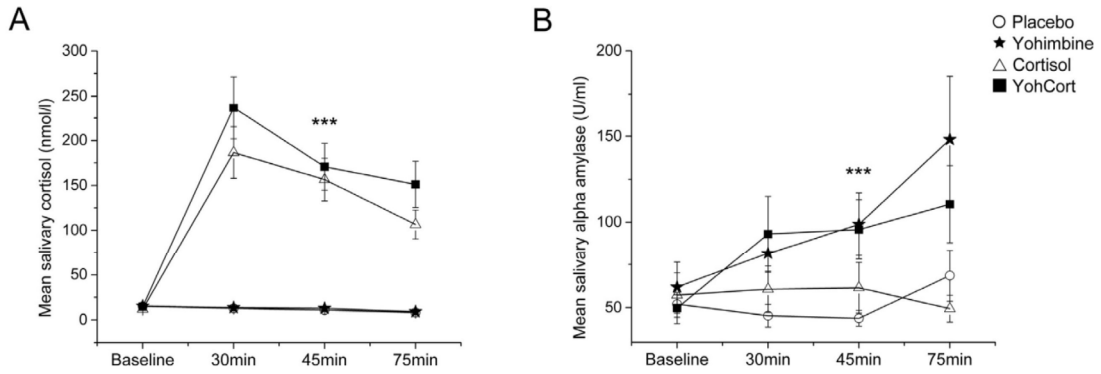

Fig. 1. Concentrations of salivary cortisol and alpha-amylase after hydrocortisone and yohimbine intake. The CRT task was performed between 45 and 75 min after pill intake. Error bars represent ±1 SE. (A) Participants taking hydrocortisone had significantly increased salivary cortisol concentrations after pill intake before the CRT task (***$p < .001$). (B) Salivary alpha-amylase levels significantly increased after yohimbine intake. (***$p = .005$).

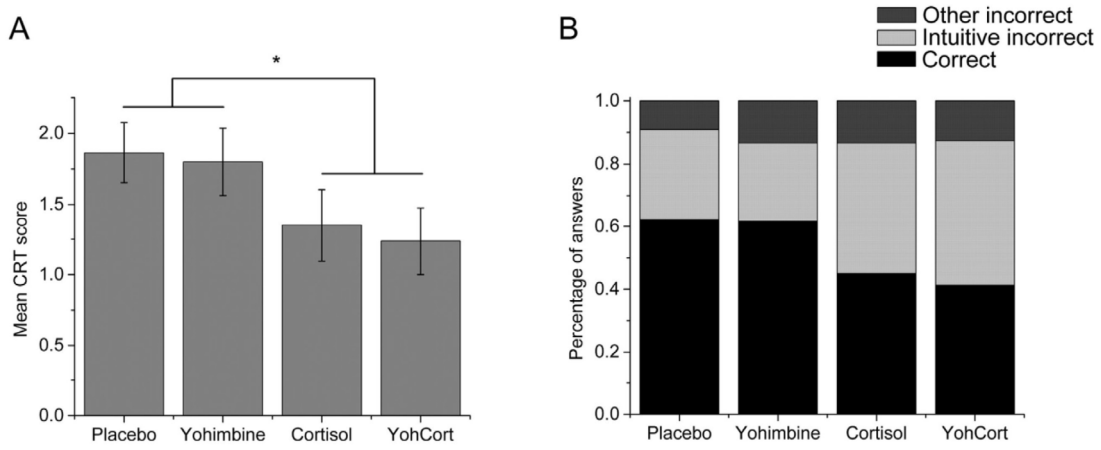

Fig. 2. CRT performance in the different treatment groups. (A) Individuals who received hydrocortisone showed decreased performance compared to those who did not (error bars represent ±1 SEM), *$p < .05$. (B) Percentage of correct, intuitive incorrect and other incorrect answers in the experimental groups.

between subject factors. This analysis revealed that individuals who received cortisol had significantly lower CRT scores than those who did not (main effect of hydrocortisone, $F_{1,79} = 5.25$, $p = .025$, $\eta^2 = .062$, Fig. 2A). There was neither a significant effect of yohimbine, nor a significant interaction between the two substances on CRT scores (both $p > .709$).

Moreover, participants who received cortisol showed decreased rates of correct (=deliberate) answers, paralleled by increased rates of intuitive incorrect answers ($\chi^2(1, N = 219) = 9.21$, $p = .002$), while the proportion of other incorrect replies did not differ between conditions ($Z = -.46$, $p = .65$). This demonstrates that cortisol affected the CRT by inducing a genuine shift from deliberative to intuitive thinking, rather than by simply making the problem solving process noisier (Fig. 2B).

3.5. Belief about treatment

After the experimental tasks we asked participants to indicate whether they believe to have received placebo or an active substance during the experiment. The number of participants who believed to have been given placebo versus active substances differed between the four treatment conditions on trend-level ($\chi^2(3, N = 83) = 5.48$, $p = .061$, Cramer's $V = .30$). However adding individuals' belief about the treatment as a covariate in our main analysis does not alter our findings (main effect of CORT on CRT scores: $F_{1,78} = 5.15$, $p = .026$, $\eta^2 = .062$).

4. Discussion

We demonstrated that pharmacologically elevated cortisol, but not noradrenaline, levels impaired performance in the CRT by increasing reliance on intuitive over deliberate judgments. We thus provide direct, causal evidence that cortisol is likely involved in setting the balance between automatic and deliberate thinking. Our findings provide two novel insights that delineate the effects of stress neuromodulators on human judgment and decision-making. First, we used a task that is specifically designed to test the engagement of intuitive versus deliberate reasoning, allowing us to make a direct conclusion about the involvement of the two information processing systems. This complements prior studies that used more complex decision making, reasoning and cognitive tasks (Porcelli and Delgado, 2009; Putman et al., 2010) which only allowed indirect conclusions about the involvement of automatic versus deliberate processing as an explanation for their findings. Second, by employing a direct, pharmacological manipulation we were able to provide causal conclusions about how endocrine stress mecha-

nisms influence cognition while excluding confounding factors that accompany paradigms in which stress is induced behaviorally, such as the element of social evaluation or physical pain (Dickerson and Kemeny, 2004; Porcelli and Delgado, 2009).

Stress-related increases in cortisol and noradrenergic action follow distinct temporal profiles: while cortisol in concert with noradrenaline synergistically and transiently modulate neural activity and cognition during an initial fast-acting wave of stress-neuromodulators, noradrenergic action wears out within minutes after stress onset, and the brain is mainly influenced by slower cortisol effects alone in the aftermath (Joëls et al., 2011; Schwabe et al., 2012). Our experimental design allows dissociating the functional difference of the combined and isolated effects of cortisol and noradrenaline on cognitive reflection. Our results suggest that deliberate thinking is affected by cortisol alone, and that this effect is not moderated by noradrenergic activity. This extends recent findings indicating that cortisol biases the engagement of different cognitive systems (Schwabe and Wolf, 2013) and complement prior evidence that the pharmacological blockade of a receptor for cortisol abolishes the stress-induced shift from cognitive to habit memory in spatial and classification learning, pointing also to a crucial role of cortisol in the modulation of flexible cognition (Schwabe et al., 2013b, 2010a). By contrast, in instrumental learning, the stress-induced bias toward habit performance has been shown to require cortisol actions in concert with noradrenergic activity (Schwabe et al., 2010b). Our results complement these data by showing that higher-order cognitive reflection is cortisol-dependent, but, unlike reinforcement learning, it is independent of fast-acting noradrenergic action.

As response patterns in the CRT correlate with behavior in various domains of decision making and cognition (Campitelli and Labollita, 2010; Cokely and Kelley, 2009; Frederick, 2005; Hoppe and Kusterer, 2011; Liberali et al., 2012; Oechssler et al., 2009; Toplak et al., 2011), our findings have broader implications for the influence of cortisol on reasoning, decision making and cognitive function. For example, because the CRT is known to predict behavior in decisions under risk, our results may extrapolate to existing findings on the effects of stress-modulators on risky decisions (Coates and Herbert, 2008; Kandasamy et al., 2014; Pabst et al., 2013; Porcelli and Delgado, 2009; Putman and Roelofs, 2011; Van den Bos et al., 2009) and make a first step toward providing a common mechanism through which stress-modulators affect economic decisions. Additionally, as CRT performance correlates with performance on heuristics-and-biases tasks (Toplak et al., 2011), predicts susceptibility to behavioral biases, such as overconfidence, conservatism bias and endowment effects (Hoppe and Kusterer, 2011), and is associated with individual differences in probability judgement (Liberali et al., 2012) our findings generate novel testable behavioral hypotheses regarding the effects of cortisol on everyday decision and judgement fallacies.

The exogenous drug administration used in the present study carries the benefit of allowing causal conclusions about the involvement of the major stress mediators cortisol and noradrenaline in cognitive reflection. However, it is important to note that physiological reactions to pharmacological manipulations are not necessarily identical to those occurring after a natural stress situation, and might result in, for example, supraphysiological levels compared to natural stressors (Lupien et al., 1999), or might lack the affective response to threatening situations. Hence, it remains to be shown whether natural stressors have similar effects on deliberative thinking.

In conclusion, we demonstrated that exogenously administered cortisol impairs cognitive reflection and potentiates a shift from deliberate to intuitive information processing. We provide causal evidence of one mechanism through which stress impairs human judgement and decision-making that could explain several findings of how stress fosters decision biases in several areas of economic decision making.

Author contributions

All authors contributed to the study design and developing the concept. Z. Margittai performed testing and data collection. Z. Margittai, G. Nave, T. Strombach and T. Kalenscher performed the data analysis. Z. Margittai prepared the manuscript and all authors provided critical revisions. All authors approved the final version of the manuscript before submission. Z. Margittai and G. Nave are joint first authors of this article. T. Kalenscher supervised the project.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2015.11.018.

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Supplemental Online Materials (SOM)

Participants, eligibility criteria and trait variables

Participants were screened to ensure they met the eligibility criteria. Psychology and Economics students, individuals who reported the use of medication, heavy smoking, heavy drinking, chronic mental or physical illness, drug use or current psychiatric treatment were excluded. All participants were fluent German speakers, gave informed consent and were financially compensated for their participation. Participants were instructed to refrain from sexual activities, consuming alcohol or medication 24 hours prior to participation, and refrain from smoking and consuming caffeine 4 hours, and from exercise, consuming food and drinks other than water 2 hours prior to participation. These criteria were chosen to be comparable to prior research (e.g. (Vinkers et al., 2013). In order to control for potentially confounding variables, participants completed a series of online questionnaires before the experimental session. The four experimental groups did not differ in preexisting levels of anxiety (State Trait Anxiety Inventory-STAI; (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), impulsivity (Barratt Impulsiveness Scale – BIS-15; (Meule, Vögele, & Kübler, 2011), reward and punishment sensitivity (BIS/BAS scale; (Carver & White, 1994), social desirability (SDS-17; (Ströber, 2001), body mass index (BMI), propensity to take risk (Wagner, Frick, & Schupp, 2007), empathy (German version of the Interpersonal Reactivity Index, Paulus, 2007), chronotype (Morningness-Eveningness Questionnaire, Randler, 2013), baseline subjective feelings of stress (VAS), baseline pulse and blood pressure, cortisol and alpha-amylase, age or years until last completed school education (Table S1). In a post-test interview, we asked participants if they had any prior acquaintance of the CRT questions; no participant indicated any knowledge. All tests took place between 14:00 and 17:00 to control for diurnal variations in cortisol levels.

Even though we matched subjects for age, education level and the other cognitive, affective, trait and demographic factors mentioned above, we did not control for differences in working memory capacity and mathematical abilities to avoid mental fatigue and to remain economic with respect to the duration of the experiment. While it is unlikely that the randomly assigned treatment groups significantly differed with respect to these measures, further research should formally rule out this possibility.

Table S1.

Demographic and control measures

	Placebo		Yohimbine		Cortisol		Yohimbine + Cort				
	M	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**F**	**p**	***η2***
STAI	38.18	9.49	37.35	6.54	37.80	10.68	37.62	9.45	.03	.993	.001
BIS-15	32.05	5.59	33.15	5.87	35.85	6.02	33.19	5.11	1.69	.177	.060
BIS	15.68	1.86	16.10	2.59	16.10	2.05	15.62	2.36	.28	.837	.011
BAS	23.27	4.39	22.25	3.95	22.75	4.19	23.52	4.47	.36	.780	.014
SDS-17	9.59	3.17	9.40	3.22	9.35	2.89	9.52	2.36	.03	.993	.001
BMI	23.01	2.48	22.83	1.88	22.89	2.24	22.88	2.49	.02	.995	.001
VAS Baseline	16.14	14.67	10.80	12.31	14.58	13.50	11.67	12.76	.73	.539	.027
Systolic Baseline	126.66	18.45	129.02	15.20	126.45	13.83	127.55	12.54	.12	.950	.004
Diastolic Baseline	72.88	6.49	71.00	7.72	73.85	7.12	73.79	8.02	.64	.593	.024
Pulse Baseline	76.68	14.67	73.16	14.17	77.18	23.15	74.02	15.52	.27	.848	.010
Alpha-amylase Baseline	52.02	25.53	61.91	64.76	57.27	57.41	49.78	41.37	.25	.859	.010
Cortisol Baseline	15.00	13.96	15.35	10.22	12.01	6.34	14.65	8.99	.44	.728	.016
Age	25.19	5.31	22.95	3.00	24.68	4.51	24.47	9.41	.52	.668	.021
Years of education	13.00	2.21	12.55	1.39	12.95	1.76	12.81	1.81	.25	.863	.009
Risk taking	3.82	1.22	4.15	.88	4.50	.69	4.14	1.24	1.50	.220	.054
Empathy	39.45	5.60	42.00	6.81	42.40	5.15	40.62	6.30	1.06	.371	.039
Chronotype	14.95	1.46	14.70	1.22	14.35	1.75	14.33	1.43	.87	.460	.032

Although there was no significant difference in any of the control variables between experimental groups (Table S1), we found significant correlations between CRT score and social desirability (r_s=-.27, p=.015) and CRT score and chronotype (r_s=.28, p=.012). However, additional 2x2 analyses of covariance with hydrocortisone (yes/no) and yohimbine (yes/no) as between-subject factors, and social desirability and/or chronotype as added covariates

revealed that the effect of cortisol on CRT performance was robust on the $p<.05$ level to including these covariates ($F_{1, 77}=4.16$, $p=.045$).

The CRT was administered as a paper-and-pencil task. Thus, we were unable to collect response times. Based on prior research it is common to not report or collect response times for the CRT questions (see for example Oechssler et al. 2009; Campitelli and Labollita 2010; Toplak et al. 2011). However, it might be informative to analyze reaction times to be indicative of faster intuitive versus slower deliberative reasoning. Future projects should consider measuring response times.

All analyses were performed using SPSS 22.0 (IBM).

Additional decision making tasks

In addition to the CRT, participants carried out two decision making tasks in a counterbalanced order that have no relation to the present experiment. One task assessed social discounting (Margittai et al., 2015), the other was aimed at risk and loss aversion, using a task similar to (Chumbley et al., 2014). The CRT was always in between, and there was no effect of order on CRT performance nor an interaction between order and the pharmacological manipulations (all $p>.10$).

Subjective feelings of stress

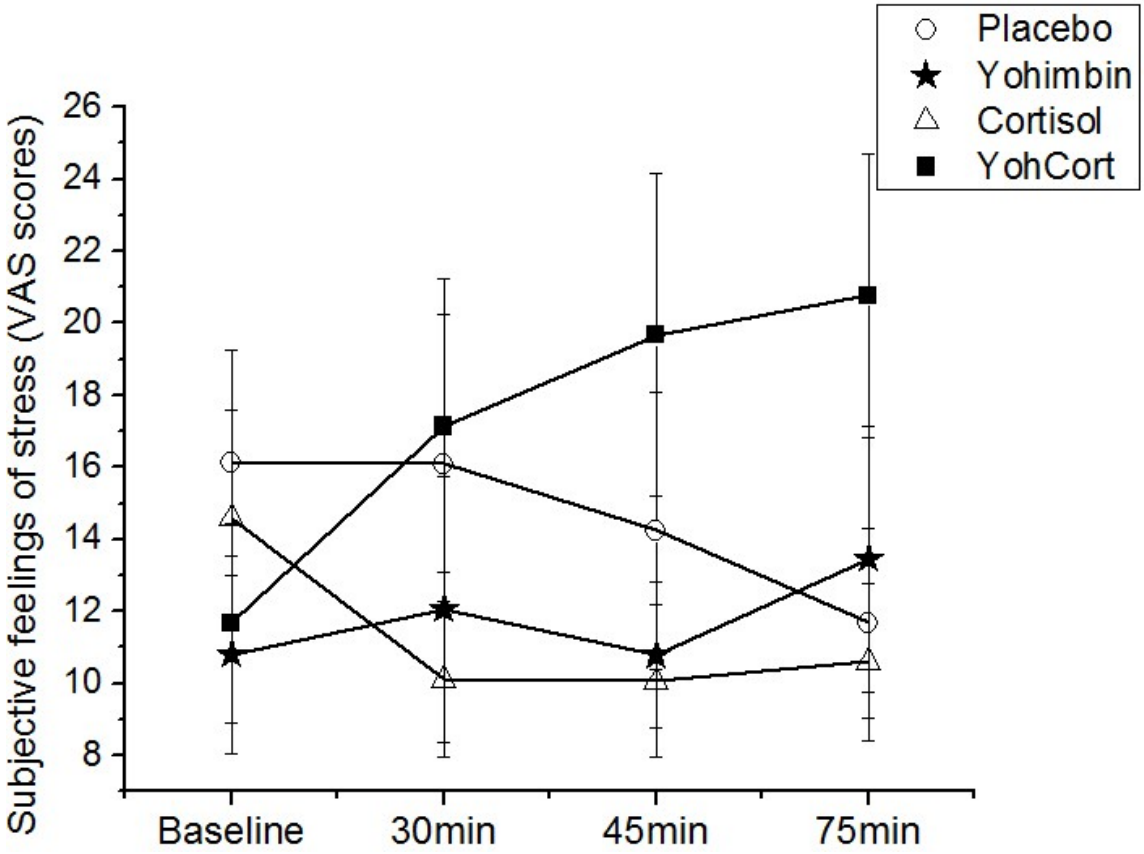

Figure S1. Changes in subjective feeling of stress over the course of the experiment in the four experimental groups.

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CHAPTER 4

A friend in need: Time-dependent effects of stress on social discounting in men

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A friend in need: Time-dependent effects of stress on social discounting in men

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ABSTRACT

Stress is often associated with a tend-and-befriend response, a putative coping mechanism where people behave generously towards others in order to invest in social relationships to seek comfort and mutual protection. However, this increase in generosity is expected to be directed only towards a delimited number of socially close, but not distant individuals, because it would be maladaptive to befriend everyone alike. In addition, the endocrinological stress response follows a distinct temporal pattern, and it is believed that tend-and-befriend tendencies can be observed mainly under acute stress. By contrast, the aftermath (>1 h after) of stress is associated with endocrinological regulatory processes that are proposed to cause increased executive control and reduced emotional reactivity, possibly eliminating the need to tend-and-befriend. In the present experiment, we set out to investigate how these changes immediately and >1 h after a stressful experience affect social-distance-dependent generosity levels, a phenomenon called social discounting. We hypothesized that stress has a time-dependent effect on social discounting, with decisions made shortly after (20 min), but not 90 min after stress showing increased generosity particularly to close others. We found that men tested 20 min after stressor onset indeed showed increased generosity towards close but not distant others compared to non-stressed men or men tested 90 min after stressor onset. These findings contribute to our understanding on how stress affects prosocial behavior by highlighting the importance of social closeness and the timing of stress relative to the decision as modulating factors in this type of decision making in men.

Introduction

Stress is a ubiquitous part of modern life, and almost all of us are intuitively aware of the benefits of a supportive social network in difficult times. Although the fight-or-flight response was traditionally seen as the predominant biobehavioral way of responding to acute stress (Cannon, 1932) findings are emerging in favor of an alternative standpoint. According to this new line of evidence and in contrast to the offensive attack or defensive social withdrawal associated with fight-or-flight, in certain situations, the neuroendocrinological stress response can be buffered by the presence of others (Häusser et al., 2012) and acute stress can even promote prosocial behavior (Takahashi et al., 2005; Taylor et al., 2000; Von Dawans et al., 2012).

Taylor et al. (2000) proposed the tend-and-befriend reaction, a putative coping mechanism under which individuals behave generously towards others after stress to seek and provide mutual protection. This was initially thought to be a characteristically female response to stress, however increments in prosocial behavior after acute stress have since also been demonstrated in men (Von Dawans et al., 2012). By contrast, however, Vinkers et al. (2013) found reduced generosity after stress when male subjects were asked about their willingness to donate money to a charity. The key difference between these studies is that, while in that of Von Dawans et al. (2012) participants dealt with anonymous, but real people, in the study by Vinkers et al. (2013), participants were asked about donating to an impersonal charitable organization.

Thus the decision maker's social closeness to the target may be a key factor in determining the way stress affects generosity. This also makes intuitive sense from the perspective of the tend-and-befriend hypothesis, as it is more strategic to focus our costly support efforts on a delimited group of socially close others from whom we may expect support than indiscriminately befriend anyone. This hypothesis blends in with recent findings in social psychology on a phenomenon called social discounting showing that people are generous towards individuals they

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feel close to, such as family or good friends, while generosity decreases hyperbolically with increasing social distance between donor and recipient (Jones & Rachlin, 2006; Strombach et al., 2014, 2015; Takahashi, 2007).

Besides potentially exerting diverging effects on generosity according to social distance, stress may also affect generosity differently with respect to the amount of time that has elapsed between the stressor and the moment of decision making. It has repeatedly been demonstrated that the physiological and endocrinological changes caused by stress affect cognition in two distinct temporal domains (Joels & Baram, 2009). Immediately after stress, short-term actions of corticosteroid hormones in concert with noradrenaline effects synergistically modulate neural activity in brain regions implicated in cognitive and emotional functioning, including amygdala and hippocampus, while suppressing higher cognitive, prefrontal-cortex-dependent functions (Hermans et al., 2014; Joëls et al., 2011). The time-dependent changes in the neuroendocrinological response to stress go along with distinct effects on cognition and behavior: acute stress promotes habitual over goal directed behaviors (Schwabe et al., 2010, 2012), affects memory systems (Schwabe & Wolf, 2013; Zoladz et al., 2011), results in reduced sensitivity to monetary outcomes in the dorsal striatum and orbitofrontal cortex (Porcelli et al., 2012) and reduced strategy-use in economic games (Leder et al., 2013). Altogether, this may result in an increased level of emotional reactivity directly after stress, leading to a heightened tendency to tend-and-befriend as a way of coping. By contrast, in the aftermath of stress, thus >1 h after stressor onset, slower, genomic effects of corticosteroids promote higher cognitive functions and contribute to restoring emotional responses to pre-stress levels (Hermans et al., 2014; Joëls et al., 2011), arguably resulting in less need for tend-and-befriend. In agreement, individuals tested in the aftermath of stress showed decreased levels of altruistic punishment and increased tendency for selfish decisions in the Ultimatum game (Vinkers et al., 2013).

In the current experiment, we formally test the influence of the early and late effects of psychosocial stress in men on generosity across a range of social distances. We expect that individuals tested shortly after being stressed will be more generous towards people at close, but not necessarily towards people at distant social distances, revealing a higher tendency to tend-and-befriend those who are likely to provide comfort and support. Furthermore, we predict to find this social-distance-dependent effect of stress on generosity only shortly after stress, but not in its aftermath. Participants played a variant of the dictator game in which they repeatedly decided how much of an endowment they wanted to share with other people at variable social distances. By fitting a well-established mathematical social-discount function to participants' choice data to approximate their individual social-distance-dependent changes in generosity, we determined a) their generosity at close social distance, and b) the decrease of generosity across social distance.

Materials and methods

Participants

Seventy-eight adult male subjects participated in the experiment, pseudo-randomly allocated to four experimental groups as follows: early control: N = 20, early stress: N = 19, late control: N = 19, late stress: N = 20. We used male subjects in order to avoid the differential HPA-Axis reactivity caused by the menstrual cycle and the use of oral contraceptives in women (Kirschbaum et al., 1999). Each subject was screened via a telephone interview prior to the experiment; those who reported current use of psychoactive drugs, steroids, beta blockers, heavy smoking (>5 cigarettes per day), alcohol or drug abuse, current psychological or psychiatric treatment/illness or chronic physical illness were excluded from further participation. These exclusion criteria were chosen to be in line with prior publications investigating the effects of stress on decision making (e.g. Von Dawans et al., 2012). All participants were fluent German speakers and were not enrolled in either Psychology or Economics study programs. None of the participants participated in stress-research before and the subjects were unfamiliar with each other. Sociodemographic characteristics of the participants are listed in Table 1. All participants gave their written, informed consent prior to the experiment. The study was approved by the ethical committee of the Heinrich Heine University Düsseldorf and was performed in line with the Declaration of Helsinki. Participants were financially compensated for their participation and were instructed to refrain from taking alcohol or medicine as well as engaging in sexual activities 24 h before participation, and furthermore to refrain from smoking, exercise, consuming food, caffeine and drinks other than water 2 h before the experiment. The experiment was fully incentive-compatible, did not include deception and met the experimental standards in behavioral economics.

Experimental design

We employed a 2 × 2 between-subjects design. The two factors were condition (stress/control) and timing of behavioral testing relative to stress induction (early/late). Individuals in the early groups completed the experimental behavioral task 20 min after stress onset, that is, directly after the end of the stress induction procedure (see below), while participants in the late groups carried out their tasks 90 min after stressor onset. These timescales were chosen because they are compatible with the bidirectional time-dependent effects of stress (Joëls et al., 2011) and to facilitate comparisons with other designs using similar temporal profiles, such as Vinkers et al. (2013).

General procedure

After completing a number of online questionnaires (further details below), participants were invited to the laboratory. All experimental sessions took place between 14:00 and 17:00 h to control for diurnal variation in cortisol levels. We tested all participants in groups of 4 subjects. Upon arrival, participants were pseudo-randomly allocated to one of the four experimental conditions (early control, early stress, late control, late stress), so that in each session two participants were allocated to the early and two to the late groups of one of the conditions. The timeline of the experiment is depicted in Fig. 1. After giving informed consent, participants were asked to refrain from communicating with each other for the entire duration of the experiment. After initial baseline saliva and heart rate measurements and questionnaires (details below), participants underwent either a stress protocol, or a control condition.

Participants were subjected to psychosocial stress, using the group version of the Trier Social Stress Test (TSST-G; Von Dawans et al., 2011). Before commencement of the TSST-G, participants received information about the condition they were in. During the 20 min long TSST-G procedure, participants in the stress condition were asked to carry out a fictional job interview and a mental arithmetic task in front of an evaluative panel of experts while being videotaped. The control condition consisted of tasks comparable in terms of cognitive load but without the socio-evaluative aspect: participants were instructed to speak simultaneously, describing a friend and completing the subsequent mental arithmetic task; they were neither videotaped nor directly observed by the panel, who was present in the room but did not watch participants. After completion of the stress induction or control condition participants were asked to carry out the social discounting task immediately (early groups) or 70 min later, that is, 90 min after stress onset (late groups). During the waiting period, participants were provided with individual headphones and laptops showing a neutral, cognitively undemanding documentary film. After the behavioral task participants were asked to complete a demographic questionnaire as well as a manipulation check for the behavioral task, also detailed

Table 1
Baseline parameters and sociodemographic characteristics of all participants. BMI = Body Mass Index, BIS/BAS = behavioral inhibition/approach scale, STAI = State Trait Anxiety Inventory, BIS-15 = Barratt Impulsivity Scale, VAS = visual analogue scale, PANAS = positive and negative affect schedule.

	Early control		Early stress		Late control		Late stress		*F*-value	*P*-value	Effect size (η^2)
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
BMI	22.36	2.07	23.32	1.86	23.73	2.45	22.42	3.24	1.44	0.24	0.06
Baseline cortisol (nmol/l)	15.32	8.09	14.24	9.50	16.67	9.14	13.71	7.79	0.43	0.73	0.02
Baseline heart rate (bpm)	90.03	21.71	93.94	23.17	89.06	14.84	90.76	20.49	0.20	0.89	0.01
PANAS positive mood	27.90	6.60	26.58	5.62	28.74	6.09	27.85	5.43	0.42	0.74	0.02
Social desirability	8.95	3.43	9.89	2.56	8.68	3.16	8.45	2.72	0.86	0.46	0.03
BIS	15.65	2.91	16.37	3.11	16.58	3.55	15.90	3.01	0.35	0.79	0.01
BAS	23.50	5.38	23.16	4.19	24.00	5.00	22.30	3.77	0.47	0.70	0.02
Empathy	42.65	5.95	39.58	6.30	40.26	3.89	40.80	6.00	1.07	0.36	0.04
STAI	45.20	6.66	40.95	7.07	43.74	3.37	43.75	5.35	1.50	0.22	0.06
BIS-15	34.15	6.11	34.84	6.54	32.00	5.13	34.30	5.28	0.89	0.45	0.04

	Early control	Early stress	Late control	Late stress	X^2	*P*-value	Effect size (η^2)
	Median	Median	Median	Median			
Age	23.00	25.00	24.00	22.00	1.72	0.63	0.01
Baseline alpha amylase (U/ml)	58.39	75.48	73.44	64.29	4.46	0.22	0.02
PANAS negative mood	12.00	12.00	12.00	11.50	2.92	0.40	0.04
VAS baseline	12.50	11.00	20.00	15.00	1.05	0.79	0.02
Morningness	14.00	14.00	13.00	12.00	1.52	0.68	0.06

below. At the end of the experiment, participants were paid for their participation (see below) and fully debriefed.

Elicitation of social environment

As the purpose of the task was to investigate social distance dependent prosocial behavior, participants were asked to describe their social environment before receiving instructions for the experimental behavioral task. We used a method similar to that of Strombach et al. (2014, 2015) to quantify social distances. To introduce the concept of social distance, each participant was shown a scale consisting of 101 icons, with the leftmost icon representing the participant and the others representing his social environment. Participants were told that social distance 1 (the most leftward icon closest to the participant) represents the socially closest person, while distance 100 (the most rightward icon) would be a stranger who they may have randomly met on the street. Social distance 50 stands for a distant acquaintance, whose name they may not know. Once participants were familiar with the concept of social distance, they were asked to write down the names of representatives for the following social distances: 1, 2, 3, 5, 10, 20. Although distances 50 and 100 were also included in the experiment, participants could, but were not required to provide a name, as these distance levels often represent remote individuals. Participants were specifically asked not to include anyone in their list whom they have negative feelings towards.

Social discounting task

We measured generosity using a dictator game where, in each trial, participants were endowed with a fixed amount of money, and asked how much of their endowment they would give up to a person at a

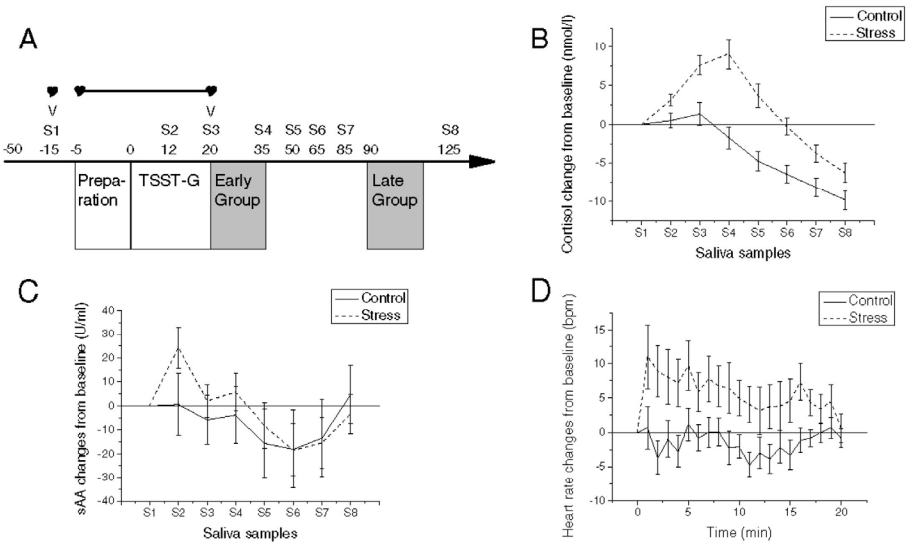

Fig. 1. Task design and physiological measurements. A) Timeline of the experiment: S = saliva samples, ♥ = heart rate measures, V = subjective stress ratings (VAS, PANAS). Numbers indicate time in minutes. B) Salivary cortisol changes from baseline. C) Salivary alpha amylase changes from baseline. D) Heart rate changes from baseline. Error bars indicate +/−1 standard error of the mean, SE.

specific social distance. We used three different endowment levels (EUR13, EUR15 and EUR17), and eight social distance levels (1, 2, 3, 5, 10, 20, 50 and 100; cf. Strombach et al., 2014, 2015). In total, participants completed 24 trials (8 social distances, 3 amounts) presented in a fully randomized order, each lasting 10 s. The main readout of this task was the percentage of money shared with a person at each social distance level. Participants then carried out a further task investigating intertemporal decision making. This task served as a non-publishable pilot study for a different project and is not reported here. Completion of the tasks lasted less than 10 min. Participants were informed that, at the end of the experiment, one of their decisions would be randomly chosen and paid out, therefore they and potentially another person would be able to earn money based on their decisions. The money the participant allocated to themselves was paid out directly after the experiment, in addition to the fixed compensation of EUR20, and for the money shared, subjects were asked to indicate the address of the other person in the randomly chosen trial. In case participants were concerned to disclose the address of a friend for privacy reasons, we asked to only disclose the name of the particular friend to allow us to prepare a cheque that only the recipient could cash and gave this cheque to the participant to forward to the particular person. If the randomly chosen trial was about an anonymous person or stranger, e.g. at higher social distances, a random person on the campus of the University of Düsseldorf, Germany received the reward.

Detailed instructions regarding the behavioral tasks were given before stress induction, followed by a series of multiple-choice questions to ensure participants understood these instructions. In addition, short booster instructions and a test trial were provided on the computer screen directly before the start of the behavioral task. As participants were specifically instructed to think, at each social distance elicitation, of the individuals they indicated prior to the experiment, we performed a stability check at the end of the experiment and asked participants to write down the names of and further information about their relationship to the person (how long and how well they know them) they chose for each social distance prior to the task. The behavioral task was programmed and presented using Presentation Software (Neurobehavioral Systems, Albany, CA).

Saliva sampling

To confirm a hormonal stress response to the TSST-G procedure, saliva samples were collected at 8 different time points throughout the experiment as shown in Fig. 1, using Salivette (Sarstedt, Germany) devices containing a cotton wool swab that participants had to lightly chew on for 60 s to allow the swab to fill with saliva. Saliva samples were analyzed as reported by Rohleder et al. (2004). Samples were frozen and stored at −20 °C until analysis. After thawing, Salivettes were centrifuged at 3000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary cortisol concentrations were measured using commercially available chemiluminescence immunoassays with high sensitivity (IBL International, Hamburg, Germany). The intra and interassay coefficients for cortisol were below 8%.

Concentrations of alpha amylase in saliva were measured by an enzyme kinetic method: Saliva was processed on a Genesis RSP8/150 liquid handling system (Tecan, Crailsheim, Germany). First, saliva was diluted 1:625 with double-distilled water by the liquid handling system. Twenty microliters of diluted saliva and standard were then transferred into standard transparent 96-well microplates (Roth, Karlsruhe, Germany). Standard was prepared from "Calibrator f.a.s." solution (Roche Diagnostics, Mannheim, Germany) with concentrations of 326, 163, 81.5, 40.75, 20.38, 10.19, and 5.01 U/l alpha amylase, respectively, and double distilled water as zero standard. After that, 80 ml of substrate reagent (*a*-amylase EPS Sys; Roche Diagnostics, Mannheim, Germany) were pipetted into each well using a multichannel pipette. The microplate containing sample and substrate was then warmed to 37 °C by incubation in a waterbath for 90 s. Immediately afterwards, a first interference measurement was obtained at a wavelength of 405 nm using a standard ELISA reader (Anthos Labtech HT2, Anthos, Krefeld, Germany). The plate was then incubated for another 5 min at 37 °C in the waterbath, before a second measurement at 405 nm was taken. Increases in absorbance were calculated for unknowns and standards. Increases of absorbance of diluted samples were transformed to alpha amylase concentrations using a linear regression calculated for each microplate (Graphpad Prism 4.0c for MacOSX, Graphpad Software, San Diego, CA).

Heart rate measurement

Heart rate was monitored using POLAR RCX3M training computers. Measurements were taken at baseline in an upright standing position to match the position maintained during the stress induction procedure. Heart rate was monitored throughout the stress induction until the end of the TSST-G.

Subjective stress ratings

In order to check whether subjective perception of stress and mood changed in response to the TSST-G procedure, participants completed the Visual Analogue Scale (VAS, 100 mm scale) and the Positive and Negative Affect Schedule PANAS (Watson et al., 1988) before and after the stress induction procedure.

Trait questionnaires

Although trait measures were not the primary focus of our study, we included several questionnaires in our design to ensure that the groups did not differ on characteristics that could modulate generosity. Participants completed the behavioral approach/inhibition scale (BIS/BAS), a widely used measure of reward and punishment sensitivity (Carver & White, 1994) prior to the experimental tasks and stress induction. To control for potential preexisting anxiety that may influence subjects' reaction to the TSST-G procedure, each subject completed the trait scale of the State Trait Anxiety Inventory (Spielberger et al., 1983). As empathy is known to influence prosocial behavior, each participant completed the German version of the Interpersonal Reactivity Index (Davis, 1980). Furthermore, impulsivity was measured using the short German version of the Barratt Impulsiveness Scale (BIS-15; Meule et al., 2011). As the TSST-G procedure involves social evaluation, it is possible that the participants' responses reflected social desirability effects in addition to their true preferences. To control for social desirability, each participant completed the Social Desirability Scale 17 (SDS-17; Ströber, 2001). As chronotype may have an effect on cardiovascular responses to stress, participants also filled out the short version of the Morningness–Eveningness Questionnaire (Randler, 2013).

Data analysis

Baseline parameters

To ascertain that our experimental groups did not differ in baseline parameters, we carried out one-way analyses of variance (ANOVAs) or Kruskal–Wallis H tests (in case of non-normally distributed measures).

Stress induction

We tested whether the psychosocial stress induction resulted in a change in stress-hormone levels as follows: We calculated the area under the curve increase across all eight saliva sample measures (S1-S8; AUCi) for each participant and each hormone, as well as heart rate measures for the 20 min duration of the TSST in line with the procedure described by Pruessner et al. (2003). We additionally calculated the maximum percent change from baseline for sAA during

the stress induction procedure. This was done because stress-induced changes in sAA can fade quickly, therefore measures over a longer period of time such as the AUCi involving all 8 sampling time points may not reveal the differences between the two treatment conditions effectively. To assess subjective stress and mood ratings, change scores (post TSST-G minus baseline) were calculated for the VAS as well as the PANAS scales. The AUCi of cortisol as well as the VAS and PANAS positive mood change scores were analyzed using two-way ANOVAs with condition (stress/control) and timing (early/late) as the between subject factors. The AUCi of heart rates and sAA, the maximum percent change in sAA during the TSST-G as well as change in negative affect were analyzed using non-parametric tests, as the data were not normally distributed.

Social discounting

We used a psychometric approach to address the effects of stress on social discounting. The decline of generosity across social distance is best described by the following standard hyperbolic function (Jones & Rachlin, 2006; Strombach et al., 2014, 2015; Takahashi, 2007):

$$v = \frac{V}{(1 + kD)} \quad (1)$$

where v is the discounted other-regarding value of the reward (here: percentage of money shared), V describes the height of the function independent of its steepness and can be interpreted as the generosity level at close social distance, D is a measure of social distance, and k describes the degree of discounting. We fitted this hyperbolic social-discount function to the percentage of money shared at each social distance level, both on an averaged group level (separately for the four experimental groups) and individually for each participant to approximate their individual social-distance-dependent changes in generosity. We used the best-fitting social discount parameters V and k as estimates of a) participants' generosity at close social distance (parameter V), and b) the decrease in generosity across social distance (parameter k), respectively. The time-dependent effects of stress on V (generosity at close social distance) and k (decline in generosity across social distance, log-transformed to obtain non-skewed distributions) parameters were analyzed using two way ANOVAs with condition (stress/control) and timing (early/late) as the between subject factors. In case of significant interaction, t-tests were carried out as post-hoc tests to determine which of the four experimental groups differed from each other. We applied Bonferroni-correction to control for multiple comparisons.

Overall measure of generosity

As an overall measure of generosity independent of social distance, we calculated the area under the curve of the amount shared by each participant (AUCSD) using the same approach that had been used by Strombach et al. (2014). In accordance with the procedure described by Pruessner et al. (2003) we used the 'area under the curve with respect to ground' (AUCg) formula for this analysis, as this measure is better suited to assess the overall strength of generosity, rather than focus on changes across social distance (Pruessner et al., 2003).

Neuroendocrinological correlates of generosity

To determine whether there is a relationship between hormone levels and social discounting we carried out a Spearman rank order correlation analysis between the discounting parameters V and k, the overall measure of generosity (AUCSD), changes in hormone levels as well as baseline levels of sAA and cortisol. As we expected diverging relationships between stress and social discounting depending on the time point of testing, we carried out separate tests for the early and late groups.

Effect sizes

The effect sizes reported are eta-squared (η^2) for ANOVAs and Kruskal–Wallis tests, Cohen's d for pairwise comparisons and r for Mann–Whitney U tests.

Results

Baseline parameters

There was no significant difference in any of the trait personality measures (empathy, reward and punishment sensitivity, trait anxiety, social desirability, chronotype and impulsivity), physiological measures (baseline measures of heart rate, cortisol, sAA), personal measures (Body Mass Index, age) and baseline subjective ratings of mood and stress between the experimental groups (Table 1). Age, baseline sAA, PANAS Negative Mood, VAS baseline and Morningness were not normally distributed and hence subjected to non-parametric testing. These parameters are shown separately at the bottom of the table.

Stress induction

Cortisol

One participant had to be excluded from the analysis due to insufficient saliva in the samples. The AUCi of the cortisol response was significantly larger in the stress than in the control condition indicating that our stress manipulation resulted in pronounced increases in cortisol level (main effect of condition: $F_{1,73} = 15.19$, $P < 0.001$, $\eta^2 = 0.17$), while changes in the control group followed circadian rhythms. As expected, there was no significant effect of timing of behavioral testing (early vs. late) or an interaction between timing and condition (timing x condition: $F_{1,73} = 0.69$, $P = 0.41$, $\eta^2 = 0.01$; timing: $F_{1,73} = 0.59$, $P = 0.44$, $\eta^2 = 0.01$; Fig. 1B).

Alpha amylase (sAA)

One participant had to be excluded from the analysis due to insufficient saliva in the samples and a further participant who only provided usable samples at 4 of the 8 measuring time points was also excluded. The AUCi computed over all sample time points (S1–S8) did not differ between the stress ($Mdn = -0.01$) and control ($Mdn = -0.01$) groups (Mann–Whitney U test, $U = 633.50$, $Z = -0.92$, $P = 0.36$, $r = 0.11$). However, we found that the maximum percent increase from baseline in sAA during the stress induction protocol was significantly higher in the stress ($Mdn = 0.37$) than in the control group ($Mdn = 0.11$; Mann Whitney U test, $U = 503.5$, $Z = -2.27$, $P = 0.02$, $r = 0.26$), suggesting that sAA levels significantly rose in response to stress, but that the response was relatively short-lived (Fig. 1C).

Heart rate

Heart rate measures were not recorded for one participant due to technical difficulties with the measuring device. A Mann Whitney U test with the AUCi of heart rates revealed that the stress group had a much larger increase in heart rates than the control group during the stress induction procedure ($Mdn_{Control} = -0.04$, $Mdn_{Stress} = 0.14$, $U = 387$, $Z = -3.61$, $P < 0.001$, $r = 0.41$) (Fig. 1D).

Subjective stress ratings

The 2 × 2 ANOVA showed that the increase in subjective feelings of stress, measured by changes in VAS scores, did not significantly differ between the control and stress conditions in either the early (early stress: M = 12.21, SD = 15.86, early control: M = 6.13, SD = 15.35) or the late groups, although there was a descriptive difference, with larger increases in the stress groups than in the control goups

(late stress: M = 10.15, SD = 8.46, late control: M = 5.58, SD = 19.03; main effect of condition: $F_{1,74} = 2.43$, $P = 0.12$, $\eta^2 = 0.03$; main effect of timing: $F_{1,74} = 0.15$, $P = 0.70$, $\eta^2 = 0.002$).

Changes in negative affect did not differ between the stress and control conditions ($Mdn_{Control} = 0$, $Mdn_{Stress} = 1$; Mann–Whitney U test: $U = 624.50$, $Z = -1{,}37$, $P = 0.17$, $r = -0.16$).

Positive affect increased in the stress group (early stress: M = 1.68, SD = 7.77, late stress: M = 1.65, SD = 4.94) after the TSST-G, while it decreased in the control group (early control: M = −1.55, SD = 3.87, late control: M = −2.26, SD = 4.56), resulting in significant differences between the two conditions, with no difference between the early and the late groups (main effect of condition: $F_{1,74} = 8.33$, $P = 0.005$, $\eta^2 = 0.10$, main effect of timing: $F_{1,74} = 0.09$, $P = 0.77$, $\eta^2 = 0.001$, timing × condition: $F_{1,74} = 0.08$, $P = 0.79$, $\eta^2 = 0.000$).

Stress modulates generosity to close others in a time-dependent manner

We examined whether stress had an effect on the shape of the social discounting function in our male sample, reflecting changes in generosity to close others as well as changes in the decline of generosity with increasing social distance. To this end, we fitted, for each participant individually, a standard hyperbolic model (Eq. 1) to the individual percentages of money shared with recipients at variable social distance levels, similar to the procedures reported in previous publications (Jones & Rachlin, 2006, Strombach et al., 2014, 2015). The hyperbolic model provided a good fit to the data (averaged adjusted R^2 early control: 0.99, early stress: 0.98, late control: 0.95, late stress: 0.98). Fig. 2 shows the mean amounts shared and the best-fitting hyperbolic function to the mean amounts shared for each experimental group.

As described above, the hyperbolic equation contains two free parameters. V describes the height of the function independent of its steepness (Jones & Rachlin, 2006) and could be interpreted as an indicator of generosity at close social distances, with larger values indicating higher generosity to close others. The parameter k describes the degree of social discounting, that is, the general degree of decline in generosity with increasing social distance, with higher values indicating a steeper decline.

First, to test for stress- and time-effects on generosity towards close others, we calculated a two-way ANOVA with condition (stress/control) and timing (early/late) as between-subject factors and V as the dependent variable. This analysis revealed a significant main effect of timing ($F_{1,74} = 11.31$, $P = 0.001$, $\eta^2 = 0.14$) and a non-significant main effect of condition ($F_{1,74} = 1.22$, $P = 0.27$, $\eta^2 = 0.01$). Most importantly, as predicted, a significant interaction effect between condition and timing on V ($F_{1,74} = 9.01$, $P = 0.004$, $\eta^2 = 0.09$) was found. In line with our hypothesis, Bonferroni corrected post hoc tests revealed that the early stress group had significantly higher V parameters than the late stress group ($t(37) = 4.60$, $P < 0.001$, $d = 1.47$) confirming that generosity to socially close persons was affected by stress in a time-dependent manner. The early stress group also had significantly higher V parameters than the early control group ($t(37) = -2.51$, $P = 0.02$, $d = 1.07$), indicating that generosity towards socially close individuals was increased directly after stress. The late stress group had on average lower V parameters than the late control group, but this difference was not significant ($t(37) = 1.66$, $P = 0.11$, $d = 0.53$; Fig. 3). Overall, our analyses revealed that stress had a time-dependent effect on generosity towards socially close individuals in men, with increased generosity right after stress, but not in its aftermath. The non-significant difference between the V parameters of the late control and late stress groups leaves open the possibility that the stress effects on generosity were only transient.

We next tested whether stress or time-point of testing had an effect on the log-transformed k-values, i.e. on the general decline in generosity as a function of social distance. We found no significant difference in log-k between any of the conditions (main effect of condition: $F_{1,74} = 0.01$, $P = 0.92$, $\eta^2 = 0.000$; main effect of timing: $F_{1,74} = 0.13$, $P = 0.73$, $\eta^2 = 0.002$, condition × timing interaction: $F_{1,74} = 3.24$, $P = 0.08$, $\eta^2 = 0.042$; Fig. 3).

Effect of stress on overall generosity

Our analyses showed that stress had no effect on overall generosity, i.e., average generosity independent of social distance, measured as the area under the curve of the shared fractions of the endowments (AUCSD; main effect of condition: $F_{1,74} = 0.09$, $P = 0.77$, $\eta^2 = 0.001$; main effect of timing: $F_{1,74} = 0.37$, $P = 0.55$, $\eta^2 = 0.01$ condition x timing: $F_{1,74} = 0.12$, $P = 0.73$, $\eta^2 = 0.002$).

Neuroendocrinological correlates of generosity

We found no significant correlation between any of the hormonal measures and the discount parameter V, neither in the early, nor the late groups (all $P > 0.36$), suggesting that the stress-effects on V may have been mediated by stress-related factors other than noradrenaline or cortisol action. There was a significant negative correlation between k and the changes in sAA levels ($r_s = -0.32$, $P = 0.05$) in the late stress group, while correlations between k and hormonal measures remained non-significant in the early stress group (all $P > 0.13$). Overall generosity (AUCSD) showed a negative relationship with baseline cortisol levels in the early ($r_s = -0.34$, $P = 0.04$) group, but correlation between hormonal measures and overall generosity remained non-significant in the late group (all $P > 0.12$).

Discussion

In the present study, we demonstrated that psychosocial stress altered social discounting in male decision-makers. Critically, the way stress affected the social discount function was dependent on the time

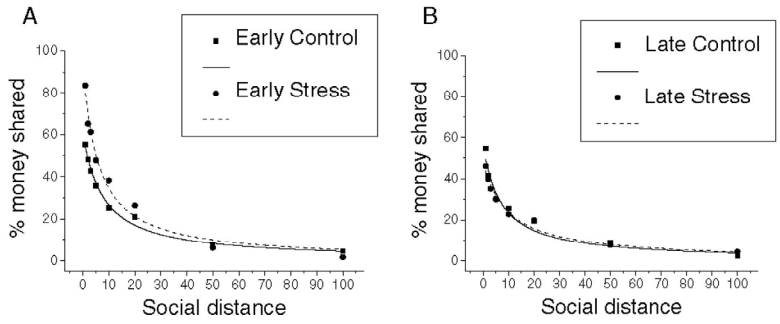

Fig. 2. Mean percentage of money shared with recipients at variable social distance levels: The lines represent the best-fitting hyperbolic model to the mean values in the early (A) and late (B) groups.

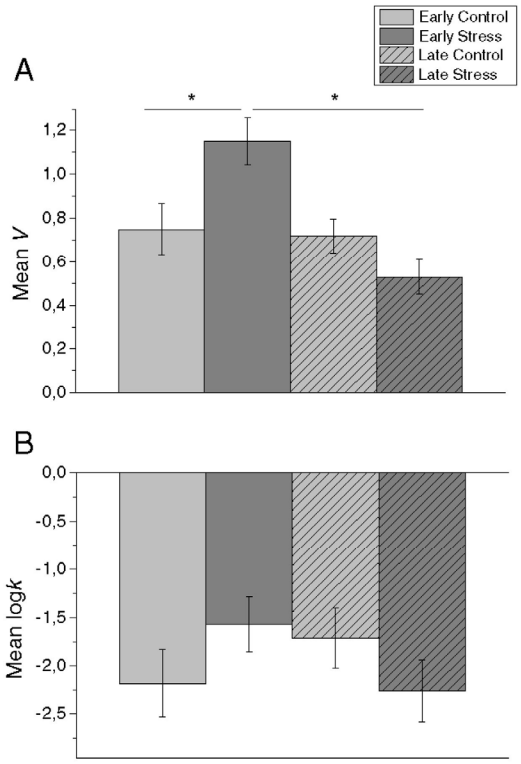

Fig. 3. The effects of stress and time point of testing on social discounting parameters A) *V* parameter of the four experimental groups. B) log-transformed *k* parameters. Error bars indicate +/− 1 standard error of the mean, SE. Significant differences are indicated by an asterisk.

that elapsed between the stressor and the task. To elicit social discounting, we used an adapted version of the dictator game in which participants had to indicate how much money of an initial endowment they were willing to share with recipients at variable social distances. During decisions made shortly after stress induction, stressed participants, relative to non-stressed control subjects, showed elevated levels of generosity specifically towards socially close individuals, as reflected by differences in the *V* parameter of the social discount function. However, the steepness by which generosity levels decayed across social distance was less affected by stress, as reflected by the non-significant effects of stress on the *k* parameter of the social discount function. Taken together, our results confirm and extend the tend-and-befriend hypothesis by the observation that directly after stress higher generosity levels are restricted to socially close others from whom support in stressful times could be expected.

Our study reconciles findings from two earlier studies in male samples that found opposing effects of stress on generosity. Using the dictator game, Von Dawans et al. (2012) showed that exposure to acute stress increased sharing, while Vinkers et al. (2013) presented evidence to the contrary. The fundamental difference between the two studies was that in the former, participants made decisions to share money with real human individuals, while Vinkers et al. (2013) asked participants about donating to an impersonal charitable organization. We show here that social distance is an essential factor that modulates the way stress affects prosocial behavior.

Evidence has recently emerged showing that the physiological stress response follows a particular temporal pattern (Joels & Baram, 2009) with specific time-dependent neuroendocrinological changes that have differential effects on memory retrieval (Schönfeld et al., 2014; Schwabe & Wolf, 2014) as well as economic (Takahashi et al., 2005) and social decision making (Vinkers et al., 2013). It has already been demonstrated that decision making >1 h after stress was associated with decreased levels of altruistic punishment and increased tendency for material self-interest compared to decisions made directly after stress (Vinkers et al., 2013). Accordingly, we hypothesized and confirmed that stress may also have a time-dependent effect on the stress-related increase in generosity towards close others, reflected in the *V* parameter of the social discount function. These results fit well with neurobiological findings about time dependent effects of cortisol on prefrontal functioning. Henckens et al. (2010) showed that slow, genomic effects of corticosteroids increased connectivity between the amygdala and the mPFC, facilitating prefrontal control over hypervigilance and anxiety associated with increased amygdala activation. This heightened prefrontal functioning increases executive control and reduces emotional reactivity which may have resulted in the observed patterns of normalized generosity to close others, suggesting a reduced need for a tend-and-befriend reaction >1 h after stress.

We found a negative relationship between the changes in sAA levels and the parameter *k* in the late stress group, indicating that altered levels of sympathetic activation did indeed modulate prosocial behavior by making the decline in generosity as a function of social distance less steep. Similarly, we found that in the early group, overall generosity showed a negative relationship with changes in sAA levels, thus indicating that a heightened sympathetic drive response is associated with heightened generosity in the early group as well. However, these effects were rather weak and we found no relationship between stress-induced hormonal changes and *V*, i.e. generosity to close others. Thus, the exact physiological or psychological mechanisms by which stress modulates generosity seem to be complex, and not merely the linear consequence of altered cortisol and/or noradrenergic action. In order to establish the precise role of the hormones cortisol and noradrenaline in modulating prosocial behavior, a direct, causal, pharmacological manipulation is necessary and should be the topic of future research.

A minor point that remains to be addressed is the unexpected results we found in subjective ratings of mood and stress, such as no significant difference between the stress and control conditions in subjective feeling of stress, and increase in positive mood in the stress group as well as decrease in positive mood in the control group. We believe this was due to the fact that we only took subjective measures at baseline and *after* the TSST-G, at which point feelings of relief could have overshadowed feelings of stress. In hindsight, it would have been better to take these measures during the stress protocol as well. Overall we find it unlikely that these subjective reports in mood interfere with our results, as hormonal stress responses confirmed a successful stress manipulation and control condition.

A limitation of our study is that we only used male participants. Therefore we cannot generalize our findings to women. A direct comparison of men and women should be a topic of future research. Nonetheless our findings add further support to the presence of a tend-and-befriend reaction in men, which was, until recently thought to be a characteristically female response to stress (Taylor, 2006).

Conclusion

In conclusion, our study demonstrated that the modulation of prosocial behavior by stress in men is time- and social-distance-dependent. We showed that generosity increases after direct exposure to psychosocial stress, but only towards socially close individuals and only directly after stress. These results support and extend the tend-and-befriend hypothesis and reconcile findings from previous studies that found divergent effects of stress on prosocial behavior. Furthermore, our study has important real life implications by highlighting that not only does our social closeness to individuals in our social environment influence the way we make prosocial decisions, but that

exposure to stress can shift the balance in those decisions favoring socially close others, perhaps sharpening distinctions between those others perceived as ingroup and outgroup. Our study thus opens up new avenues to understand and tackle tensions arising whenever individuals make decisions within a stressful social network, in the contexts of cultural and ethnic conflicts, parochialism, and racism.

Acknowledgments

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CHAPTER 5

Dissociable roles of glucocorticoid and noradrenergic activation on social discounting

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Dissociable roles of glucocorticoid and noradrenergic activation on social discounting

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ABSTRACT

People often exhibit prosocial tendencies towards close kin and friends, but generosity decreases as a function of increasing social distance between donor and recipient, a phenomenon called social discounting. Evidence suggests that acute stress affects prosocial behaviour in general and social discounting in particular. We tested the causal role of the important stress neuromodulators cortisol (CORT) and noradrenaline (NA) in this effect by considering two competing hypotheses. On the one hand, it is possible that CORT and NA act in concert to increase generosity towards socially close others by reducing the aversiveness of the cost component in costly altruism and enhancing the emotional salience of vicarious reward. Alternatively, it is equally plausible that CORT and NA exert dissociable, opposing effects on prosocial behaviour based on prior findings implicating CORT in social affiliation, and NA in aggressive and antagonistic tendencies. We pharmacologically manipulated CORT and NA levels in a sample of men (N = 150) and found that isolated hydrocortisone administration promoted prosocial tendencies towards close others, reflected in an altered social discount function, but this effect was offset by concurrent noradrenergic activation brought about by simultaneous yohimbine administration. These results provide inceptive evidence for causal, opposing roles of these two important stress neuromodulators on prosocial behaviour, and give rise to the possibility that, depending on the neuroendocrine response profile, stress neuromodulator action can foster both tend-and-befriend and fight-or-flight tendencies at the same time.

1. Introduction

Although almost all people engage in prosocial behaviour at times, generosity tends to decrease with increasing social distance between donor and recipient. After all, while many of us do not hesitate to donate money to our close family members in need, very few of us would be willing to give the same amount to disadvantaged strangers. This decline in generosity as a function of increasing social distance is called social discounting, a phenomenon which has triggered significant research interest in recent years (Jones and Rachlin, 2006; Kalenscher, 2017; Margittai et al., 2015; Strang et al., 2017; Strombach et al., 2015, 2014; Vekaria et al., 2017).

Due to the high prevalence of acute stress in daily life, research focusing on how it impacts social decision making has increased manifold in recent years (Porcelli and Delgado, 2017; Starcke and Brand, 2012). Acute stress is associated with the activation of the hypothalamic-pituitary-adrenal axis (HPA axis) system as well as autonomic arousal (Selye, 1950), and increases in two main neuromodulators, cortisol (CORT) and noradrenaline (NA) respectively. These substances impact brain function in a symphonic, time-dependent fashion, with imminent elevations of NA, shortly followed by non-genomic CORT effects after stress onset, and subsequent genomic CORT response in the aftermath of stress (Hermans et al., 2014; Joëls and Baram, 2009).

In stark contrast to the canonical view that acute stress primarily leads to fight-or-flight, it has now been reliably shown that it can also foster prosocial behaviour in some situations, in both men and women (Buchanan and Preston, 2014; Margittai et al., 2015; Taylor et al., 2000; Tomova et al., 2017; Von Dawans et al., 2012).

In recent work (Margittai et al., 2015), we specifically focused on whether social closeness is a determining factor in acute stress effects on prosocial behaviour, and thus investigated how it altered social discounting. Results showed that exposure to psychosocial stress (Trier Social Stress Test for Groups, Von Dawans et al., 2011) increased generosity, but only towards individuals who were socially close to the decision maker. These findings were interpreted in the context of the

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tend-and-befriend hypothesis (Taylor, 2006), a coping mechanism that helps to counteract the negative effects of stress by investing into social networks providing help and comfort. As socially close others are more likely to offer protection in time of need, it is reasonable to focus affiliative efforts, and thus become more prosocial only towards them. Extending these findings Berger et al. (2016) demonstrated, that CORT responses to psychosocial stress were positively correlated with the tendency to affiliate amongst men, lending support to the idea that CORT plays a key role in social affiliative coping and thus in prosocial behaviour after stress. Furthermore, CORT has already been implicated as a positive predictor of empathy, a concept indisputably related to prosocial behaviour (Zilioli et al., 2015). The role of NA in prosocial behaviour, and its putative interaction with CORT, is less clear. CORT and NA acting in concert reduce loss aversion (Margittai et al., 2018), promote attention to salient stimuli (Hermans et al., 2011), and sharpen vigilance contrasts, and NA-related arousal caused by observing another person in distress has been found to be related to subsequent costly helping (Hein et al., 2011). This may suggest that generosity towards socially close others after stress might be boosted by the conjoint action of CORT and NA, by reducing the aversiveness of the costs in costly altruism, and at the same time enhancing the emotional salience of vicarious reward signals and feelings of warm glow. By contrast, NA has been widely associated with arousal and aggression both in animal and human studies (Nelson and Trainor, 2007), and it is known to reduce social play and affiliation in animals (Achterberg et al., 2016). Thus, it is equally plausible that CORT by itself promotes prosocial behaviour, particularly towards socially close others, while the concomitance of NA inhibits these prosocial tendencies.

Here, we set out to decide between these two competing hypotheses by investigating the causal effect of CORT and NA manipulation on social discounting. We pharmacologically manipulated CORT and NA levels by oral, exogenous administration of hydrocortisone or yohimbine (an alpha-2 adrenergic receptor antagonist) respectively. These substances were given separately or concomitantly in a placebo-controlled double-blind experimental design. We measured how elevations in CORT and NA level impact on social discounting using the same task that has been reported by (Margittai et al., 2015).

2. Materials and methods

2.1. Participants

One hundred and fifty male participants took part in the experiment. We opted to employ male participants only because there is evidence of gender differences in HPA-axis reactivity as well as effects of oral contraceptives and menstrual cycle phase on HPA-axis reactivity in female participants (Kirschbaum et al., 1999). Sample size was determined using G*Power (Faul et al., 2007). Assuming a medium effect size (also see Margittai et al., 2015), the sample size necessary to achieve a power of 0.8 was n = 128. We eventually opted to collect data from 150 participants, thus exceeding the minimum sample size requirement, to have a contingency for potential exclusions or other problems. Hence, we are confident that our study was sufficiently powered to detect the required effects.

Before participation individuals completed a screening interview and those who reported regular use of medication, chronic physical or mental illness, heavy smoking, drinking or drug use or being students of Psychology or Economics were not invited to participate. 7 participants disclosed after the experiment that they either had illnesses or were taking medication, and they were consequently excluded from further analyses. All participants had fluent knowledge of German, gave their written, informed consent and received financial compensation for participation. The study was approved by the ethics committee of the University Hospital Düsseldorf and conformed to the regulations of the Declaration of Helsinki. Participants were instructed not to engage in sexual activities, take medication or alcohol for 24 h prior to participation, not to smoke, or drink anything containing caffeine for 4 h prior to participation, and to refrain from physical exercise, eating and drinking anything other than water for 2 h before participation. These criteria were similar to what had been employed in other studies (e.g. Vinkers et al., 2013).

2.2. Trait measures

Prior to being invited to the laboratory, all participants completed a number of trait questionnaires online, designed to exclude potential confounds between the experimental groups:

We measured trait anxiety (State-Trait Anxiety Inventory – STAI, (Spielberger et al., 1983), impulsivity (Barratt Impulsiveness Scale – BIS-15, (Meule et al., 2011), reward and punishment sensitivity (BIS/BAS scale, Carver and White, 1994), social desirability (Social Desirability Scale – SDS-17, Ströber, 2001), empathy (Saarbrücker Persönlichkeitsfragebogen – SPF, Paulus, 2007), chronotype (reduced version of the Morningness-Eveningness Questionnaire – rMEQ, Randler, 2013) and general willingness to take risks. Additionally we recorded age, BMI, baseline salivary cortisol, baseline salivary alpha-amylase, baseline subjective feelings of stress (VAS) and mood (PANAS; Watson et al., 1988).

2.3. Pharmacological manipulation, physiological and subjective stress measures

Participants were randomly assigned to one of four experimental conditions: (A) placebo (PLAC, N = 36), (B) placebo + yohimbine (YOH, 20 mg, Cheplapharm, N = 38), (C) placebo + hydrocortisone (CORT, 20 mg, Jenapharm, N = 38), (D) yohimbine + hydrocortisone (YOHCORT, 20 mg each, N = 38). The number of tablets taken was identical in the four conditions, thus participants were unable to guess which condition they were in on the basis of the number of pills. The dosage was chosen to be in line with previous studies (Margittai et al., 2018, 2016; Schwabe et al., 2012, 2010). To assess increases in cortisol levels and noradrenergic activation, saliva samples (using Salivette devices from Sarstedt, Germany) were collected at baseline and +30, +60 and +75 min after pill ingestion and subsequently frozen at −20 °C until transport and analysis using the same method as reported by (Rohleder et al., 2004). 25 of the 1500 samples were compromised and thus could not be analysed. These values were excluded from analyses. All other samples were analysed for concentrations of salivary cortisol (CORT) and salivary alpha amylase (sAA), an indirect marker of noradrenergic activity. For each participant, two samples were taken approximately 10 min and 20 min before pill intake and their values averaged to determine individual baseline. In case one of the values was missing, we used the remaining value as the baseline. Subjective feelings of stress (using visual analogue scales – VAS) were taken at the same time as the saliva samples. Changes in positive and negative mood were assessed once at baseline and once 60 min after drug intake (shortly before the experimental tasks), using PANAS (Watson et al., 1988) scales. Change scores were calculated by subtracting baseline from the later measure.

2.4. Elicitation of social environment and experimental task

Our aim was to investigate how the decline in generosity across social distance is affected by CORT and NA. Thus, we asked participants prior to pill intake to describe their social environment using a similar method reported by Margittai et al. (2015) and Strombach et al. (2014, 2015). Individuals were asked to give the names of representatives for social distances (SD) 1, 2, 3, 5, 10 and 20, with SD 1 representing the person they feel closest to, with decreasing closeness as a function of increasing social distance. Although we also included distances 50 and 100 in the experiment, participants were not asked to provide a name for these, as they represent remote individuals or strangers whose

names are likely to be unknown to the participant.

The social discounting task used was identical to that reported in Margittai et al. (2015) consisting of 24 rounds of a dictator game presented in randomized order, where participants had to indicate how much of a given endowment (EUR13, EUR15 and EUR17) they would be willing to donate to the individuals at the 8 social distance levels mentioned before. Our dependent variable was the percentage of money shared at each SD. The task was fully incentive compatible, thus, participants were informed that, subsequent to task performance, one of their choices would be selected randomly and paid out, potentially resulting in payment for the participant and another person. The other person either received the money via cheque, or if the choice was about remote individuals or strangers (SD 50 and SD 100), the money was distributed randomly at the university campus.

2.5. Social discounting function

To assess social distance dependent changes in generosity, we fitted a standard hyperbolic function (Eq. (1)) to the percentage of money shared at each social distance level, using robust nonlinear regression with an iterative least square estimation procedure. Fits were done both individually for each participant and at a group level (separately for each experimental group), similarly to the method described in Margittai et al. (2015), Fig. 3A.

$$v = \frac{V}{(1 + kD)} \quad (1)$$

Eq. (1) is identical to that employed by Jones and Rachlin (2006); Margittai et al. (2015); Strombach et al. (2014, 2015) & Takahashi, (2007), with v representing the discounted other-regarding value of the percentage of money shared, V referring to the height of the function which can be interpreted as generosity at close social distance, D as a measure of social distance and k describing the degree of discounting. We used individual V and k parameters as a measure of a participants' generosity at close social distance (parameter V), and the decrease in generosity as a function of social distance (parameter k).

2.6. Procedure

Individuals arrived at the laboratory between 2:00PM and 6:00PM for their experimental sessions in order to control for diurnal variations of cortisol levels. After providing informed consent, participants completed a number of baseline measures as detailed in Table 1, and completed a questionnaire aimed at eliciting the social environment. Thereafter, participants ingested the drugs and a waiting period commenced, during which instructions for the experimental task were given, followed by a quiz to ensure comprehension. Subsequently, participants were free to read a number of magazines that were provided by the experimenters, but they were instructed not to leave the room or to communicate. The experimental task started approximately 65 min after pill intake and lasted less than 10 min to complete.

3. Results

3.1. Trait and baseline measures

To ensure that there was no difference between the four experimental groups in baseline and trait variables that could confound our findings, we carried out a number of univariate analyses of variance (ANOVA) with the between subject factor experimental group (placebo, yohimbine, hydrocortisone, yohimbine + hydrocortisone) and the trait and baseline measures listed in 2.2 above. We found no significant differences between the groups on any of these measures, see Table 1 for a detailed description.

3.2. Pharmacological manipulation check

Baseline corrected changes in CORT and NA concentration values over time were analysed using mixed ANOVAs with the within subject variable timepoint of testing (+30, +60 and +75 min post pill intake) and between subject factors yohimbine intake (yohimbine vs. placebo) and hydrocortisone intake (hydrocortisone vs. placebo). Sphericity violations were corrected using Greenhouse-Geisser correction. Salivary cortisol increased over time in participants who received hydrocortisone (timepoint x hydrocortisone interaction: $F_{1.47,193.90} = 20.79$, $p < .001$, $\eta_p^2 = 0.14$), but not in those who received yohimbine (timepoint x yohimbine interaction: $F_{1.47,193.90} = 0.50$, $p = .550$, $\eta_p^2 = 0.00$), nor was there an interaction between yohimbine and hydrocortisone on salivary CORT changes over time (timepoint x yohimbine x hydrocortisone: $F_{1.47,193.90} = 0.25$, $p = .711$, $\eta_p^2 = 0.00$, Fig. 1A). Salivary alpha-amylase levels increased over time in those who received yohimbine (timepoint x yohimbine interaction: $F_{1.63,216.48} = 3.36$, $p < .05$, $\eta_p^2 = 0.03$), but not in those who received hydrocortisone (timepoint x hydrocortisone interaction: $F_{1.63,216.48} = 0.43$, $p = .613$, $\eta_p^2 = 0.00$), nor was there an interaction between hydrocortisone and yohimbine on sAA levels over time (timepoint x hydrocortisone x yohimbine: $F_{1.63,216.48} = 0.24$, $p = .742$, $\eta_p^2 = 0.00$, Fig. 1B).

3.3. Subjective stress and mood ratings

Baseline corrected changes in positive and negative mood and

Table 1
Trait and baseline measures.

	Placebo M (SD)	Yohimbine M (SD)	Hydrocortisone M (SD)	YohCort M (SD)	F-value	p-value	Effect size (η_p^2)
Age	24.80 (5.42)	23.44 (3.82)	26.59 (10.09)	26.00 (5.64)	1.56	0.201	0.03
BMI	22.53 (2.13)	22.79 (1.80)	22.85 (2.03)	23.58 (2.02)	1.80	0.150	0.04
Baseline cortisol (nmol/l)	19.34 (11.38)	15.36 (5.14)	20.42 (19.54)	15.98 (12.44)	1.27	0.288	0.03
Baseline alpha-amylase (U/mL)	58.62 (40.64)	45.31 (34.62)	67.30 (64.39)	57.26 (41.18)	1.35	0.259	0.03
VAS	11.18 (12.56)	11.56 (10.42)	13.34 (14.07)	14.77 (12.37)	0.63	0.598	0.01
PANAS positive mood	30.62 (6.33)	28.83 (6.42)	29.35 (5.74)	27.59 (7.48)	1.27	0.288	0.03
PANAS negative mood	12.03 (3.15)	12.94 (2.99)	12.39 (3.19)	12.57 (2.85)	0.55	0.652	0.01
STAI	38.46 (10.61)	43.08 (9.38)	39.65 (9.31)	38.51 (7.52)	1.96	0.122	0.04
BIS-15	29.06 (4.67)	32.06 (8.11)	32.27 (5.24)	31.74 (6.31)	2.05	0.110	0.04
BIS total	18.71 (3.94)	18.78 (4.12)	18.92 (3.55)	18.14 (3.50)	0.29	0.834	0.01
BAS drive	12.94 (1.97)	12.69 (2.20)	12.40 (1.82)	12.03 (1.76)	1.44	0.235	0.03
BAS fun seeking	11.91 (1.92)	12.42 (2.98)	12.65 (1.60)	12.40 (1.85)	0.98	0.406	0.02
BAS reward responsiveness	16.77 (1.86)	16.19 (2.76)	16.78 (2.26)	16.34 (2.11)	0.62	0.602	0.01
SDS-17	9.71 (3.09)	9.92 (2.48)	10.08 (2.71)	10.37 (2.41)	0.38	0.771	0.01
SPF	38.66 (7.79)	39.47 (6.12)	41.27 (7.22)	41.94 (4.29)	1.96	0.124	0.04
Chronotype	12.03 (4.42)	11.56 (3.08)	12.94 (3.95)	11.54 (3.58)	1.10	0.350	0.02
Risk taking	4.17 (1.10)	4.17 (.81)	4.14 (.89)	4.03 (1.20)	0.15	0.927	0.003

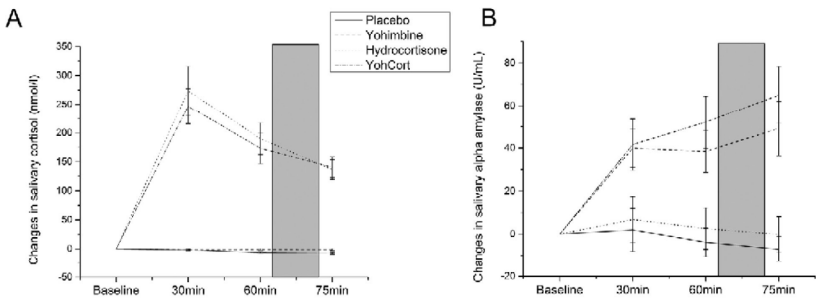

Fig. 1. (A) baseline corrected changes in salivary cortisol +30, +60 and +75 min after pill intake. Individuals who received hydrocortisone had increased salivary cortisol levels compared to those who did not. (B) baseline corrected changes in salivary alpha-amylase +30, +60 and +75 min after pill intake. Individuals who received yohimbine had higher concentrations of sAA than those who did not. The timing of experimental tasks is indicated by grey shaded bars. Error bars indicate ± 1 SEM.

baseline corrected changes in subjective feelings of stress +30 and +60 min after pill intake were analysed with ANOVAs with the between-subject factors yohimbine (yohimbine vs placebo) and hydrocortisone (hydrocortisone vs. placebo).

Baseline corrected change in positive affect from baseline to directly before the experimental task was not significantly affected by the treatment (main effect of hydrocortisone: $F_{1,132} = 2.83$, $p = .095$, $\eta_p^2 = 0.02$, main effect of yohimbine: $F_{1,132} = 0.004$, $p = .949$, $\eta_p^2 = 0.00$, yohimbine x hydrocortisone: $F_{1,132} = 1.19$, $p = .277$, $\eta_p^2 = 0.01$), but the decrease in negative mood was less pronounced in those who received yohimbine than in those who did not (main effect of yohimbine: $F_{1,137} = 4.61$, $p < .05$, $\eta_p^2 = 0.03$). Change in negative mood was not significantly affected by hydrocortisone intake ($F_{1,137} = 0.01$, $p = .930$, $\eta_p^2 = 0.00$), nor was there an interaction between the two substances on changes in negative mood ($F_{1,137} = 1.21$, $p = .273$, $\eta_p^2 = 0.01$, Fig. 2A).

We additionally carried out two one sample *t*-tests to compare baseline corrected changes in positive and negative mood against the value 0. These analyses confirmed that these changes were significantly different from 0 (Positive change: $M = -2.31$, $SD = 4.68$, $t(134) = -5.76$, $p < 0.001$: Negative change: $M = -0.57$, $SD = 2.16$, $t(139) = -3.16$, $p = .002$).

In a similar vein we also carried out two one-sample *t*-tests to compare baseline corrected changes in subjective feelings of stress at +60 min against the value 0. These analyses revealed that individuals who received yohimbine had a slight increase in feelings of stress, albeit only marginally significantly different from 0 ($M = 3.14$, $SD = 13.52$, $t(69) = 1.95$, $p = .056$), while those who received no yohimbine showed a marginally significant decrease ($M = -2.34$, $SD = 10.20$, $t(69) = -1.92$, $p = .059$). Though these changes were not significantly different from 0, due to their opposing trends we wanted to test whether there was a difference in feelings of stress between those who received yohimbine than those who did not. Baseline corrected increase in subjective feelings of stress directly before the experimental task (at the +60 min testing time point) were higher in those who received yohimbine than in those who did not (main effect of yohimbine: $F_{1,136} = 7.36$, $p < .05$, $\eta_p^2 = 0.05$), which is in line with prior research (e.g. Elman et al., 2012; Margittai et al., 2017). In contrast, hydrocortisone intake had no effect on subjective feelings of stress, nor was there an interaction between the two substances (main effect of hydrocortisone: $F_{1,136} = 0.53$, $p = .468$, $\eta_p^2 = 0.00$, hydrocortisone x yohimbine: $F_{1,136} = 0.13$, $p = .721$, $\eta_p^2 = 0.00$). Changes in subjective feelings of stress did not differ between the groups 30 min after pill intake (all $p > .184$, Fig. 2B). As changes in negative mood and subjective feelings of stress differed between the experimental groups, their potential confounding effects on our main findings were investigated (see Section 3.4).

3.4. Generosity to close others is boosted by hydrocortisone but this increase is offset by noradrenergic action

To investigate how CORT and NA impact social discounting in isolation as well as in combination, we analysed individual social discounting parameters *V* (representing generosity to close others) and *k* (representing the decline of generosity as a function of social distance) using 2 × 2 between subject ANOVAs with the factor yohimbine intake (yes/no) and hydrocortisone intake (yes/no). While we did not find any significant main effects on the *V* parameter (all $p > .284$), we found a significant interaction effect between yohimbine and hydrocortisone intake ($F_{1,139} = 5.94$, $p < .05$, $\eta_p^2 = 0.04$). Holm-Bonferroni corrected planned comparisons revealed that individuals who received hydrocortisone had higher *V* parameters, compared to those who received placebo ($t(64.72) = -2.30$, $p < .05$, $d = 0.54$), or cort + yohimbine ($t(59.77) = -2.00$, $p < .05$, $d = 0.55$, Fig. 3B). Thus, while CORT action alone increased generosity towards close others, additional YOH administration offset the CORT-induced boost in generosity. None of the other comparisons reached significance (all $p > .170$).

Subjective feelings of stress and changes in negative mood differed between the experimental groups at the +60 min timepoint (see Section 3.3), therefore we carried out a correlation analysis between the *V* parameter and subjective feelings of stress as well as changes in negative mood to exclude any potential confounding effects. The results of

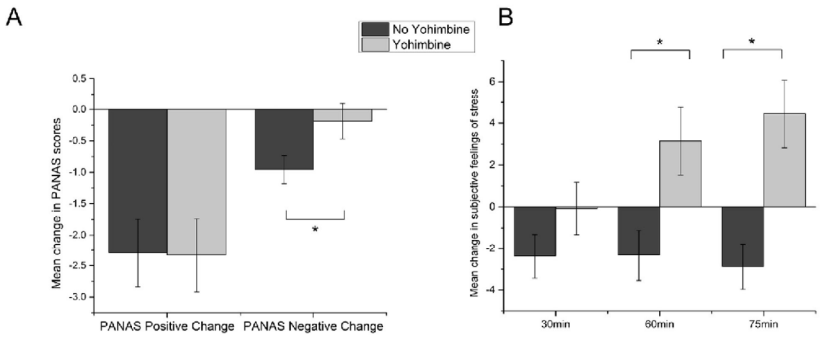

Fig. 2. (A) changes in positive and negative mood from baseline to directly before the experimental tasks. Individuals who received yohimbine had a smaller reduction in negative mood than those who received no yohimbine. Changes in positive mood were not affected by the treatment. (B) baseline corrected changes in subjective feelings of stress. Subjective levels of stress were perceived to be higher in those who received yohimbine than in those who did not +60 and +75 min post pill intake. Significant differences are indicated by an asterisk (* $p < .05$, ** $p < .01$, ***$p < .001$). Error bars indicate ± 1 SEM.

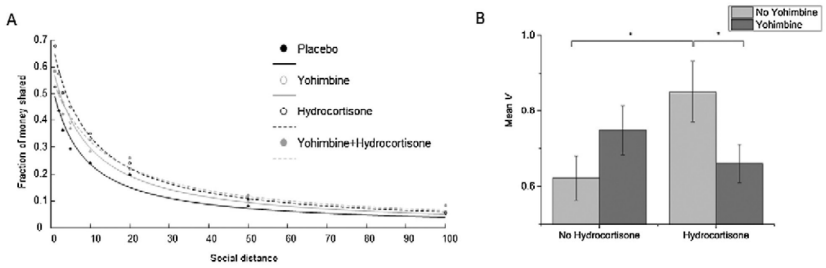

Fig. 3. (A) Decline in generosity across social distance in the four experimental groups as described by the hyperbolic model. (B) Individuals who received hydrocortisone had significantly higher V parameters, reflecting increased generosity at close social distance, which was offset by additional NA activation. Significant differences are indicated by an asterisk (* $p < .05$). Error bars indicate ± 1 SEM.

these analyses were not significant ($p = .164$ and $p = .670$ respectively). Furthermore, we repeated the main analyses with changes in negative mood and increases in subjective feelings of stress as covariates, which did not change the results. Thus subjective feelings of stress and changes in negative mood were unlikely to have interfered with the CORT- and NA-effects on *V*.

There were no main or interaction effects of CORT and YOH on the log-transformed *k* parameters (all $p > .285$), thus there was no evidence suggesting that CORT and NA affected the general decline in generosity across social distance.

In order to test whether belief about treatment may have influenced results, we asked participants to indicate at the end of the experiment whether they believe to have been in the treatment or placebo groups. A chi-square test revealed that participants who believed to have received placebo vs. active substances differed between the four experimental conditions (placebo: $belief_{placebo} = 27$, $belief_{treatment} = 8$, yohimbine: $belief_{placebo} = 26$, $belief_{treatment} = 10$, cortisol: $belief_{placebo} = 32$, $belief_{treatment} = 5$, yohcort: $belief_{placebo} = 16$, $belief_{treatment} = 19$; $\chi^2(3, N=143) = 15.72$, $p = .001$). However, a point-biserial correlation between treatment expectancy and individual *V* parameters did not reach significance ($r = -0.002$, $p = .979$), suggesting that treatment expectancy was unlikely to have interfered with our findings. We carried out a further chi-square test to investigate whether participants did better than chance in estimating what they received. This analysis showed that there was no difference from chance in their guessing performance ($\chi2(3, N = 143) = 3.08$, $p = .094$).

4. Discussion

Acute stress and associated elevations in CORT and NA have been known to impact social decision making (Buchanan and Preston, 2014; Starcke and Brand, 2012) with some studies showing that acute stress facilitates prosocial behaviour (Buchanan and Preston, 2014; Margittai et al., 2015; Taylor et al., 2000; Tomova et al., 2017; Von Dawans et al., 2012), in stark contrast to the traditionally held view that the primary reaction to acute stress is fight-or-flight. In support of the tend-and-befriend hypothesis, we recently showed that psycho-social stress boosts giving behaviour towards socially close others from whom support can be expected in stressful times, but not towards socially distant others who are less likely to help (Margittai et al., 2015). Here, we asked if the effects of psycho-social stress on social discounting are mediated by the stress neuromodulators CORT and/or NA. Crucially, we contrasted two competing hypotheses about how CORT and NA could be involved in the observed effect: both neuromodulators could either act in concert to boost generosity, or, alternatively CORT and NA may have opposing roles, with CORT fostering generosity, and NA inhibiting CORT-induced prosocial tendencies. Our results support the latter hypothesis: exogenous administration of hydrocortisone alone led to increased prosocial behaviour towards socially close recipients, reflected in higher *V* parameters in the social discount function, but additional noradrenergic activation brought these levels back to baseline. In line with prior findings (Margittai et al., 2015), neither drug affected the slope of the social discount function.

Taken together, the fact that CORT and NA had dissociable roles in promoting generosity, or inhibiting it, respectively, potentially resolves one of the most perplexing puzzles in the current stress literature: why does stress, or psychopharmacological challenges aimed to investigate the effects of the main stress neuromodulators, sometimes trigger tend-and-befriend (Margittai et al., 2015; Von Dawans et al., 2012), and at other times more socially antagonistic responses (FeldmanHall et al., 2015; Steinbeis et al., 2015)? Here, we propose that stress does not always provoke one *or* the other response, but *can boost either tendency,* depending on the intensity of the stressor, and the time-dependent dynamics of neuroendocrine action. Immediately after stress onset, noradrenergic activation is high, and NA and CORT (non-genomically) affect brain functioning in concert, but once the short-lived NA elevations subside, CORT dominates the endocrine stress response particularly via slow genomic actions (Hermans et al., 2014). Thus, our theory predicts that fight-or-flight tendencies should occur only in the acute phase of stress when NA- and arousal levels are high, but tend-and-befriend responses should predominantly emerge in the immediate or delayed aftermath of stress, where NA action fades while CORT action remains (Bendahan et al., 2017; Pabst et al., 2013). The implied timeframe of this hypothesis also fits with the general idea that fight-or-flight tendencies are aimed at ending, removing, or escaping from, the acute stressor, while tend-or-befriend responses are a putative coping strategy (Taylor, 2006) that becomes mostly relevant later.

As many prior studies neglected to measure noradrenergic activation and focused solely on cortisol increases after stress, it has so far been difficult to ascertain whether unmeasured noradrenergic activation may have explained some variance in the reported findings. This is particularly true for those studies that measured decision making at a time window where both NA and CORT should have been high, such as approximately 10–20 min after stress onset. As the interplay between the two stress hormones changes very rapidly over time (Pabst et al., 2013), a few minutes difference in the time of behavioural testing may lead to a shift in the balance of dominance between NA and CORT. This has made it difficult to disentangle the roles of the two stress neuromodulators on pro- and antisocial behaviour, and may explain the divergence in existing literature. The results presented here hope to make a valuable contribution to the resolution and reconciliation of these issues.

Our findings that CORT boosted generous behaviour corroborate and extend prior reports of a correlation between CORT elevations and social affiliation after stress (Berger et al., 2016). Furthermore, the fact that the increase in generosity was restricted to individuals socially close to the decision maker lend further support to the idea of a tend-and-befriend reaction (Margittai et al., 2015; Taylor et al., 2000; Von Dawans et al., 2012) by demonstrating that social affiliative efforts are primarily focused on individuals from whom help and protection can reasonably be expected, (Margittai et al., 2015) as opposed to indiscriminately befriending everyone. More broadly, our findings are in line with research focusing on the role of CORT in emotional contagion (Buchanan and Preston, 2014) in particular with those of Engert et al. (2014) who found that observing individuals undergo a stressful

situation resulted in cortisol responses in observers, which was particularly pronounced when the observer and the observed were socially close.

Importantly, our finding that the CORT-related boost in prosocial behaviour was offset by NA action provides novel insights into the role of NA in social cognition. However, although our findings are in line with prior studies demonstrating the role of NA in arousal and aggressive behaviour (Nelson and Trainor, 2007), we did not observe actual other-harming behaviour in our participants. Hence, one might plausibly ask why NA did not produce genuinely antagonistic tendencies, as would be expected from a true fight-or-flight reaction. It is possible that, instead of promoting antagonistic fight-or-flight responses, NA might simply inhibit CORT-induced prosocial motives, while leaving aggressive predispositions aimed at harming others unaffected. Alternatively, it is also conceivable that NA induces true aggression, but the nature of our task masked those putative NA-driven antagonistic tendencies. As our primary focus was to examine the psychopharmacology of *prosocial* behaviour, we used the dictator game (Kahneman et al., 1986) which is ideally suited to study prosociality, but it does not provide a real opportunity for probing other-harming behaviours. Thus, to extend these findings, future research should investigate whether, when given an opportunity for aggression, individuals with increased levels of NA indeed show a propensity to be more antisocial.

Although the pharmacological manipulation used in the present study presents an excellent opportunity to study the causal effects of CORT and NA on decision making, it is also important to consider that it does not directly parallel a naturally occurring stress response. For instance, the levels of hormone concentrations are significantly higher and longer-lasting after the pharmacological manipulation than after naturally occurring stress (Lupien et al., 1999; Margittai et al., 2016), and the subjective emotional experience also differs between the two situations (Margittai et al., 2017). Furthermore, CORT increases in natural stress always happen subsequent to and in combination with NA, which is different from administering the two substances in isolation.

A further question that arises is what neural mechanisms may underlie the observed effects. Speculatively we propose that the right temporoparietal junction (rTPJ) may play a crucial role the effect of stress neuromodulators on social discounting. Two research papers from our group and collaborators have highlighted the prominent role of this brain region in social discounting. Strombach et al. (2015) demonstrated that rTPJ activation facilitated generous decision making by overcoming the bias to be egoistic and Soutschek et al. (2016) applied transcranial magnetic stimulation to the rTPJ and found altered social discounting which was accompanied by perspective taking deficits. As stress is known to affect TPJ function (e.g. Hermans et al., 2014), the stress-neuromodulator effects on social discounting reported here might be mediated by changes in TPJ operation. To elucidate the exact neural underpinnings of our findings, future neuroimaging studies are necessary.

As we only tested male participants, it is important to consider whether the results presented here also apply to women. Gender differences in stress effects on social cognition (Smeets et al., 2009; Tomova et al., 2014) have already been documented. For instance, Tomova et al. (2014) found that exposure to acute stress leads to decreased self-other distinction in men, with the opposite pattern being observed in women. Smeets et al. (2009) showed that cortisol elevations after stress were negatively correlated with social cognition in men and positively in women. Thus, the present results cannot readily be generalized across genders.

A further point to clarify is related to potential expectancy effects of the drugs received. Although we asked participants about the drugs they thought they had received, it is plausible that this question alone was not sufficient to quantify expectancy effects. Popular belief of a drug's effect might influence how participants behave during psychopharmacological challenges. However, even if participants had been aware of what they had ingested, it is unclear if, and how, popular belief about hydrocortisone and yohimbine action affect behavior, as these drugs are not as clearly associated with an expected psychological effect in general public perception in the same way that, for example, testosterone is believed linked to aggression.

Overall, our results demonstrate dissociable roles of CORT and NA on prosocial behaviour. We show that CORT in isolation promotes prosocial tendencies, particularly towards close others, evidential of increased social affiliative tendencies. Furthermore, concurrent noradrenergic activation prevents this CORT-related increase in generosity from occurring. Our findings contribute to the understanding of the neurobiological basis of acute stress effects on social behaviour, and they suggest the intriguing possibility that the neuroendocrine stress response triggers both tend-and-befriend as well as fight-or-flight responses in chorus.

Conflict of interest declaration

The authors declare no conflict of interest.

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CHAPTER 6

General discussion

Research presented in this dissertation was aimed at broadening our understanding of how acute stress and its biological markers cortisol and noradrenaline alter the way we make certain types of decisions. In our first experiment we investigated whether CORT and NA impact the way we make decisions about money by way of altering how we perceive losses and gains as well as risk. We used a pharmacological manipulation and discovered that the concurrent administration of yohimbine and hydrocortisone resulted in decreased loss aversion in our participants compared to those who received only one of the two substances. In contrast, we found no effect of our manipulation on risk attitudes. Our findings make two notable contributions to our understanding of how CORT and NA affect our economic decision making. Firstly, we were able to conceptually disentangle risk attitude from loss aversion, which are often entangled in decision making paradigms and are likely to be responsible for the diversity and contradiction in existing findings. We were also able to show that it is our attitude to loss and not to risk that is altered by the biological processes underlying the stress response and provided more evidence that the action CORT and NA together drive behavior in the opposite direction to each neuromodulator alone. Considering the real life implications of our findings, decreased loss aversion after combined NA and CORT action may reflect the adaptive advantage of our natural stress response. Accordingly, when faced with a threat and our body releases noradrenaline followed by cortisol, these biological processes prepare us to be more vigilant and either fight back or flee. We speculate

that in such critical situations it is likely to be advantageous to worry less about losses, which might slow us down and impair our ability to deal with the situation adequately.

Our second research project was aimed at uncovering the more general effects of stress hormones on our cognition. There are several lines of evidence indicating that stress alters our memory and attentional processes and there is a lot of anecdotal and some empirical research blaming stress with clouding our judgement and our ability of sound deliberation. Though many of us can think of situations where we said or thought something under stress that we later regretted or that turned out to be wrong, there has been very little in the way of direct empirical research testing how stress affects our cognitive reflection ability. In 2016 Yu published a review titled “Stress potentiates decision biases: A stress induced deliberation-to-intuition (SIDI) model” (Yu, 2016) in which the author collected and reviewed a multitude of research findings that indirectly confirmed the idea that acute stress impairs our ability to deliberate and drives us towards more automatic processes, but a direct test of this hypothesis was still lacking. With this in mind, we set out to test this question directly using the aforementioned pharmacological manipulation and the Cognitive Reflection Test, a paradigm designed to directly tap into automatic and deliberate thinking processes. Our results showed that individuals who were given hydrocortisone, either alone or in combination with yohimbine, had significantly lower scores on this test, than individuals who did not receive hydrocortisone. The idea that increased levels of CORT result in less deliberate and more automatic thinking fits well with the evident neural changes that take place as a result of stress. In the introduction I detailed two important brain systems, the executive control network including prefrontal areas and the salience network including limbic structures. Evidence has already shown that acute stress shifts the balance of these two systems towards dominance of the salience network and downregulates executive control regions, which is reflected in the dominance of automatic over deliberate thinking processes. Considering the real life relevance of these findings, they fit well with the idea of an acute stress reaction: in

situations of imminent threat, it is of an adaptive advantage to concentrate our abilities on quick, automatic and vigilant reactions. Arguably, making errors in such situations by reacting once too often and potentially misinterpreting a neutral situation as a threat is less detrimental than waiting and carefully analyzing the situation which can lead to delayed responding to an actual threat. However, in case of stressors of a more intellectual nature, such as taking an exam or having a meeting at work the very same reaction may lead to erroneous answers, poor judgement and increased susceptibility to biases. Our results thus raise awareness that, although the stress response was designed by evolution with good intentions, it may in some cases be to our detriment.

Shifting the focus towards social decisions we also tested whether exposure to acute psychosocial stress in the form of the group version of the Trier Social Stress Test would lead to altered social distance dependent levels of generosity in a decision making task. Our results confirmed that exposure to acute stress resulted in heightened levels of generosity, but only towards individuals who were socially close to the decision maker. In contrast, generosity after stress was unchanged towards more socially distant individuals. These findings contribute to our understanding of how stress impacts social decisions by highlighting the importance of social distance between decision maker and recipient and thus helps reconcile some existing, contradictory results that either state that stress leads to more, or that it leads to less prosocial behavior. Lastly, the findings offer an optimistic twist on the traditionally held view that acute stress primarily leads to aggression or antisocial tendencies by showing that if conditions and timing are right, stress may in fact make us more prosocial towards others. Another important aspect of our first experiment was testing whether stress effects on decision making are time dependent. The inspiration for this research question has its basis in the increasing amount of compelling evidence demonstrating that stress effects in general and the acute stress reaction in particular occur in accordance with a distinct temporal profile. Depending on how much time has passed after encountering a stressor, stress may result in

entirely opposite effects on behavior, with corresponding neurobiological changes, such non-genomic (in the early aftermath) versus genomic (in the later aftermath) cortisol effects (Hermans et al., 2014), and the presence or absence of simultaneous sympathetic and HPA axis activation. Results from behavioral studies have already begun to emerge showing that the late aftermath of stress drives behavior in a different direction than acute stress (Bendahan et al., 2017; Vinkers et al., 2013). In other words, instead of simply reverting back to baseline, behavior is driven below baseline levels (Vinkers et al., 2013). There is some evidence that these changes are also reflected in opposing patterns of neural activation in the early and late aftermath of stress (Hermans et al., 2014). Our results showed that generosity in the late aftermath of stress was indeed significantly lower than shortly after stress, but these generosity levels were no different from those observed in the control group. Thus, our results do not support the view that these homeostatic regulatory processes decrease generosity to below baseline levels. Despite the lack of behavioral effects it is nonetheless possible that changes corresponding to the two distinct temporal niches were visible at a neural level. This should be investigated in future research.

Although these findings made a promising first step towards determining acute stress effects on social distance dependent generosity levels, they left a number of important questions open. Firstly, what exact roles did CORT and NA play in the observed effects? In our initial study, we opted for a time window for our experimental task within 10 minutes after the cessation of the stressor, that is, from 20 to 30 minutes after stress onset. We chose this timing carefully in order to capture a time period where noradrenergic activation is still high and HPA axis activation and cortisol secretion reached significant elevations as well. Though we assumed that the increase in generosity was caused by the combined effect of both stress neuromodulators because it was only observed in the acute phase of stress, we needed to employ a causal pharmacological manipulation to make definitive conclusions. In order to answer these questions, we set out to repeat the first experiment, but instead of using the

TSST as a stress induction procedure, we pharmacologically manipulated levels of NA and CORT. To find out the isolated as well as combined effects of these hormones we employed separate conditions where either NA, CORT, or both NA and CORT increases were targeted using yohimbine and/or hydrocortisone administration. Based on the results of our first experiment, we expected that NA and CORT acting together would lead to the same effect observed in our experiment using the TSST as behavioral stressor. However, our results showed that CORT alone lead to the same pattern of changes that we observed in the first study, namely increased generosity towards close others. Interestingly, when NA was added to CORT, generosity levels decreased back to baseline. Thus, our study not only provided novel insights into the dissociable and opposing effects of NA and CORT on prosocial behavior but also put the findings of our first experiment into a new perspective. As mentioned above, we had originally assumed that the increased levels of generosity to close others after the TSST was caused by the combined effects of CORT and NA as the timing of the decision making tasks had been chosen so that both neuromodulators would be increased. However, given our pharmacological results where the effect was dominated by CORT we must consider that this had also been the case in our behavioral study. This further highlights the importance of using causal, pharmacological designs to confirm findings from experiments using behavioral stressors. This point is particularly important to consider, as the field of stress research is plagued with diverse and often contradictory findings. Our results raise attention to the fact that this discrepancy may partly be explained by experimental designs that only measure or manipulate one of the two stress neuromodulators while leaving the other uncontrolled for, or use behavioral stressors where the distinct roles of the two stress neuromodulators may be difficult to disentangle.

Overarching message

Having looked at all the individual findings from the research projects presented here the question naturally follows, what do these results say about stress and decision making overall. We learned that acute stress has a profound effect on the way we make decisions about money and people close to us and the way we think and reason in general. We know that, given the right timing, acute stress can win us friends, or at the very least consider the wellbeing of those closest to us. We also have evidence to suggest that this effect is driven by the hormone cortisol, the same substance that leads us to quick, intuitive and automatic replies in tests of cognitive reflection. Perhaps these two findings have a common ground: maybe increased generosity towards those close to us after stress is simply an increased tendency to do what we would automatically do anyway, that is, be nice to those who matter to us most. This theory is in line with a study published by Rand, Greene, & Nowak (2012), who found that quicker decisions were associated with more cooperative tendencies in economic games, which was particularly pronounced when individuals were primed to trust their intuitions and goes in line with findings of our own group (Strombach et al., 2015).

The research projects presented here also shed more light on the complex and intricate pattern of interactions between the neuromodulators cortisol and noradrenaline: their effects in combination can run counter to their effects in isolation. This insight will hopefully provide an important point to keep in mind for future studies on the effects of stress or stress neuromodulators on behavior, and will help scientists design systematic experiments that lead to distinguished conclusions.

The "tend and befriend" and "fight or flight" model

In our study on the effects of CORT and NA on social behavior presented in Chapter 5 we proposed a speculative but promising new idea about how stress may affect how we relate to others. So far most researchers have either held the view that acute stress leads to antisocial tendencies in form of the fight-or-flight reaction, or that it promotes prosocial behavior in line with the tend-and-befriend hypothesis. However, findings presented here, in combination with some existing results, give rise to the possibility that the acute stress reaction is not associated with either fight-of-flight or tend-and-befriend tendencies, but it can promote *both* leanings, depending on the timing of the decision in relation to stress and relative concentrations of CORT and NA. More specifically, immediately after encountering the stressor, where sympathetic activation and NA levels surge, we may react to stress in a fight-or-flight manner, whereas later on, as the levels of glucocorticoids rise and sympathetic activation diminishes the dominance of social affiliative tendencies and coping strategies in the form of a tend-and-befriend reaction may take over.

This idea is most clearly supported by the results of our experiment presented in Chapter 5: only those in the cortisol group showed increased levels of prosocial tendencies, while once NA was administered simultaneously with CORT prosocial tendencies were reduced back to baseline levels. Of course one could argue that baseline levels of prosocial tendencies do not represent fight-or-flight tendencies. While this is a valid point, the paradigm we used did not really allow for an option to fight, thus we may simply have been unable to capture these tendencies. Future studies should investigate this in more detail using decision making paradigms incorporating an option for aggressive tendencies such as the intergroup prisoner's dilemma game (IPD-MD; De Dreu et al., 2010), which allows participants to decide between being egoistic, benefitting their ingroup and/or damaging an outgroup.

The idea that cortisol may foster social affiliative tendencies as well as prosocial behavior already has some foundation in existing research findings. For instance, high cortisol responders to the TSST exhibited stronger affiliative bonds after exposure to the group-TSST. Environmental donations were positively associated with stress induced increases in cortisol levels in a male sample (Sollberger, Bernauer, & Ehlert, 2016) and Barraza & Zak (2009) found that charitable donations as well as more generous offers in the UG were positively correlated with changes in cortisol in response to viewing emotional videos, and the dual-hormone hypothesis also states that high basal cortisol plays an important role in the relationship between testosterone and empathy (Zilioli, Ponzi, Henry, & Maestripieri, 2015). Though Steinbeis, Engert, Linz, & Singer (2015) found no correlation between stress-induced cortisol levels and trusting behavior, there was a positive correlation between this behavior and baseline cortisol levels. In contrast, blunted cortisol awakening response has been associated with lack of empathy and psychopathic traits (Johnson, Caron, & Mikolajewski, 2014).

Of course findings demonstrating the opposite pattern also exist. For instance Starcke, Polzer, Wolf, & Brand (2011) found that cortisol responses to a stressor were positively correlated with egoistic decision making in moral dilemmas, and other studies reported no correlation between stress induced changes in cortisol levels and prosocial behavior (Bendahan et al., 2017; FeldmanHall, Raio, Kubota, Seiler, & Phelps, 2015; Steinbeis et al., 2015) as well as our own experiment reported in Chapter 4. Whether the lack of correlation between behavioral and cortisol measures reflects that such behaviors are genuinely driven by other biological processes, or whether it is due to issues such as sample size, task characteristics or the relatively low number of cortisol responders in some studies (e.g. Steinbeis 2015) is unclear. However, our pharmacological design delivers positive, causal evidence that cortisol may indeed be involved in social affiliative tendencies.

The role of noradrenaline in the fight-or-flight reaction and aggression is also well established. Animal studies have shown that the rapid surge in catecholamines brings about peripheral as well as central nervous system changes that prepare an animal for a physical fight (Haller, Makara, & Kruk, 1998) and NA and aggression have also been linked in human studies. However, evidence from human studies about the involvement of NA in aggression primarily comes from clinical studies on antisocial behavior (e.g. Susman, 2006) and aggressive behavioral problems (Raine, 2002). As most studies on decision making focus on cortisol, little is known about the role of noradrenergic arousal in this context, and evidence of a correlation between egoistic or hostile decision making and noradrenergic arousal in response to acute stress is lacking. So far only one study found involvement of NA activation in decision making by demonstrating that individuals who engaged in altruistic punishment in an ultimatum game also exhibited increases in the levels of salivary alpha amylase pre and post decision making (Takagishi, Fujii, Kameshima, Koizumi, & Takahashi, 2009).

If we were to try to apply our proposed model to decision making findings published so far, we would expect that the higher NA activation was during the decision making tasks, the less prosocial behavior should have been observed and vica versa. Unfortunately, the number of published results directly investigating the effects of acute stress on decision making is very low and they all use various different paradigms making a comparison difficult. Furthermore only some studies reported measuring correlates of NA activation, thus it is difficult to conclude whether and to what extent sympathetic activation was still present when participants made their decisions. One other possibility to infer the likely extent of NA activation during a decision making tasks is considering when these were carried out, as we know that sympathetic activation usually goes back to baseline approximately 10 minutes after cessation of the stressor. FeldmanHall et al. (2015), Steinbeis et al. (2015) and Bendahan et al. (2017) all had their participants complete decision making tasks at time periods where sympathetic activation is likely to have been high and overall observed reduced prosocial

behaviour. Though this fits well with our proposed model, there are contradictory findings: Von Dawans, Fischbacher, Kirschbaum, Fehr, & Heinrichs (2012) reported increased prosocial behavior after stress while also employing a similar timing profile as the three aforementioned studies. Furthermore another study that found decreased donations in the DG both immediately and 90 minutes after the task, when NA activation was certainly no longer increased (Vinkers et al., 2013).

Furthermore, while results of our second experiment, as mentioned above, fit well with our proposed theory, findings of our first experiment also raise some questions. Most importantly, why did we find increased levels of prosocial behavior at a time window, where both stress neuromodulators should have still been active, when our proposed model suggests that a surge in NA should promote fight or flight. While our data do not allow for a certain answer to this question, we may speculate about a number of possible explanations. Firstly, perhaps we did not successfully capture heightened levels of NA thus our effect had been dominated by CORT. It may also be that other, unmeasured elevations of hormones such as oxytocin and/or 5HT may have confounded the effect. Unfortunately the lack of correlation between behavioral measures and hormonal elevations in our first experiment also make it difficult to propose a definitive conclusion.

A possible solution could be to test decision making at additional time points that may help to disentangle between the dominance of NA and CORT in the acute stress reaction. Accordingly, to test NA dominance, the task could be carried out immediately after stress, whereas the dominance of CORT could be tested after about 20 minutes, where CORT levels surge and NA levels subside. This idea is paralleled in recent research. Pabst, Brand, & Wolf (2013) already found that acute stress impacted decision making differently 5, 18 and 28 minutes after stress exposure, and similar findings were also reported by Bendahan et al. (2017). These findings suggest that the first hour after stress is temporally dynamic adding a

further dimension to the stress reaction. Furthermore, the acute stress reaction is followed by genomic cortisol effects that develop later, which may drive behavior in yet another direction.

Overall, findings reported here together with the existing evidence related to the aggression inducing properties of NA and the putative role of CORT in social affiliation, social cognition and empathy support the idea that the differential dominance of NA and CORT may shift behavior towards either fight or flight or tend and befriend tendencies. However, due to the heterogeneity of findings and scarcity of existing results there is only ambiguous support for our theory and extensive future research is needed to consolidate and solidify the model taking into consideration the intricate temporal niches of the stress response.

Future directions

The findings presented here open up a list of new research questions that would be worthwhile to address in future projects. In one of the experiments presented here we investigated the time-dependent effects of stress on social distance dependent generosity. Our hypothesis was based on the dichotomous effect of early, non-genomic and late, genomic cortisol effects. Though we aimed to choose the timing in a way that the early and late conditions tapped into these two temporal niches, we cannot conclude with certainty what changes took place at a neural level at the time our participants completed their decision making tasks. As a next step, it would be interesting to repeat the experiment and use neuroimaging methods to elucidate these neural processes, such as upregulated salience network function shortly after stress and deactivation and decoupling of limbic regions in the aftermath of stress (Henckens et al., 2012). This information may also shed light on why we did not find any behavioral differences between our experimental and control groups in the late condition.

Follow up neuroimaging studies would also be worthwhile for our pharmacological studies presented in this dissertation. This would be particularly relevant for our study on loss aversion, as we interpreted our findings in the context of altered reward and punishment sensitivity. That is, we proposed that the combined effects of CORT and NA resulted in decreased loss aversion, by leading to decreased punishment and increased reward sensitivity, an idea that goes in line with several existing findings (for a review see Mather & Lighthall, 2012). In a further step, with the help of neuroimaging methods we could investigate whether corresponding altered neural activation in reward and punishment related brain systems is indeed present. The same holds for our experiment on the stress induced shift from deliberate to automatic thinking. This theory predicts neural activation such as reduced executive functioning and increased activation in limbic structures, which would be worthwhile to confirm using fMRI.

Additionally, there is evidence that more temporal niches may exist in the stress response than what has been proposed so far (Bendahan et al., 2017) and Pabst et al., 2013). Thus, it would be interesting to expand the time-dependent design of our first experiment to other temporal domains. Finally, as there is evidence that cortisol effects on cognition may be dose dependent, the pharmacological manipulations used here could be repeated in a design that compares different doses of the drug (see detailed discussion below in the 'Limitations' section).

Stress effects on decision making – potential mechanisms

While it is clear from research evidence that stress affects decision making, it is unclear through what mechanism stress exerts its effects. In the following section I will discuss some that have been suggested in the literature.

In their excellent and comprehensive review (Starcke & Brand, 2012) proposed four mechanisms through which stress can alter decision making: dysfunctional strategy use, impaired ability to switch from automatic to deliberate cognitive processing, altered reward and punishment sensitivity and altered feedback processing. It is important to note that these four mechanisms are not mutually exclusive, nor are they the only potential mechanisms that have been identified. Additionally, they might interact or exert their effects in parallel, thus findings could fit to more than one of these.

Dysfunctional strategy use

Research evidence suggests, that individuals may show dysfunctional strategy use in decision making and problem solving after real life or laboratory induced stress. More specifically, those who were under stress showed premature closure (decision is made before considering all alternatives) and non-systematic scanning (for a review of related literature see Starcke & Brand, 2012). Furthermore, evidence from neuroimaging studies showed that successful task performance in the GDT was associated with activation in regions including the DLPFC (Labudda et al., 2008), whose function is downregulated in situations of acute stress (Hermans et al., 2014), which may lead to impaired strategy use and impulsive decisions (Figner et al., 2010).

Dominance of automatic as opposed to deliberate processes

Stress-induced shift to lower level automatic over higher level deliberative processes may further account for stress effects on decision making and is central to the findings reported in the present thesis (see Chapter 3 and the Introduction for more detail). These two cognitive

processes also form the basis of the dual systems approach (Kahneman, 2011) according to which the analytical system is associated with slow, serial, flexible, controlled, rule-governed and effortful information processing, while the intuitive system offers fast, associative, parallel and emotional, heuristic based processing (Epstein, Pacini, Denes-Raj, & Heier, 1996). In situations of some degree of uncertainty both systems may act in parallel, characterized by a fast, first automatic response which is then adjusted by deliberative thought. However, as the deliberative system requires prefrontal-controlled cognitive resources which are downregulated by stress (Hermans et al., 2014), stress may lead to the dominance of low-level, automatic processes and lead to susceptibility to biases, more impulsive decision making and impaired ability for emotion regulation. It is also worth noting however, that the dual systems approach has been subject of some controversy in neuroscience literature (Kable & Glimcher, 2007).

Altered reward and punishment sensitivity

As discussed above stress impacts brain regions associated with the processing of rewards as well as emotionally salient stimuli such as threats and punishment. Both individual findings as well as comprehensive reviews on the subject (Mather & Lighthall, 2012; Starcke & Brand, 2012; Yu, 2016) report divergent results on stress effects on reward and punishment sensitivity. Mather & Lighthall (2012) presented the STARS model promoting increased reward salience after stress. However, this model is difficult to reconcile with a list of other findings which showed that acute stress resulted in reduced reward responsiveness, and/or increased punishment sensitivity (see Yu et al for a detailed review). **How the pharmacological manipulation of CORT and NA impact reward and threat salience was the main question addressed in our study reported in Chapter 2.**

Altered feedback processing

Starcke & Brand (2012) also proposed that stress may affect decision making through altering feedback processing, especially where the evaluation of and learning from feedback is essential to reach optimal decisions. This would be the case for decisions under ambiguity, where advantageous options have to be deduced through evaluating, and learning from the outcome of previous choices (Starcke & Brand, 2012). This is the case with the Iowa Gambling Task, where it has been shown that individuals exposed to acute stress require longer to learn the rules than their non-stressed counterparts (Preston, 2007).

The fact that the amygdala, anterior cingulate cortex, and DLPFC are known to be associated with feedback processing (e.g. Woo et al., 2015), and are also known to be impacted by exposure to stress provides a plausible biological basis for the effects of stress on decisions via altered feedback processing. Interestingly, while activation in the amygdala and dACC has been associated with emotional reactions to negative feedback, negative feedback coupled with informative task-related information (proactive feedback) resulted in stronger activation in the DLPFC and a negative coupling between DLPFC and amygdala (Woo et al., 2015), indicating that proactive feedback may help downregulate the negative emotions after failure. Considering these patterns of activation in the context of stress gives rise to the proposition, that stress-related upregulation of limbic structures and simultaneous downregulation of prefrontal areas may lead to overemphasis on the emotional aspects of feedback provided (such as positive feeling after receiving a reward and negative feeling after encountering a loss) coupled with an impaired ability to integrate task-relevant information that would be required to develop successful decision making strategies, and may lead to reliance on lower-level systems to guide decision making. Thus, altered feedback processing, as opposed to exerting its function in isolation, is likely to impact decision making in combination with the other mechanisms listed in this section, or may serve to strengthen their

effects. For instance, altered feedback processing combined with altered sensitivity to rewards was evidenced by an EEG study which showed that brain activation patterns related to feedback learning in stressed participants showed stronger involvement of the reward system in feedback processing (Glienke, Wolf, & Bellebaum, 2015).

Limitations

Though the experiments presented here delivered some insights about the effects of stress on decision making, naturally they are not without methodological limitations. In particular, I will focus on two main points: using only male participants for the experiments and issues related to the choice of pharmacological substances for our manipulations.

Although we are aware that employing only male participants restricts the generalizability of our findings, we nonetheless opted for this under consideration of the numerous problematic issues that might arise from using a mixed gender design. Evidence exists that males and females not only differ in their stress reaction profiles, but also in the way they make economic and social decisions. With regards to prosocial behavior, while both genders exhibit such tendencies in general, women are likely to be more prosocial towards close kin and friends, and men seem to be more prosocial towards strangers than women (Eagly, 2009). Though direct comparison of how stress effects on social discounting differ between the two genders does not exist, we tested the effects of cognitive load on social discounting and found that men and women are affected differently (Strombach, Margittai, Gorczyca, & Kalenscher, 2016). Therefore, including both genders in our experiments on social discounting would have likely added a complicated additional factor resulting in the need for a significantly inflated sample size.

Evidence also exists, that men and women differ in their performance on the cognitive reflection test with males scoring higher than women (Primi, Morsanyi, Chiesi, Donati, & Hamilton, 2016; Toplak, West, & Stanovich, 2014). Primi et al. (2016) showed that one of the main factors accounting for these effects is math anxiety. As the differential feeling of anxiety in the two genders may complicate the design and interact with the pharmacological stress manipulation above and beyond the issue of overall gender differences, using only one gender was thought to be preferable in our cognitive reflection project as well. Lastly, there is mounting evidence that men and women differ in how they make economic decisions (Eckel & Füllbrunn, 2015), with women generally being viewed as more risk averse (e.g. Booth & Nolen, 2012), as well as more loss averse (Gaechter, Johnson, & Herrmann, 2010; Schmidt & Traub, 2002). Though overall the use of only males was methodologically more economical, the experiments reported here should be repeated with a female sample to improve generalizability.

The second limitation of our study is related to our use of pharmacological substances. In order to increase noradrenergic stimulation, we administered yohimbine. This substance has been shown to be a potent alpha-2 adrenoreceptor (NA autoreceptor) antagonist, but results from animal studies have shown that it also directly alters levels of serotonin and dopamine in the brain, even though its affinity to serotonin and dopamine receptors is smaller by an order of magnitude (Brannan, Martinez-Tica, & Yahr, 1991; Millan et al., 2000; Rodriguez-Manzo, 1999; Scatton, Zivkovic, & Dedek, 1980). As we were primarily interested in investigating the effects of NA and CORT on behavior, the increased action of other monoamine systems could have presented a confound. However, to our knowledge no substance exists for human studies that has selective affinity for noradrenergic receptors only. Furthermore, naturally occurring stressors also affect dopamine concentrations (Pruessner et al., 2004; Scott et al., 2006; Ungless et al., 2010), and involve interactions with the serotonin system (Foley &

Kirschbaum, 2010), thus the selective manipulation of NA only, even if possible, would likely lack ecological validity.

Another important point to mention is that effects of pharmacological manipulations may be dose dependent. There is some evidence suggesting that hydrocortisone effects on memory performance have an a non-linear pattern, with different doses affecting memory function in different ways (Beckwith, Petros, Scaglione, & Nelson, 1986; Lupien, Gillin, & Hauger, 1999; Schillig et al., 2013; Young, Drevets, Schulkiin, & Erickson, 2011). More specifically, there is some evidence of an inverted U shaped pattern according to which very low and very high doses impair memory performance, while moderate doses improve it. Buchanan, Brechtel, Sollers, & Lovallo (2001) compared 5mg and 20mg doses of hydrocortisone and found that the higher dose increased and the lower dose decreased the startle reflex. These findings were interpreted in the context of anxiolytic effects of hydrocortisone at higher doses. Putman, Antypa, Crysovergi, & van der Does (2010) specifically investigated motivated decision making in men and used a high dose of hydrocortisone (40mg) 2 hours before decision making and showed that at this dosage and timing cortisol resulted in more risky decision making. Similarly to Buchanan et al. (2001), these findings were also discussed in the context of cortisol's anxiolytic effects. From these findings it is clear that dosage and timing are crucial factors that need to be considered when planning pharmacological experiments, and their diverse application may account for some of the discrepancies in the literature. In our studies we opted for a dosage of 20mg in line with several other studies that used hydrocortisone manipulation to investigate cognition and decision making (Schwabe et al., 2010, 2012). However, it is possible that the effects we observed here may not hold for different dosages of the drug. Additionally, it is important to consider is the differences between the stress manipulation we used in the first study in the form of the Trier Social Stress test, and the pharmacological manipulation used in the others. Though the purpose of the pharmacological manipulation was to test the same biological processes that take place

during an acute stress reaction the two have notable differences. Firstly, the levels of hormonal responses reached after the pharmacological manipulation are significantly higher than in case of naturally occurring stress (Lupien et al., 1999). This is particularly important to keep in mind given the evidence about the dose-dependency of stress hormone effects discussed above. Furthermore, the two procedures also differ in their subjective characteristics. While the TSST is appraised as a stressful and uncomfortable situation by most participants, individuals who go through the pharmacological manipulation rarely report the same extent of discomfort and subjective stress those undergoing the the TSST.

Individual differences in stress reactions

Importantly, individual responses to stress are highly variable. Not everyone responds to stress with the same level of increase in cortisol and activation of the HPA-Axis. Kudielka and colleagues published an excellent and comprehensive review on the subject of individual differences in human salivary cortisol responses to challenge and identified several interesting factors. Gender differences were one of the most prominent findings on individual differences in stress reactivity, with men exhibiting a stronger cortisol response to stress than women do (Kudielka & Kirschbaum, 2005). In women, menstrual cycle phase is thought to make a difference, as well as the ingestion of oral contraceptives (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). Habitual smoking was another factor identified as chronically raising cortisol levels and therefore blunted cortisol responses to laboratory stressors (Kudielka & Kirschbaum, 2005). Research evidence about the disruptive effects of alcohol (Spencer & Hutchinson, 1999), caffeine (Lovallo et al., 2005) and exercise also exist (Kirschbaum & Hellhammer, 1994). Even without external factors, genetic variability may account for individual differences in HPA-Axis reactivity to stress. Wüst et al. (2004) presented evidence that glucocorticoid receptor gene polymorphisms impact cortisol reactivity

to psychosocial stress, results along the same lines were also reported by Kumsta et al. (2007) and DeRijk et al. (2006).

A final word: What did we learn about stress and decision making overall?

Hopefully the findings reported in this thesis will make a contribution to our understanding about how stress shapes the way we make decisions. Though intuitively we all know that being under stress, be it acute or chronic, changes the way we think, decide and relate to others, many of us would agree that we sometimes tend to underestimate its effects. Likely, most of us have had experience of having to function under stressful conditions and many decisions we have made happened under such circumstances. Increasing our understanding of how our decisions are shaped when make them under stress may raise awareness and encourage us to take note of our current state of mind when we reach important decisions. In the present thesis, we have shown that stress can make us to jump to quick conclusions at the expense of careful deliberation. Keeping this insight in mind might inspire us to think again before we make an important decision under stress. We have also presented evidence, that stress can make us more prosocial to those close to us, especially when we hope that those we help will also be there for us when we need them. This positive message not only shows that stress may have a constructive effect on our social behavior but should also motivate us to "tend-and-befriend" those who are dear to us, which is especially important to consider, as keeping a close knit social network can be particularly hard if we have stressful, busy lives. Finally, we have learned that we may care less about losing something under stress than we would normally do. With this in mind we can be more careful to not give something up that is important to us while we are stressed, which we could regret losing once the stress subsides.

Acknowledgements

I first became interested in how people make decisions a long time before I started working on this thesis. When I lived in London working in real estate, it always made me wonder why my clients decided to choose one apartment over another, as I often failed to see reason behind their decisions. For instance I often observed that those who appeared to be under a lot of stress, which was pretty commonplace in the London financial district, often decided on the spur of the moment and ended up regretting their decision later. Had I had the data of my experiments back then, I could have warned them, that increased levels of cortisol which go hand in hand with acute stress will make them jump to quick, erroneous conclusions at the expense of careful deliberation. My interest in decision making increased further during my Psychology studies, where I also learned about the biological basis of stress, and the effects stressful states have on our bodies and behavior. During my Masters in Psychology I started working as a student assistant at the Comparative Psychology department, were I was later offered a position as a doctoral researcher working on exactly the topic that had always interested me: decision making and stress. My colleagues, particularly Marijn van Wingerden and Tobias Kalenscher provided immense support during my research projects. Without their help and guidance this dissertation would not exist today. I am also thankful to all my colleagues at the Comparative Psychology team for the stimulating discussions and awesome lab trips, dinners, Symposia and other events together. I would also like to thank my coauthors for their support with the publications. Last but not least I would like to express my gratitude to Christian Bellebaum, who agreed to be the second supervisor of my thesis.

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