Bachelor Thesis

Behavioural Changes after Repeated Social Defeat:
Exploring the neurophysiological mechanisms that determine susceptibility to stress

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Abstract
The behavioural and physiological responses of long-lasting exposure to social stress differ between individual animals. While some animals avoid social interaction after chronic social stress, others appear unaffected. Social avoidance after chronic stress tends to be interpreted as a pathological, depressive-like state. However, this assumption is challenged by the idea that social avoidance after chronic defeat is an adaptive style of coping with stress, rather than a maladaptive response. Different stress coping styles are known to be determined by individual variation in the activation of a basic, well-conserved corticolimbic circuit. One of the subregions in this circuit is the mesolimbic pathway, which consist of the ventral tegmental area (VTA) and its projections to the nucleus accumbens (NAc). This pathway is associated with the attribution of salience to emotional stimuli, and appears to be activated after social interactions. Additionally, activity of the mesolimbic system is known to play a regulatory role in the behavioural response to stress. Although the neuroanatomical features of the mesolimbic area and its projections to other limbic and cortical regions are well-described, it remains challenging to understand how the properties of individual neurons within this pathway ultimately regulate differences in coping styles. This paper is aimed at explaining the mechanisms that underlie different responses of mesolimbic neurons to social stressors. I will argue that social avoidance of reactive coping individuals after chronic social defeat is the consequence of increased excitability of VTA neurons, while animals that are unsusceptible to social stress show no changes in neuronal excitability. Increased excitability has profound influences on transcriptional activity, neuronal plasticity and ultimately the allocation of memory in newly formed neural circuits. Additionally, the initial differences in neuronal excitability in the VTA could be the consequence of epigenetic regulation.

Contents

1. Introduction

It has long been recognized that defeat following social conflict elicits psychosocial stress, which in turn affects physiological and behavioural states such as body weight, stress responsivity and social behaviour over prolonged periods of time [Buwalda et al., 2005; Meerlo et al., 1996]. In humans, the most predominant form of stress is of a social nature [Wood et al., 2012] and chronic exposure to social stress is recognized as an important risk-factor in psychological disorders such as anxiety, clinical depression and mood disorders [Post, 1992; Kessler, 1997]. Interestingly, notwithstanding the large amount of people whose physical and mental health is affected by stress-related disorders, the vast majority of the population seems capable of coping with the stressors they experience on a daily basis. For example, an epidemiological study by Frans et al [2005] found that 73% of the younger to middle-aged population have experienced a traumatic episode of stress at some point in their lives, while less than 10% of the population develops PTSD. Prevalence of other psychological disorders such as anxiety (16%) and mood disorders (8%) are also considerably smaller than the part of the population that experiences severe stress [Kessler et al., 2005].

In order to better understand the pathophysiology of stress-related disorders, and the interpersonal differences in vulnerability to stress, researchers often rely on the use of animal models. Early models of chronic and acute stress differed with respect to the nature of the stressor that was used to induce a stress-response [Chaouloff, 2013]. After discovering that the nature of the stressor influences the specific neurobiological circuit that is associated with the following physiological response [Herman et al., 2010; Ulrich-Lai, and Herman, 2009], and with it the relevance a stress paradigm has to human psychological pathologies, several paradigms of stress became more frequently used than others. Discussing all these paradigms in detail lies beyond the scope of this paper and henceforth, this paper will focus solely on a paradigm that is often used to study social stress: the chronic social defeat stress (CSDS) paradigm (for a more detailed description of other stress paradigms, see Chaouloff, 2013; Maier Amat, J., Baratta, M. V., Paul, E. and Watkins, L. R., 2006; Willner, 2005)

The chronic social defeat paradigm relies on the display of aggressive behaviour in rodents that is elicited after an experimental male animal is introduced in the home-cage territory of a resident male. The resident male is either a male from the same strain that has been selected for its high aggressive behaviour, or a male from a more aggressive strain. Shortly after introduction of the intruder male, the resident male will approach and attack the intruder male, which subsequently displays submissive behaviour, indicating social defeat. Repeated exposure to the resident male will, when animals are singly housed [Ruis et al., 1999] induce acute and long term physiological and behavioural changes in the experimental animal (see also: Koolhaas et al., 2013; Koolhaas et al., 2017). Most aspects of the classic stress response, including increased cardiovascular, endocrine and sympathic nervous responses, are reduced to baseline within 48 hours [Sgoifo et al., 1994; Meerlo et al., 1996; Buwalda et al., 2005] but some effects last for a much longer period of time. Chronic defeated mice display decreased sucrose preference, increased immobility in a Forced Swim Test (FST), increased freezing behaviour and reduced social interaction up to 30 days after chronic social defeat [Venzala et al., 2012].

Interestingly, the behavioural effects of the social defeat paradigm and the clinical manifestations of depression in humans are to some extent similar. Depression, just like CSDS, is associated with anhedonia and reduced social interaction [American of Psychiatric Association, 2013], which has led to belief that CSDS can be used to model the etiology of human depression. Indeed, treatment with anti-depressive drugs that have beneficial effects in humans also seem to prevent the development of behavioural changes after chronic social defeat in rodents [Krishnan et al., 2007; Cao et al., 2010; Berton et al., 2006; Nestler, and Carlezon, 2006]. This is often assumed to support the idea that the behavioural effects that are observed in animal models after social defeat are to be interpreted as 'depressive-like' maladaptive behaviour. In recent years however, this biomedically-centered interpretation of social stress models has received increasing amounts of criticism. In an review of social stress models, Chaouloff et al. argues that reduced sucrose intake after chronic exposure to stress is not necessarily an indication of reduced motivational, but rather of reduced consumatory behaviour that is more likely to be a result anxiety-like, rather than depressive-like behaviour [Chaouloff, 2013]. Additionally, it is argued that immobility in the FST is not necessarily a reliable measure of reduced motivational behaviour, but might just as well be interpreted as animals displaying increased acceptance of the inescapability of the test. Considering the fact that swimming behaviour requires more energy than immobility, spending more time immobile might be adaptive, rather than pathological [Chaouloff, 2013].

The idea that the observed behavioural effects of stress might have an adaptive component originates

from the observed individual difference in stress-susceptibility in both animal and human populations [Krishnan et al., 2007; Kessler et al., 2005; Nestler, and Carlezon, 2006]. Within the same strain, animals show several distinct patterns of behavioural responses to environmental stressors, even under highly controlled conditions that are aimed at reducing individual variation [Koolhaas et al., 1999]. The significance of these individual phenotypic differences has long been underestimated and neglected due to a tendency to reduce individual variation in animal research. And while several studies of social stress have recognized that individual variation in the response to stress exists, the interpretation of these results is dominated by a biomedically-centered approach to stress-induced changes, which assumes the behavioural responses to stress are equivalent to symptoms of human disorders such as clinical depression and PTSS. This view is challenged by studies that indicate that individual variation in the stress-induced behavioural response might be adaptive styles of coping with environmental stressors. A study in great tits has revealed that individual differences in exploratory behaviour are associated with different fitness consequences, depending on the particular environmental conditions over time [Dingemanse et al., 2004]. Van Oortmerssen et al. (1989) found that in semi-wild populations of house mice, selection of aggressive phenotypes combined with increasing population densities results in disruptive selection, resulting in differential fitness of aggressive and non-aggressive phenotypes over successive generations. These studies show that individual variation in patterns of behavioural responses to environmental demands have a considerable adaptive nature. Assuming that these response patterns are mere negligible individual variation does not appreciate the ecological significance of phenotypical variation in a population.

Coping styles are used to describe a pattern of consistent behavioural responses towards a stressor. [Koolhaas et al., 1999; Coppens et al., 2010]. In many animals including rodents, birds and fish [Dingemanse et al., 2009; Dingemanse et al., 2004; Groothuis, and Carere 2005; De Boer and Koolhaas, 2003] two coping styles, proactive and reactive, are recognized. Animals that display a proactive coping style are generally more aggressive, rely more on rigid predictions about the environment and on impulsive decision making, while the reactive coping style is less aggressive, and is more dependent on contextual information [Coppens et al., 2010]. Proactive coping animals tend to actively modify their environment when dealing with a stressor, while reactive animals are more conservative in their approach, and will try to avoid confrontation with the stressor [Boersma et al., 2017].

Differences in coping styles are observed in several different behavioural paradigms. In the defensive burying test, animals are confronted with an electrified rod that is placed in their home cage. In response to the aversive stimulus that follows after brief contact with the rod, animals can avoid additional aversive stimuli by either burying the rod with bedding, or freeze and keep away from the rod. In this paradigm, proactively coping animals tend to display defensive burying behaviour, while reactively coping animals will freeze to avoid a second shock [Koolhaas et al., 2013]. Similar behavioural responses are observed in the forced swim test, where animals are placed in a water bath from where escape is impossible. Again, different strategies include active swimming behaviour or passive floating behaviour. Veenema (2005) found that after a single forced swim test, swimming behaviour is positively correlated with aggressive phenotypes, and floating behaviour is positively correlated with non-aggressive phenotypes. Moreover, it has recently been argued that the forced swim test measures coping style, rather than depressive-like behaviour. [De Kloet and Molendijk, 2016].

Although coping styles have been well described in terms of behavioural traits and ecological significance, the neurobiological mechanisms that underlie individual differences in coping style remain poorly understood. It is known that differences in coping style are the result of differences in the activity of a well-conserved, corticolimbic circuit that is known as the social decision making network [O'Connell and Hofmann, 2012]. This network includes the prefrontal cortex, amygdala, hypothalamus, hippocampus and their input and output projection nodes, such as the thalamus, dorsal and ventral striatum and the ventral tegmental area [Boer et al., 2017]. Although the neuroanatomical features of this network are well described, it remains difficult to understand how physiological properties of neurons within specific areas of this network ultimately determine coping style.

Within the social decision making network, the mesolimbic system is of particular interest due to its role in the behavioural response to emotional stimuli and stress [Nestler, and Carlezon, 2006; Cao et al., 2010; Krishnan et al., 2007]. The mesolimbic pathway is a dopaminergic pathway in the midbrain, that consists of the ventral tegmental area (VTA) and its projections to the nucleus accumbens (NAc, also known as the ventral striatum) (Wise 2004) The predominant type of neurons in the VTA are dopaminergic medium spiny neurons (MSN's), that together form about two thirds of neurons in the VTA. Other cell types are glutamatergic neurons

(about one third of the neuronal population) and to a lesser extent GABA-ergic neurons (2-3%) [Nair-Roberts et al., 2008].

The VTA-NAc pathway is activated by natural rewards and addictive substances [Wise, 2004; Nestler, and Carlezon, 2006; Berton et al., 2006]. Furthermore, interaction with a social partner increases expression of the immediate early gene *cFOS* in the VTA and NAc, which indicates that social cues also activate the mesolimbic pathway [Berton et al., 2006]. Additionally, activation can also be observed after exposure to novel objects [Wise, 2004] and glucocorticoids [Piazza et al., 1996]. Several studies have indicated a regulatory role of the mesolimbic pathway in experience dependent learning behaviour and the behavioural response to chronic social stress. Lesion of the NAc is known to prevent conditioning to aversive stimuli [Parkinson et al., 1999]. Additionally, optogenetic stimulation of the VTA increases social avoidance after CSDS, while optogenetic inhibition prevents stress-induced behavioural changes [Chaudhury et al., 2013]. It remains unclear, however, how individual differences in susceptibility to social stress are represented in the VTA-NAc. This paper is aimed at describing the neurophysiological processes within the VTA-NAc pathway that regulate different behavioural reactions to chronic social defeat stress. By examining the role of intracellular signalling cascades, altered gene expression and epigenetic regulation, it might be possible to gain better understanding of the function of VTA-NAc signalling within the corticolimbic circuits that are responsible for different coping styles.

1. Activation of the VTA-NAc after social stress

The VTA-NAc pathway is innervated by a complex network of serotonergic, glutamatergic and neuropeptide projections from the cortical and limbic system [Legault and Wise, 2001; Wise 2004; Kelley and Berridge, 2002] and discussing this network in its entirety lies beyond the scope of this paper. It is however worthwhile to highlight the role of the efferent projections from the amygdala, prefrontal cortex and hippocampus to the VTA. These glutamatergic projections are able to activate NMDA and AMPA receptors in the VTA, and have been shown to regulate the activity of the VTA-NAc pathway. For example, increases in NAc dopamine levels are observed after mice are exposed to a novel object, but are reduced when the VTA is simultaneously infused with a glutamate antagonist [Legault, and Wise, 2001]. After glutamate-binding, NMDA and AMPA receptors facilitate influx of Na^+ and Ca^{2+} [Macdermott et al., 1986] which results in a membrane depolarization of VTA neurons. In addition to glutamate, activation of VTA-neurons can also be induced by stress. In response to a stressful stimulus, hypothalamic neurons projecting to the VTA release CRF [Sarnyai et al., 2001]. Whole-cell patch clamp recordings reveal that CRF has an excitatory effect on VTA dopamine neurons, which is mediated through the CRF-receptor-1 dependent signalling cascade [Wanat et al., 2008; Henckens et al., 2016]. It is important to note that stimulation of the VTA-NAc pathway by itself does not necessarily result in the behavioural changes that are observed after exposure to chronic stress. Neither acute nor repeated optogenetic stimulation of DA neurons in the VTA of stress-naïve mice increases social avoidance [Walsh et al., 2014]. Intra-VTA infusion of a CRF antagonist in stressed mice prevented behavioural changes, suggesting that CRF plays a regulatory role in the behavioural response to stress. However, stress-naïve mice that received an intra-VTA infusion of CRF did not display an increase of social avoidance, even if dopamine neurons in the VTA were stimulated simultaneously [Walsh et al., 2014]. This implies that CRF is necessary, but not sufficient to induce behavioural changes after VTA stimulation, and that social stress influences the VTA-NAc pathway through other mechanisms than only CRF signalling. In particular, these mechanisms might be associated with the social nature of CSDS. This hypothesis is supported by the observation that non-social stress paradigms such as the chronic mild stress (CMS) paradigm induce anxiogenic behaviour, but do not affect social avoidance in rats [D'Aquila et al., 1994]. Additionally, chronic defeated mice show sensitized expression of *cFOS* in the VTA and NAc after social interaction, which indicates that social stress increases neuronal activity after exposure to social cues [Berton et al., 2006].

2. Susceptibility to social stress is associated with distinct patterns of VTA-NAc firing

Several studies have provided evidence that differences in activation of the VTA-NAc pathway are associated with individual variation in the behavioural response to repeated social stress. Cao et al (2010) measured social avoidance after 10 day social defeat and distinguished between mice that showed increased social avoidance, and mice that did not show any behavioural effects. Individual cell recordings of VTA DA neurons show that an increase of social avoidance is associated with increased neuronal activity, while no increased neuronal activity was observed in mice that were unsusceptible to CSDS (Fig. 1A, B). In particular, increased social avoidance is associated with alterations in firing patterns of VTA neurons. Dopaminergic neurons in the VTA display two firing types. Rapid burst firing, compared to slow-fre-

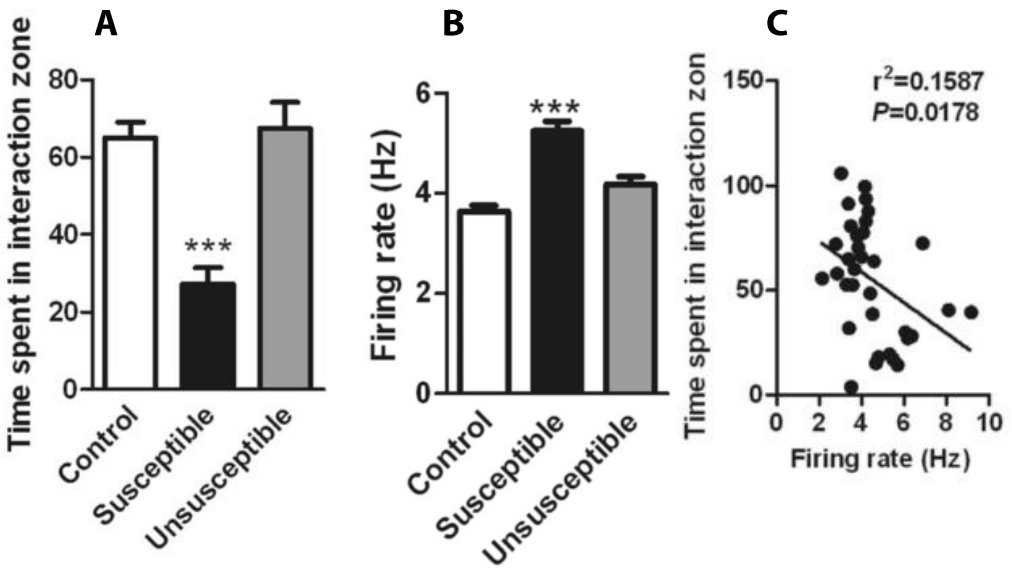

Fig. 1. VTA DA neuron activation differs between susceptible and resilient animals after chronic social defeat stress. A) time spent in interaction zone after 10 day social defeat (***p<0.0001 vs control or unsusceptible; 8–20mice/group) B) Overall VTA firing rates in control, susceptible, and unsusceptible mice (***p<0.0001 vs control or unsusceptible mice, n=58–72 cells, 15 mice/group). C) Average VTA firing rate for each mouse is significantly negatively correlated with the time spent in interaction zone measured on day 11 (p<0.05, n=35 mice) Data and graphs from Cao et al. (2010)

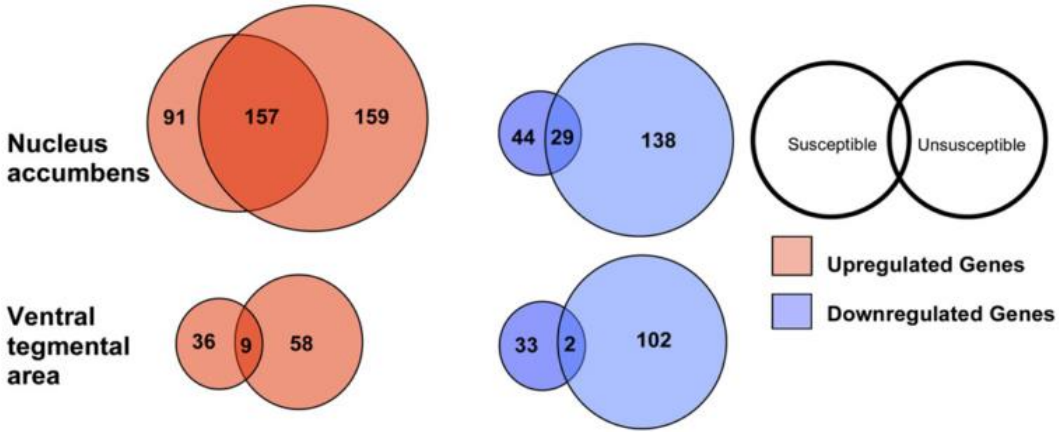

Fig. 2. Changes in transcriptional activity are altered after exposure to chronic defeat stress, and differ between susceptible and resilient phenotypes. DNA microarrays of VTA and NAc were performed one day after a 10 day social defeat paradigm. Venn diagrams show the number of uniquely regulated genes in Susceptible and Unsusceptible mice (as compared to non-defeated controls), with the over- lap depicting genes that were identically regulated by both conditions. Upregulated (red) and downregulated (blue) genes are shown separately (criteria for significance: R1.5-fold change compared to respective anatomical control group at p < 0.05). Data and graphs from Krishnan et al. (2007)

quency single spike firing, is associated with substantially increased DA release and more effective regulation of target areas of dopamine neurons [Grace et al., 2007; Anstrom et al., 2009]. The relative amount of burst firing cells is negatively correlated with social interaction time [Cao et al., 2010] (Fig. 1C). Similar results were obtained by Krishnan et al (2007), who observed that firing rates of VTA DA neurons were increased in mice that are susceptible to stress-induced behavioural changes, with no effect being seen in control mice or resilient mice. Additionally, the increase of firing of VTA neurons was not observed after a single defeat experience or after chronic isolation stress, which suggest that increased neuronal firing after stress occurs specifically after exposure to repeated social defeat stress. Genome-wide expression analysis has provided new insights in the underlying causes of individual differences in VTA-DA firing patterns. In a study that did not take stress susceptibility into account, it was found that CSDS is associated with long lasting increased transcriptional activity in the NAc (24h after CSDS: 309 genes upregulated, 17 downregulated; 4 days after CSDS 127 genes upregulated, 9 downregulated) compared to control mice (Berton et al. 2010). Changes in gene expression that are specific to either stress-susceptible or -resilient phenotypes were observed by Krishnan et al (2007) (Fig. 2), who found

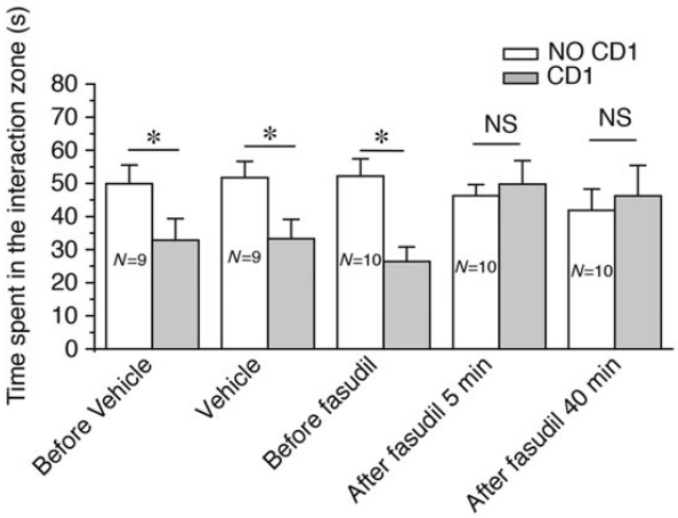

Fig. 3. Infusion of K_v7.4-channel opener in the VTA prevents social avoidance after chronic social defeat. Infusion of fasudil increase time spent in an interaction zone in mice that were subjected to CSDS. No effect of vehicle treatment was observed. *p<0,05 vs control, where no CD1 mouse was present in the interaction zone. Data and graphs from Li et al. (2017)

that the absence of increased social avoidance is associated with upregulation of several voltage gated potassium (K^+) channels. Since increased expression of K^+-channels decreases neuronal excitability by stabilizing the resting potential of the membrane, it is tempting to propose that altered excitability of VTA dopaminergic neurons underlies the individual differences in stress-response. Indeed, overexpression of inward rectifying K^+-channels in VTA dopamine neurons reduces social avoidance in mice that had previously developed social avoidance after CSDS [Krishnan et al., 2007]. Moreover, a knockout of K_v7.4 potassium channels, which are selectively expressed in VTA-DA neurons, increases burst-firing [Li et al., 2017]. Acute administration of fasudil, a selective K_v7.4-channel opener that enhances K_v-currents, reverses CSDS-induced social avoidance behaviour (fig. 3). Finally, K_v7.4-mRNA and –protein levels are increased in mice that do not display social avoidance after CSDS. Hence, selective expression of K_v7.4-channels in the VTA seems to play a regulatory role in the excitability of the VTA-NAc pathway and the possible behavioural response that follows upon CSDS. Interestingly, Li et al. administered the K_v7.4-channel opener 8 days after the end of a 10 day social defeat paradigm, indicating that increased VTA-activity is sustained for a prolonged period of time after social defeat.

Other studies have also provided evidence for a connection between stress and VTA-excitability. The activity of another non-specific cation channel, the hyperpolarization activated I_h-channel, is regulated by CRF-dependent signalling pathways. CRF-binding to the G-protein coupled receptor CRF-R1 activates PKA and PKC signalling pathways [Hauger et al., 2006] which increases I_h-currents in dopamine neurons in the VTA through the PKC, but not the PKA signalling pathway [Wanat et al., 2008]. The increased I_h-current is associated with increased burst firing of VTA-DA neurons [Henckens et al., 2016; Wanat et al., 2008] and infusion of I_h channel blockers reverses stress-induced social avoidance [Cao et al., 2010] which indicates a regulatory role of I_h-channels in the behavioural response to social stress.

Interestingly, CSDS increases I_h-current not only in mice that display social avoidance, but also in mice that show no behavioural effects of CSDS. Since resilient animals show no increases of burst firing neurons in the VTA, despite increased I_h-channel activity, other mechanisms that reverse the excitatory effect of increased I_h-currents are involved. It seems plausible that K^+-channel expression could mediate this difference.

3. Excitation of DA-neurons in the mesolimbic pathway regulates neuroplasticity

As discussed previously in this paper, increased activity of the VTA-NAc pathway is associated with a considerable increase in transcriptional activity [Berton et al., 2006; Krishnan et al., 2007]. Altered gene expression might influence the development of coping style by mediating neuronal plasticity in the mesolimbic pathway and its efferent target areas in the limbic system and the cortex. It is therefore crucial to identify the transcription factors that are associated with CSDS-induced VTA-NAc activity. The cyclic-AMP response element (CRE) binding protein (CREB) is a highly conserved transcription factor that regulates the transcription of genes that are required for different forms of long term memory consolidation [Benito and Barco, 2010; Kelley and Berridge, 2002; Nestler and Carlezon, 2006]. CREB is inactive in its unphosphorylated form. Phosphorylation of CREB requires the activation of both NMDA- and dopamine (D1) receptor [Das et al., 1997]. Dudman et al. (2003) found that binding of dopamine to the DA1 receptor stimulates protein kinase A (PKA), which in turn phosphorylates the NMDA receptor, facilitating an influx of Ca^{2+} and Na^+ through the NMDA receptor. The influx of Ca^{2+} stimulates the calmoduline-dependent kinase (CamK) dependent phosphorylation of CREB and the increased transcriptional activity that it is associated with [Dudman et al., 2003]. *In vitro* experiments show that overexpression of CREB in medium spiny neurons of the nucleus accumbens increases intrinsic excitability and action potential frequency, whereas expression of the dominant-negative form of CREB has opposing effects. In particular, CREB appears to modulate excitability by

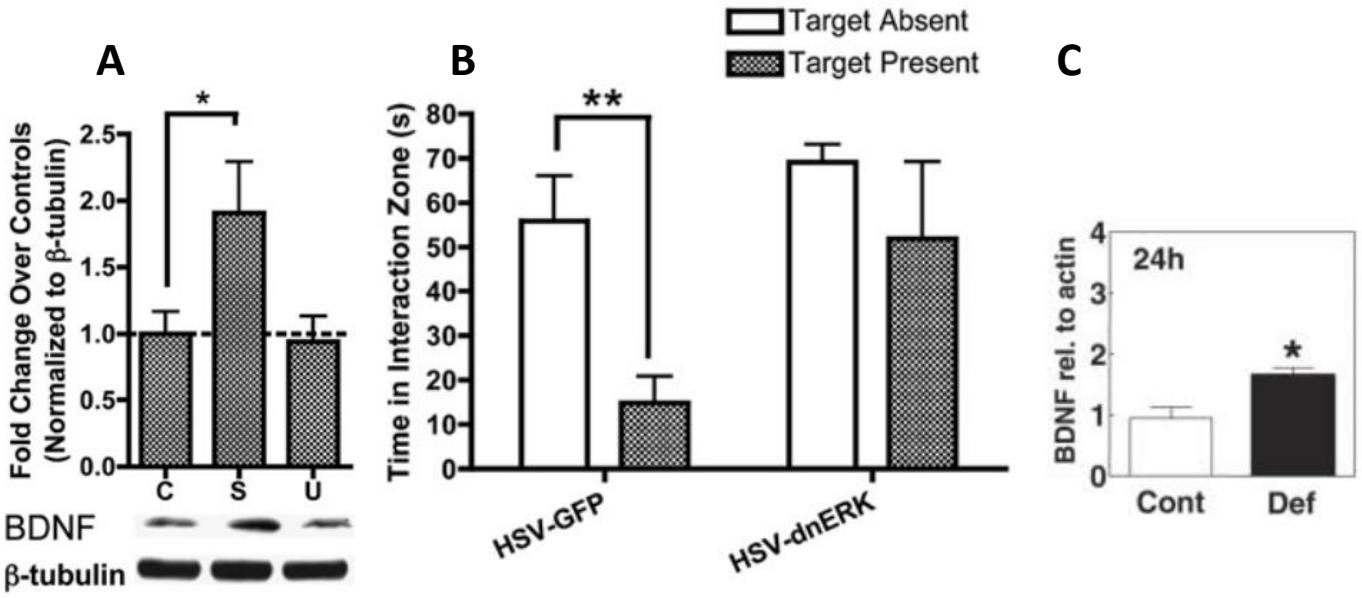

Fig. 4. BDNF-signalling induces social avoidance behaviour after social defeat stress. A) Immunoblotting shows that CSDS causes a 90% increase of BDNF levels in the NAc of mice that are susceptible (S) compared to unsusceptibe (U) or control (C). B) Overexpression of a dominant negative form of EKR2, a signaling molecule downstream of BDNF signaling, in the NAc of susceptible mice prevents social avoidance after CSDS (HSV-dnERK). Overexpression of GFP was used as a control (HSV-GFP), and did not reduce social avoidance. C) Without distinguishing susceptibility and unsusceptibility to stress, BDNF levels in the NAc are also significantly increased 24h after CSDS. *p<0,05; *<0,01 compared to respective control groups. Data and graphs A and B are adapted from Krishnan et al. (2007), C from Berton et al (2006).

increasing Na^+ and decreasing K^+ currents, either by increasing the expression of voltage-gated ion channels directly, or through the upregulation of second messenger systems that regulate the behaviour of ion channels [Dong et al., 2006]. CREB-dependent alterations in ion channels have been shown to decrease afterhyperpolarization (AHP), a process that occurs after depolarization and is responsible for the refractory period of a neuron. By decreasing AHP, CREB increases the maximum firing rate of neurons [Benito et al. 2010]. It seems therefore plausible that manipulation of CREB expression influences the behavioural response to stress. Unfortunately, no studies have investigated the role of CREB in chronic social defeat stress, although other stress paradigms have been used. In the inescapable footshock paradigm, viral vector mediated overexpression of CREB in the NAc increases escape-attempt latency, which was interpreted by the authors as 'depression-like behaviour' [Newton et al., 2002], but which also might be interpreted as an indication for a reactive coping style, comparable to immobility in the defensive burying and FST paradigm. Additionally, CREB overexpression in the NAc-shell impedes upregulation of K^+-channels after chronic isolation stress, which provides further support for the role of CREB in increasing neuronal excitability [Wallace et al., 2009]. However, since the nature of a stressor affects the associated neurophysiological response, the difference in experimental methods of these studies makes it difficult to draw decisive conclusions from these data. Nevertheless, Barrot (2002) found that foot shocks, restraint stress and social stress increased CREB expression in the NAc-shell in an equal amount. Additionally, the function of CREB well-conserved throughout different neuronal types [Benito et al. 2010]. Together, this suggests that the response to chronic social defeat stress most likely involves CREB, although future studies will have to provide conclusive evidence for this hypothesis.

Transcription factors such as CREB can influence neuronal plasticity only through modulation of expression of other proteins. One of the proteins that is known to play a role in neuronal plasticity after stress is brain-derived neurotrophic factor (BDNF). BDNF-mRNA is highly expressed in dopamine neurons of the VTA, but is observed in barely detectable levels in the NAc [Berton et al., 2006]. Phosphorylated CREB regulates BDNF expression by binding to the CRE-region in the *BDNF*-gene. Binding of BDNF to the tyrosine kinase linked receptor (TrkB) lead to the activation of three major signalling pathways [Goggi et al., 2003]. Although BDNF was initially of interest due to its role in the development of the central nervous system, it has increasingly gained attention for its function in learning- and memory processes. BDNF plays an important regulatory role in the mesolimbic pathway. It potentiates DA release in synaptosomes of striatal neurons independent of transcription

or translation, which suggests that BDNF regulates exocytosis of dopamine vesicles [Goggi et al., 2003]. Additionally, BDNF is essential for the development of CSDS-induced behavioural changes. Ten days of social defeat induces a twofold increase in NAc BDNF levels in mice that show social avoidance, while this increase was not present in mice that were unsusceptible to behavioural changes (fig. 4A). Local deletion of *BDNF*-gene in the VTA, but not in the NAc, increases the percentage of mice that display an unsusceptible phenotype after CSDS from 11% to 36%, and overexpression of a dominant negative form of the downstream signalling molecule ERK2 reduces social avoidance in susceptible animals, which implies a causal role for BDNF-TrkB signalling. [fig. 4B., Krishnan et al., 2007]. Stress-induced social avoidance is prevented by intra-NAc infusion of a TrkB-receptor antagonist, which implies a causal role for TrkB-BDNF signalling [Walsh et al., 2014]. Additionally, Coppens et al (2011) characterized coping styles in mice by measuring aggressive behaviour, and found a trend towards a significant interaction between coping style and NAc BDNF levels. Defeated reactive coping mice show a significant increase in NAc BDNF levels compared to undefeated controls, while BDNF levels were not significantly elevated in defeated proactive coping rats. This indicates that BDNF expression in the VTA mediates susceptibility to behavioural changes after CSDS, which might play a role in the more general development of coping styles. It is therefore surprising that studies that did not consider individual differences in susceptibility to stress have reported similar results. Berton (2006) also found that deletion of the *BDNF*-gene in the VTA prevents the development of social avoidance behaviour in social defeated mice, and Eisch et al. (2003) show that intra-VTA infusion of BDNF increases immobility in the FST. Both studies show a BDNF dependent increase in behavioural plasticity after stress, without relying on a distinction between susceptible and unsusceptible mice. One possible explanation is that in the study of Berton et al (2006) the relative influence of susceptible mice to the overall average BDNF level was small enough to be attributed to random variation. Indeed, Krishnan et al. (2007) determined that unsusceptible mice make up only 11% of the entire population. Both studies have used C57BL/J6 mice, which makes it plausible that in the study by Berton et al. a similar percentage of unsusceptible mice were used. Additionally, Krishnan et al observed a 90% increase in NAc BDNF-protein, while this increase appears smaller in Berton et al. (roughly 70-80 %, see fig. 4C) but the fact that no quantitative data were provided by Berton et al. makes this comparison somewhat speculative.

What is the contribution of TrkB-BDNF signalling to the response of mesolimbic neurons to social stress? Interestingly, it was found that deletion of BDNF in the VTA prevents the previously discussed stress-induced changes in gene expression [Berton et al., 2006]. Since BDNF expression is regulated by CREB, deletion of BDNF would presumably have no effect on the other target genes of CREB. A possible explanation is that not all transcriptional activity (fig. 2.) is necessarily regulated by CREB, but instead is the effect of BDNF-signalling mediated transcription. Additionally, Wook et al. (2017) found that social avoidance after CSDS was prevented by intra-NAc infusion of a TrkB-antagonist, but not by dopamine receptor (D1 and D2) antagonists. Earlier in this paper, I have discussed the role of D1 receptor mediated signalling, and argued that activation of D1 receptor by dopamine stimulates Ca^{2+} influx through the NMDA receptor, which in turn phosphorylates CREB through Ca^{2+}/CamK dependent phosphorylation. It appears however that VTA-NAc mediated behavioural responses to CSDS are not only regulated through this D1-NMDA-CREB pathway, but also require TrkB-BDNF mediated signalling cascades. Goggi et al (2003) have described that BDNF-mediated potentiation of DA release in rat-brain striatal synaptosomes requires RAS-MEK (mitogen-activated/extracellular-signal regulated kinase) and phosphatidylinositol-3 kinase (PI3K) signalling. Both of these signalling pathways have been shown to phosphorylate CREB [Peltier et al., 2007; David Sweatt, 2001] which indicates that CREB phosphorylation after chronic stress might be regulated by TrkB-BDNF signalling, and not by D1-NMDA signalling. Interestingly, Goggi et al. (2003) found that behavioural changes after acute stress, in contrast to chronic stress, were prevented by intra NAc infusion of a D1 antagonist. Together, these studies contribute to the hypothesis that behavioural changes after stress are regulated by several complex signalling cascades in the VTA-NAc that involve TrkB, D1 and NMDA receptors, and that different pathways are involved in the response to acute and chronic stress, respectively. Further analysis of these pathways could clarify the complex intracellular regulatory mechanisms that are required to produce a behavioural response after stress, but these issues will not be further addressed in this paper.

How do changes in transcriptional activity within individual neurons affect the function of neural circuits that are composed of multiple neurons? First of all, the altered excitability of individual neurons could facilitate the formation of new neural circuits that enable learning and memory acquisition. Increased neuronal excitability, for example by CREB-driven changes in ion-channel expression and reduction of AHP, has

been argued to reduce the threshold for long term potentiation (LTP) in the synapses of sensitized neurons [Benito et al. 2010]. Experience-induced neuronal sensitization increases the possibility of that same neuron being activated again after a subsequent, similar stimulus. Long term increases in excitability of individual neurons could thus promote the selective reactivation of a neural circuit after a similar stimulus, which facilitates the allocation of memory to neural circuits containing neurons that are more easily excitable [Benito et al. 2010]. In addition to changes that affect circuits containing multiple neurons, increased BDNF levels after stress could affect transmission at the level of individual synapses [Benito et al. 2010]. BDNF-TrkB signalling is involved in the regulation of synapse formation, synapse plasticity and the strength of excitatory post-synaptic potential (EPSP) [Kang and Schuman, 1995; Park and Poo, 2013]. Since CSDS elevates BDNF levels in susceptible animals, increased synaptic transmission could strengthen the connectivity of neural circuits that were formed after exposure to a social stressor. These two characteristics of neurons explain how stress-induced activation of dopamine neurons in the VTA-NAc pathway can influence the neurophysiological functions of neural networks that incorporate the mesolimbic pathway, such as the social decision making network. It is tempting to propose that stress-induced changes in neuronal plasticity form the foundation of the behavioural response after chronic stress that is observed in animals that adopt a reactive coping style, although the actual interaction between stressors, coping styles and behavioural responses are without doubt much more complex.

4. Epigenetic regulation as the origin of individual behavioural differences after CSDS

This paper has so far outlined how chronic social defeat influences excitability, firing pattern, transcriptional activity and synaptic plasticity of dopaminergic neurons in the VTA-NAc pathway. While this provides a possible mechanistic basis for individual variation in stress-induced behavioural changes, it does not explain the origin of these individual differences themselves. Since susceptibility and resilience to social stress are associated with different patterns of gene expression, it is tempting to suggest a role of epigenetic regulation of transcriptional activity.

Two common mechanisms of epigenetic regulation are histone (de-)acetylation and methylation of genes and their promotor-regions. One of the genes that is upregulated exclusively in susceptible animals after CSDS is the histone deacetylase *Hdac2*, which has previously been associated with increased immobility behaviour in the FST [Schroeder et al., 2007; Krishnan et al., 2007]. Additionally, susceptibility to CSDS is associated with decreased *Crf*-promotor methylation in the paraventricular nucleus (PVN) of the hypothalamus, while no decrease of *Crf*-promoter methylation was observed in unsusceptible animals [Elliott et al., 2010]. Moreover, Elliot et al. found that knockdown of *Crf* in the PVN reduced CSDS-induced increases in social avoidance. These results show that epigenetic regulation of *Crf* expression in the PVN mediates the behavioural response to CSDS. It is important to note that hypothalamic-derived CRF affects the mesolimbic system through projections from the PVN to the VTA. Earlier in this paper, it was established that CRF increases VTA-excitability by affecting I_h-currents. It is therefore tempting to suggest that epigenetic regulation of *Crf*-expression underlies individual differences in stress susceptibility by influencing the excitability of VTA neurons after social stress.

5. Conclusion and final remarks

The way in which animals cope with chronic social defeat stress differs between individuals. While resilient animals show little changes in social behaviour, susceptible animals are more likely to show a behavioural adaptation, which results in an increase in social avoidance behaviour. Little is known about the mechanisms that underlie this difference in behavioural plasticity. The aim of this paper was to describe the neurophysiological processes within the VTA-NAc pathway that regulate different behavioural reactions to chronic social defeat stress. So far, I have argued that whether or not an animal responds with increased social avoidance behaviour is determined by the firing pattern of dopaminergic neurons in the VTA-NAc. In susceptible animals, stress increases activity of CREB, which results in the upregulation of Na^+ channels and downregulation of K^+ channels. This induces in a neuronal state of increased excitability. Additionally, stress-dependent increases in BDNF expression cause a general increase of transcriptional activity that promotes synapse formation and synaptic plasticity. Together, these adaptations could result in stress-induced behavioural plasticity by 1) facilitating experience-induced reactivation of neuronal pathways that are responsible for the allocation of new memories, and 2) increasing synaptic transmission due to increased long term potentiation. Alternatively, the animals that don't respond to stress show no increased VTA-NAc firing after chronic social defeat. Increased K^+ channel expression reduces neuronal excitability, which in turn reduces the probability a stressor will induce CREB and BDNF dependent neuronal plasticity. The absence of increased neuronal plasticity makes it less likely that a stressor will induce remodelling of neuronal circuits. Hence, resilient animals will less often adjust

their behaviour after experiencing a stressor, which explains why these animals rely more on existing memories. One possible difference between susceptible and resilient animals that might explain the difference in VTA-NAc activity after stress is the epigenetic regulation of, for example, the Crf-gene. Due to the lack of direct evidence, this hypothesis remains somewhat speculative.

This paper specifically discussed the individual variation within the VTA-Nac pathway, due to the fact that this pathway had previously been shown to mediate social stress induced social avoidance [Berton et al., 2006; Nestler and Carlezon, 2006] However, while dopamine signalling in the VTA-NAc pathway plays a considerable role, it should by itself not be thought to determine coping style. Several other regions have been associated with the regulation of coping style and the response to stress. The hippocampus, for example, is known to exhibit strong control over the HPA-axis activation through glucocorticoid receptor dependent feedback [Franklin et al., 2012] Dysfunctional glutamatergic signalling in the hippocampus has been associated with stress-related pathologies in humans [Saab et al., 2009] and structural variation of AMPA-subregions in the CA1 and dentate gyrus of the hippocampus are associated with susceptibility to stress [Schmidt et al., 2010]. Specifically, social defeat induced stress has been shown to affect hippocampal LTD and LTP due to dendritic remodelling in the CA3 subregion [Buwalda et al., 2005]. In addition to the hippocampus, the prefrontal cortex has also been associated with behavioural flexibility, impulsivity decision making and aggression. Proactive and reactive coping styles differ in the serotonergic input to the PFC [Coppens et al., 2010] Low levels of PFC serotonin are associated with both high aggressive behaviour and reduced behavioural flexibility [Veenema and Neumann, 2007; Veenema et al., 2005; Miczek et al., 2007]. The literature that discusses the function of the prefrontal cortex and hippocampus in relation to (social) stress is too abundant and complex to be properly discussed in this paper, but the few studies that were mentioned above indicate that all adequate models of neurophysiological mechanisms of coping style should take other brain regions, such as the hippocampus and prefrontal cortex, and other neurochemical systems such as the 5HT-system, into account.

One of the difficulties of this paper was that very few studies have characterized coping styles in the social defeat paradigm. Most of the studies that have been reviewed in this paper only measured social avoidance behaviour, and did not take other behavioural aspects such as aggressiveness into account. Due to the fact that coping style was not determined, it remains speculative to argue that there is a direct relation between coping style and the behavioural adaptations after CSDS. In the FST and defensive burying paradigm, immobility and avoidance behaviour have been associated with reactive coping styles and it seems plausible to argue that coping style also influences social avoidance behaviour in the social defeat paradigm, but this assumption is yet to be supported by direct evidence. Coppens et al. (2011) have shown that after acute stress, BDNF levels in the NAc differ between coping styles, although this study did not determine whether coping styles also determines differences in social avoidance behaviour.

Additionally, coping styles may not be the only factor that determine the physiological and behavioural effects of social stress. In recent years the match-mismatch hypothesis, which was developed to explain the effects of early-life stress, has gained attention. It states that early life conditions predispose individuals to cope with stress in a certain way, and that the outcome of stress later in life depends on whether these stressors are similar to early life experiences [Buwalda et al., 2013; Koolhaas et al., 2017] In addition to the fact that the match-mismatch hypothesis enhances the validity of research by taking housing conditions into account, it can also offer an explanation for the substantial phenotypic variation in inbred laboratory animals [Krishnan et al., 2007] due to the fact that it can rely on epigenetic regulation during early life experiences as a key factor in determining the response to stress.

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