Bachelor thesis

Does coping style predict vulnerability of depression?

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Figure front page: http://drdianehamilton.wordpress.com/2012/01/12/importance-of-being-proactive-vs-reactive/

Abstract

Individuals can respond differently to stressors. This response determines whether the individual will get stressed. There are certain behavioral patterns which determines how an individual responds to stress. These are called coping styles: 'A coping style can be defined as a coherent set of behavioral and physiological stress responses which is consistent over time and situation and which is characteristic to a certain group of individuals' (Koolhaas et al., 1999). There are two coping styles: the proactive coping style and the reactive coping style. The proactive coping style is characterized by a high level of aggression and easily developing of routine patterns, while the reactive coping style is characterized by a low level of aggression and flexibility.

Stress is a risk factor for developing of depression (Korte, 2001). So the question is whether a coping style can predict the vulnerability for depression.

To answer this question it is important to know what the baseline differences are between the coping styles. This is discussed at the behavioral, neuroendocrinological and neurobiological level. On the behavioral level, the reactive coping style animals display more passive behavior after mild stress in comparison with proactive coping style animals. As regards to the HPA axis level, the reactive coping style has a higher HPA axis response after mild stress. 5-HT neurotransmission is lower in reactive animals.

To investigate the differences in vulnerability for depression, the effects of severe stress are examined at the behavioral, neuroendocrinological and neurobiological level. These results were quite varied. On the behavioral level, non-social behavior was quite the same as in baseline differences tests. Social behavior was the same for the different coping styles. HPA axis response was one time higher in the reactive coping style and the other time higher in the proactive coping style. 5-HT neurotransmission after severe stress is not yet measured in the different coping styles. In normal lines of rodents, the 5-HT neurotransmission is higher after severe stress.

Because the results are so varied, a conclusion cannot be drawn whether coping style predicts the vulnerability for depression. Much more research is needed and also the match-mismatch hypothesis should be taken into account.

Introduction

Depression is a common disease. In the Netherlands 8,6% of men and 12,1% of women suffer from depression (source: CBS). But on the other hand the rest of the people do not suffer, so not everyone develops depression. This essay will explore the possibility that some people are more susceptible for depression.

A possible reason for this can be the existence of different personalities in humans. Some people react with negative emotions upon stressors and it is likely that those people are more vulnerable for depression (Beck, 1967). It is likely that individuals who are more sensitive to negative feelings have more trouble with changing these negative feelings in positive ones. When those people are also not very assertive and have trouble to make friends, the chance to become depressed will be greater. But the relationship between personality and depression has not really been clarified, so this remains a challenging subject (Weber et al., 2011).

It is important to understand this relationship better. Certain personality traits associated with depression can be more easily detected and therefore more easily investigated (Canli, 2008). Also, personality can be used in defining more homogenous subgroups with different vulnerabilities for depression and this makes the treatment and the prediction of the treatment response of depression more easy (Beck, 1983; Quilty et al., 2008). And personality can serve as a means to identify individuals who have a greater risk to develop depression and for whom prevention may be a solution (Kovacs and Lopez-Duran, 2010).

An important factor in developing depression is the way individuals react to negative life events. People who are more vulnerable for depression react dysfunctional on negative events and this leads to negative thoughts about oneself, the world and the future

(Beck, 1967). Because of this aspect, the current essay will investigate the vulnerability of depression in animal models with different coping styles. A definition of a coping style is given by Koolhaas et al.: 'A coping style can be defined as a coherent set of behavioral and physiological stress responses which is consistent over time and situation and which is characteristic to a certain group of individuals' (Koolhaas et al., 1999). So animals with different coping styles react diverse upon stressors and therefore the vulnerability of these animals can differ. It may be that the response of a certain coping style to stress is dysfunctional and so can lead to depression. This leads to the research question of this thesis: 'Does coping style predict vulnerability of depression?' This question will be discussed by first introducing the concept of coping styles and the concept of depression and how you can measure this in animals. Then, the effect of stressors on the different coping styles and the development of depression will be discussed. In the end, a conclusion will be drawn.

Coping styles

There are different ways to react to stressors. The way in which an animal responds to stressors influences the effect of stressors on this animal and if this animal will develop a stress pathology. So in fact the way in which the animal copes with the stressor determines if this stressor is detrimental for the animal. A definition of coping given by Koolhaas et al. is: 'coping is defined by the behavioral and physiological efforts to master the situation' (Koolhaas et al., 1999). The controllability and predictability of the stressor determines if the animal can cope successfully (Weiss, 1968). When the animal cannot cope with the stressor because either it is not controllable or predictable, it is detrimental for the animal.

Many studies have shown the existence of different ways in which to cope with a stressor. This has led to the concept of different coping styles. Coping styles have likely arisen because of evolution and it is likely coping styles are adaptive in the natural habitat of the animals.

In these days, there are two major coping styles distinguished: Jim Henry was the first to suggest this (Henry and Stephens, 1977). These two coping styles are called reactive and proactive: the proactive coping style is defined behaviorally by territorial control and aggression and the reactive coping style by immobility and low levels of aggression (Koolhaas et al., 1999). The amount of aggression determines thus the way in which animals respond to stressors (Benus et al., 1991). The more aggressive animals have a proactive coping style and the non-aggressive animals a reactive coping style. Other differences are that the proactive animals easily develop routines, are impulsive in decision-making, novelty seekers, take risks in the face of potential danger while the reactive animals are more flexible. These two coping styles became evolutionary stable. In a stable environment, the proactive animals profit and in a variable environment the reactive animals profit (Oortmerssen and Busser, 1989; Steimer and Driscoll, 2005).

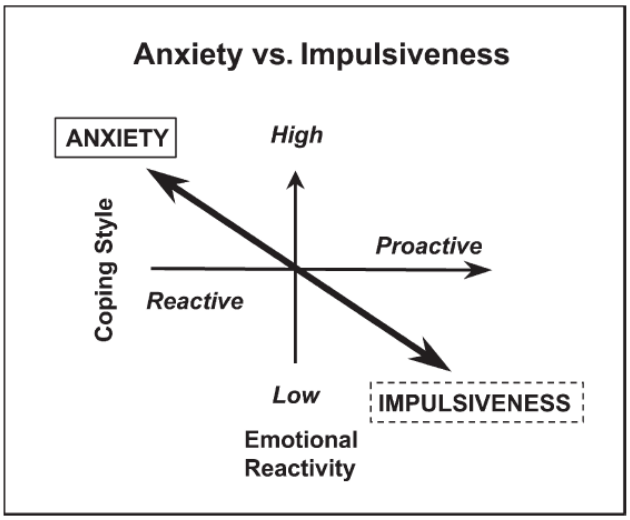

Figure 1: A theoretical model postulating that anxiety results from the combination of increased emotional reactivity (Y-axis) with a relatively passive (reactive) coping style (X-axis), whereas impulsiveness is associated with a more active (proactive) coping style and a decreased emotional reactivity. (Steimer and Driscoll, 2003)

Animals may not only differ in their coping style, they may show variation in other trait characteristics as well (Steimer and Driscoll, 2005;

Koolhaas et al., 2007). So, a two-tier model has been developed by these authors (see figure 1). A coping style is how an animal responds to a stressor but there are also differences in emotional reaction. The emotional reaction differs in how strongly the animal responds to the stressor. These differences have probably developed by selection pressure and they are part of individual fitness (Coppens et al., 2010).

The different coping styles are investigated in several species. Pigs for instance respond differently to a certain test early in life and their response is correlated to the coping style they display when they are older. The two different reaction patterns differ in aggressiveness, responses to novel environments and HPA axis (Hessing et al., 1993; Ruis et al., 2001).

For a better investigation of the different coping styles and their anxiety-related behavior, selection lines are created by selective breeding in inter alia mice and rats. One of the first selection lines were the short (SAL) and long (LAL) attack latency mice. They were selected for the latency time to attack a non-aggressive mouse introduced in their home cage (Van Oortmerssen and Bakker, 1981). SAL mice display excessive aggression but there are not differences found in anxiety between SAL and LAL mice (Haller and Kruk, 2006; Veenema et al., 2003). Selective breeding in Wistar rats on the elevated plus-maze led to a high (HAB) and low (LAB) trait anxiety line. The elevated plus-maze can measure anxiety in rodents (Wigger et al., 2001). Another selection line in rats is the Roman high- (RHA) and low (RLA) avoidance rats, selected for good (RHA) and poor (RLA) performance in a two-way, active avoidance test (Bignami, 1965). RLA rats are more anxious and have an increased neuroendocrine and autonomic reactivity to mild stressors in comparison with RHA rats (Walker et al., 1989).

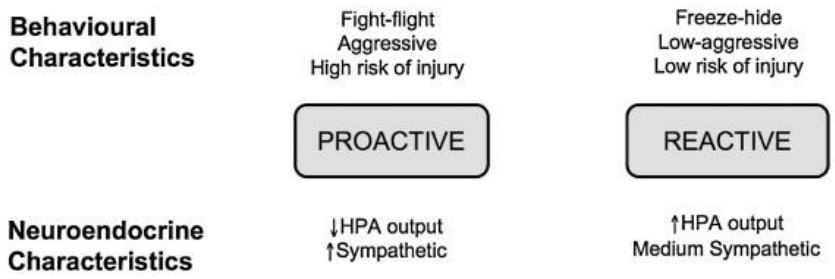

Figure 2: Scheme of behavioral and neuroendocrine (hormonal/neurobiological) characteristics of the proactive and reactive coping style (Proudfoot et al., 2012).

An important field of research is to investigate what the relation of the coping styles is with hormonal or behavioral or neurobiology stress reactivity. As told before, when a proactive animal is exposed to a stressor it reacts with excessive aggressive behavior, routine patterns and active avoidance (Koolhaas et al., 1999), a reactive animal reacts with submissive behavior, freezing and immobility (Buwalda et al., 1999; Tornatzky and Miczek, 1994). On the hormonal level, proactive animals display a lower activity of the HPA axis, lower parasympathetic activity and higher sympathetic activity than reactive animals (Koolhaas et al., 1999). On the neurobiological level, proactive animals have high 5-HT levels in comparison with reactive animals (Neumann et al., 2010; Veenema and Neumann, 2007). See figure 2 for a scheme of the behavioral and neuroendocrine characteristics of the different coping styles.

So, the prediction for their reaction on stress for the different selection lines is that the proactive animals will respond with high levels of aggression, low HPA axis activity and high levels of 5-HT and the reactive animals will respond with submissive behavior, immobility, high HPA axis activity and low levels of 5-HT.

Depression

An important model to describe the origin of depression is the cognitive diathesis-stress model of depression (Beck, 1967; Monroe and Simons, 1991). This model states that there are genetic differences in vulnerability for depression and that this vulnerability

interacts with negative life events which are stressful. Together these can contribute to the origin and maintenance of depression. The negative life events can take place prenatally or postnatally and can influence the vulnerability (see figure 3). Negative life events later in life can cause a depression. Individuals who are genetic vulnerable will become more easily depressed after a negative life event in comparison with individuals who are less genetic vulnerable (Hilsman and Garber, 1995).

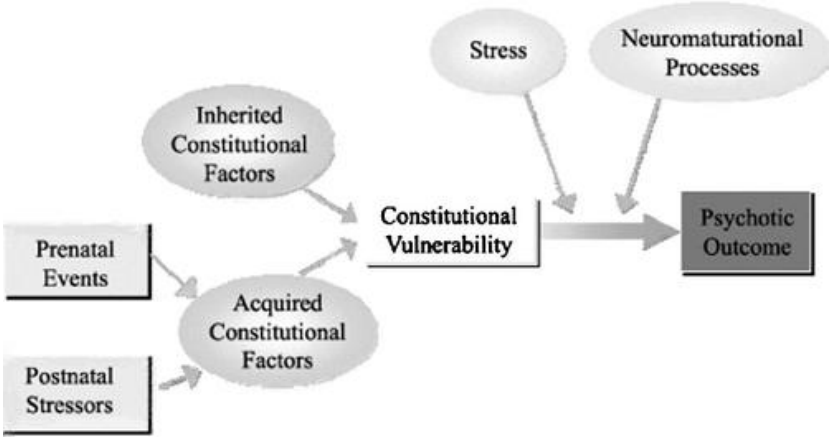

Figure 3: Scheme of stress diathesis model of depression (Walker et al., 2004)

Negative life events can affect the development of depression by stimulating the HPA axis to secrete excessive stress hormones like cortisol. This can lead to hyper-cortisolemia which is present in many depressed individuals (Gotlib et al., 2008; Parker et al., 2003).

Vulnerability for depression depends on the serotonergic system. Low intracellular serotonin is present in depressed patients. So a hyper-reactive serotonergic system can have an influence on the vulnerability of depression (Meyer et al., 2004).

In psychiatry, depression is diagnosed on the basis of the diagnostic and statistical manual of mental disorders (DSM) IV. DSM-IV has originated because there was much confusion of tongues about diagnostic criteria in the past. It pays attention to different mental disorders including depression. To be diagnosed with depression, individuals must have a couple of symptoms. In any case they have to have either a depressed mood or a loss of interest or pleasure. Other symptoms which can be part of a depression are change of appetite (increase or decrease), sleep disturbance (insomnia or hypersomnia), psychomotor change, loss of energy, feelings of worthlessness, concentration difficulty and suicidal ideation. One has to have five of these symptoms and they must be present during a period of two weeks or longer to be diagnosed with depression (APA, 2000).

The difficulty is how to translate these symptoms to animal symptoms. Things like hyper-cortisolemia, a hyper-reactive serotonergic system, change of appetite and sleep disturbance can be measured in animals, but suicidal ideation and feelings of worthlessness are impossible to measure. DSM-IV can thus not entirely be translated to animals.

Also, making animals to develop depression is difficult. The cognitive diathesis-stress model of depression states that stressful events can lead to depression (Monroe and Simons, 1991). Hence, depression is often investigated in animals by exposing the animals to stress. The behavioral, hormonal and neurobiological differences after exposure to stress are then investigated. Exposure to mild chronic stress can lead to anhedonia in animals (Shively and Willard, 2012).

There are different animal lines developed which react differently to stress to investigate depression-like behavior. The difficulty with this is that exposure to stress in these animals only lead to one or a few characteristics of human depression. It is difficult to simulate the complexity of depression in animals (Spielmans et al., 2011). Besides, distinguishing between stress responses and a depression-like state is difficult (Duman, 2010). To avoid this kind of difficulties as much as possible, there are conditions defined which the different animal models must meet. These are the face, construct and pharmacological validity. Face validity is the resemblance between the animal model and

human depression. This is often fulfilled: animals display anhedonia, hypophagia, abnormalities of the HPA axis and social withdrawal. Construct validity is if the models replicate etiological factors involved in depression. Most models use stress and stress is known to be associated with depression. Pharmacological validity is satisfied when the depression-related behaviors are abolished by antidepressants (Krishnan and Nestler, 2010).

Many animal models satisfy these conditions, but notwithstanding it remains difficult to make a distinction between a stress state and a depression-like state.

Coping style and depression

Measuring depression in animals

Depression-like behavior is mostly correlated with aggressive or anxiety-related behavior or anhedonia. Depression is associated with excessive aggression (Kohn and Asnis, 2003). The neural circuits of regulating emotions and social behavior are largely interconnected and this can be a reason for the link between excessive aggression and depression. Disturbed emotional regulation can lead to excessive aggression (Davidson et al., 2000). The type of aggression connected with depression is the impulsive-reactive-hostile-affective aggression as described by Vitiello and Stoff (Vitiello and Stoff, 1997). This type of aggression is associated with high glucocorticoids levels and high emotional responses (Haller and Kruk, 2006).

Because there are overlapping symptoms, depression is also associated with anxiety (Cryan and Holmes, 2005; Grillon et al., 2005; Landgraf et al., 2007). Anxiety-related behavior is seen as passively responding to stressors. When a passive coping strategy can be changed in an active coping strategy, it will decrease the level of stress and anxiety (Steimer, 2011).

Anhedonia is a loss of interest or pleasure. It is one of the two main symptoms of depression according to DSM-IV and therefore an important factor in determining whether an animal suffers of a depression.

Stress is a risk factor for developing of depression (Korte, 2001) and therefore stressors are used in many tests to induce depression-like symptoms as told before in the section about depression. Animals with different coping styles respond differently to stress and many researches investigate if this different response has as a consequence a greater risk to develop depression. Because depression is a human disease and so defined at human characteristics it is difficult to translate this to animals. There are several indicators used as signal for depression. Indicators of depression can be found in the behavior of the animals and on the hormonal and neurobiological level.

Figure 4: The elevated plus maze (http://www.lintoninst.co.uk/Products/tabid/63/ProdID/276/Language/en-US/401423__Elevated_Plus_Maze.aspx)

Behavioral indicators: Behavioral tests

There are many behavioral tests used to investigate depression-like behavior. Here is chosen to concentrate on a couple of tests which test differences in baselines between the two coping styles and tests which investigate differences in response to severe stress. Severe stress is a reliable factor to induce depression. Also there is chosen for a test, the sucrose preference test, which measures an important symptom of depression: anhedonia. The chosen tests which test the baseline differences are: the forced swim test, the elevated plus maze and the open field test.

In the forced swim test animals are placed in a container with water and so forced to

swim. Proactive animals show more immobility in this test (Weiss et al., 1998).

The elevated plus maze is a maze with two open alleys and two enclosed alleys connected by a central platform and so it has a plus shape, hence the name (see figure 4). Animals are placed on the central platform and given the opportunity to explore the maze. Percent entries to the open arms and percent of time spent in the open arms are often measured and are indicators of the anxiety of the animal (Rodgers and Dalvi, 1997).

In the open field test, animals are placed in a large, open arena. This test can show how the animals respond emotionally to a novel environment. It is presumed that animals which have a proactive coping style will be more active and will explore the new environment more in comparison with animals with a reactive coping style.

The chosen tests which test the response to severe stress are: the social defeat test and the social interaction test.

In the social defeat test, animals are exposed to a short physical interaction with an unknown aggressive animal. This unknown aggressive animal is placed in the home cage of the resident rat. Normally, this leads to an attack of the resident rat on the intruder and a defeat for the intruder, hence the name social defeat. The stress resulting from this interaction leads to physiological changes like elevations in corticosterone and also to behavioral changes as increased anxiety and depression-related behavior (Bartolomucci et al., 2001; Avgustinovich et al., 1997; Frank et al., 2006).

In the social interaction test an adult animal is placed in a cage together with a juvenile animal for a certain time. This results also in stress. The validity of this test to investigate anxiety is based on the effects of anxiolytics (File, 1980).

Also, you can measure an important symptom of depression, anhedonia, by using the sucrose preference test. Anhedonia is measured in rodents by looking at the consumption of a palatable sweet solution, the sucrose preference test. Before this test animals are water and food deprived for a certain time. Then they get two bottles offered, one with water and one with a sucrose solution. After a certain time, the bottles will be removed and weighed and so the preference for sucrose is tested. Anhedonia is when the intake of sucrose is decreased relative to the control group and baseline values (Pothion et al., 2004). Rats exposed to chronic mild stress have a reduced intake of sucrose solution and so this is an indicator of anhedonia (Wang et al., 2009).

Hormonal indicators: HPA axis

When investigating indicators of depression on hormonal level, the HPA axis is the main subject. The HPA axis is an important stress system. It is put in operation when the paraventricular nucleus (PVN) secretes corticotropin-releasing hormone and AVP into the pituitary. This stimulates the secretion of ACTH into the peripheral blood circulation and ACTH induces the adrenal secretion of glucocorticoids (see figure 5). Glucocorticoids regulate the reaction on stress by adaptations at physiological and behavioral levels. A disturbed HPA axis is associated with depression-related disorders and also with excessive aggression (Plotsky et al, 1998; Mello et al., 2003; de Kloet et al, 2005). Glucocorticoids are seen as important regulators of aggressive behavior, but the association of glucocorticoids and

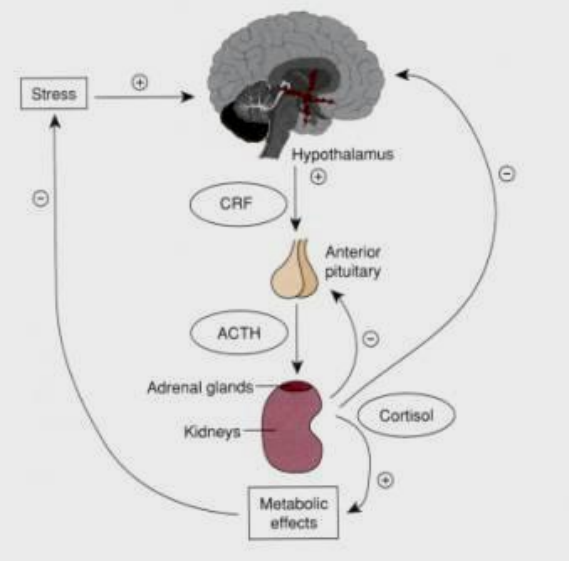

Figure 5: Scheme of the operation of the HPA axis. (http://www.montana.edu/wwwai/imsd/alcohol/Vanessa/vwhpa.htm)

aggressive behavior is not unambiguous. Both high and low levels of circulating glucocorticoids are linked with high aggression (Haller et al., 1998, 2001; Kruk et al., 2004; Summers and Winberg, 2006).

Neurobiological indicators: Serotonergic system

The serotonergic system is one of the main neurotransmitter systems involved in depression. 5-HT is synthesized in the midbrain raphe nuclei and is an important regulator of emotionality (Olivier and Van Oorschot, 2005) and therefore it is plausible that it is involved in depression, anxiety and aggression (Linnoila and Virkkunen, 1992; Baldwin and Rudge, 1995; Ressler and Nemeroff, 2005). Studies have shown that decreased 5-HT function leads to excessive aggression (Berman et al., 2007; Jensen et al., 2009), but other studies have shown the opposite (van der Vegt et al., 2003-1,2; Summers et al., 2005). 5-HT neurotransmission is also stress-dependent (Singewald et al., 1997; Linthorst et al., 2002).

Animal models

There are many animal models used to investigate the effect of stress on depression-related behavior. Here, there are three coping style models chosen to concentrate on: the short attack latency (SAL) and long attack latency (LAL) mice, the Roman high avoidance (RHA) and Roman low avoidance (RLA) rats and the high anxiety-related behavior (HAB) and low anxiety-related behavior (LAB) rats.

Below, first the baseline differences between the different coping styles will be discussed on the behavioral, hormonal and neurobiological level, then, the response to severe stress (to induce depression-related behavior) for the different coping styles will be discussed again on the behavioral, hormonal and neurobiological level.

<u>Baseline differences</u>

Behavioral

a. Forced swim test

Veenema et al. tested LAL and SAL mice several times. In the first two trials, LAL mice showed more immobility than SAL mice, see figure 6 (Veenema et al., 2003).

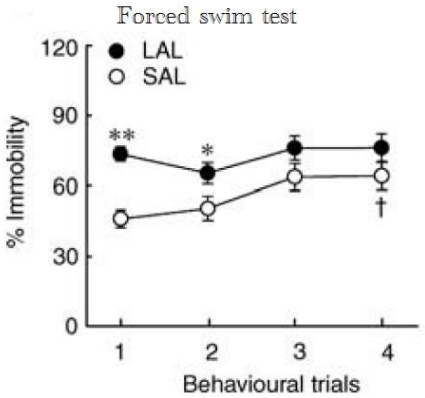

*Figure 6: Immobility behavior during the forced swim test of nonaggressive (LAL) and aggressive (SAL) mice. *P at least <0.05 versus SAL mice, †P<0.005 versus trial 1, pairwise comparisons (LSD test) following repeated measures ANOVA. (Veenema et al., 2003)*

RLA rats tried less frequent to climb to escape the container than RHA rats and also they were more often immobile (Piras, Giorgi, Corda, 2010). They tested the rats again after administering different antidepressants, namely desipramine, fluoxetine and chlorimipramine. All these antidepressants decreased immobility in RLA rats. Desipramine and chlorimipramine promoted climbing and fluoxetine swimming in RLA rats. They had no effect on these parameters in RHA rats (Piras, Giorgi, Corda, 2010). Again the rats with a more passive coping style, HAB rats, were more immobile in this test and floated more than the LAB rats (Keck et al., 2003; Liebsch et al., 1998; Muigg et al., 2007). When HAB rats were treated with the antidepressant drug paroxetine (selective serotonin reuptake inhibitor), they became less immobile and even to the same level as LAB rats. LAB

rats remained at the same level of immobility when treated with paroxetine (Muigg et al, 2007).

b. Elevated plus maze

LAL mice are less active in this test than SAL mice (Veenema et al., 2003).
Significant differences between RLA and RHA rats were for percent open arm entries and the number of open arm entries. The other parameters were not significant. Parameters which are especially associated with anxiety (Cruz et al., 1994), namely scanning and end-exploration were thus not significant (Steimer and Driscoll, 2003).
HAB and LAB rats are selected on the basis of their behavior in the elevated plus maze. HAB rats display more anxiety-related behavior in the open arm of the elevated plus-maze than in the closed arm in comparison with LAB rats (Pellow et al., 1985). When HAB rats were forced to be in the open arm they showed more anxiety-related behavior like immobility and had a more passive coping style than LAB rats (Salomé et al., 2006).

c. Open field test

LAL mice were more immobile than SAL mice, see figure 7 (Veenema et al., 2003).
RHA rats are more active while RLA rats are more immobile and also for RLA rats it takes more time towards self-grooming than for RHA rats (Steimer and Driscoll, 2003).
HAB rats spent less time in the central zone of the arena in the open field test and also entered this central zone less than LAB rats (Salomé et al., 2004).

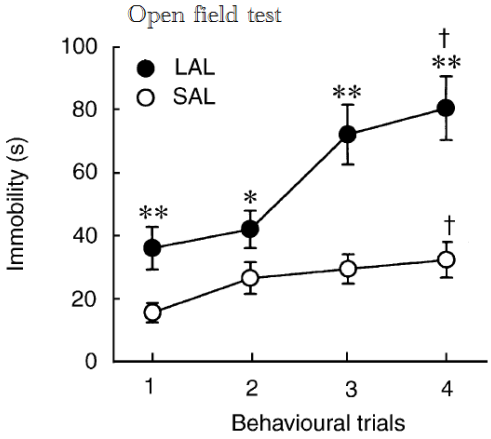

*Figure 7: Immobility in the open field test of nonaggressive (LAL) and aggressive (SAL) mice. *P<0.05, **P<0.01 versus SAL mice, †P at least <0.05 versus trial 1, pairwise comparisons (LSD test) following repeated measures ANOVA. (Veenema et al., 2003)*

Hormonal

HPA axis

When HAB rats were exposed to a mild emotional stressor that is elevated plus-maze or the open field test, their HPA axis responded hyper-actively. When they were exposed to a novel environment (a non-social stressor), they secreted more ACTH and corticosterone than LAB rats (Landgraf et al., 1999; Neumann et al., 2005; Salomé et al., 2004). Baseline concentrations of ACTH were not different between HAB and LAB rats (Salomé et al., 2004).
When baseline concentrations of corticosterone were measured in RLA and RHA rats, RLA rats had higher baseline concentrations than RHA rats (Steimer and Driscoll, 2003). After exposure to a stressor, the activation of the HPA axis was higher in RLA rats in comparison with RHA rats, shown by a higher secretion of corticosterone (Carrasco et al., 2008; Steimer and Driscoll, 2003).
The baseline concentrations of corticosterone were the same for SAL and LAL mice. LAL mice had lower ACTH baseline levels (Veenema et al., 2003-2). When LAL and SAL mice were exposed to acute stress, the HPA axis in LAL mice reacted hyper-reactive in comparison with the HPA axis of the SAL mice (Veenema et al., 2004).

Neurobiology

5-HT system

In LAB rats the release of 5-HT in the hippocampus, amygdala and lateral septum was higher than in HAB rats when confronted with non-social stressors and hippocampal 5-HT1A receptor expression was higher too. The 5-HT transporter binding sites were lower in LAB rats. Conclusion, LAB rats have mostly an increased 5-HT neurotransmission in comparison with HAB rats (Veenema and Neumann, 2007). The effect of 5-HT on depression-related behavior is shown in HAB rats when they were treated with the 5-HT

reuptake inhibitor paroxetine. Paroxetine influenced the stress response by elevating the hippocampal 5-HT only in HAB rats (Keck et al., 2005). The elevated depression-related behavior in HAB rats can thus be caused by a low 5-HT neurotransmission (Neumann et al., 2010).
When exposed to stress, SAL mice displayed a higher 5-HT activity in certain brain regions than LAL mice and the amount of aggression decreased when brain 5-HT release was inhibited (Veenema and Neumann, 2007).
When LAL and SAL mice got 5-HT_{1A} receptor agonist administered, their behavior in the forced swim test changed differently. SAL mice displayed more immobility and tried less often to escape, the opposite was true for LAL mice. Thus, the 5-HT_{1A} receptor agonist decreased not the anxiety-related behavior but changed the behavior more in the direction of the alternative response for both coping styles (Veenema et al., 2005).

<u>Response to severe stress</u>
Behavioral
a. Social defeat
HAB rats spent more time freezing than LAB rats. Also they emitted more low and high ultrasonic vocalization (USV) calls (see figure 8). LAB rats displayed more rearing and grooming behavior and showed more aggressive behavior when confronted with the resident rat (Frank et al., 2006).
After exposure to a single social defeat, both RHA and RLA rats showed a decrease of activity in the dark phase. In this social defeat test, RHA rats were attacked more often than RLA rats, but this was not significant (Meerlo et al., 1997).

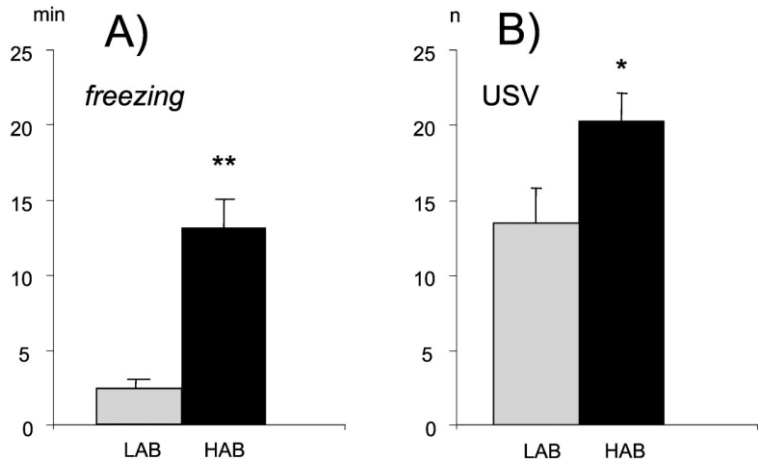

*Figure 8: Behavior of HAB (n=11) and LAB (n=10) intruders during a single social defeat representing differences in the respective coping style: (A) freezing duration and (B) number of observation points with ultrasonic vocalization calls (USV; 20–30 kHz). HAB=high anxiety-related behavior; LAB=low anxiety-related behavior. Mann–Whitney test: *p < .05 versus LAB. **p <.01 versus LAB. (Frank et al., 2006)*

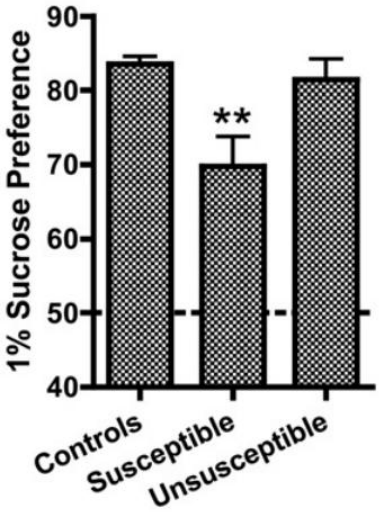

*Figure 9: Only Susceptible mice display anhedonia as measured by a reduction in 1% sucrose preference. Bars represent mean + SE (standard error) with n = 10–20, * indicates significant post hoc differences with respect to non defeated control mice, **p < 0.01 (Krishnan et al., 2007)*

b. Social interaction test
The behavioral analysis of this test is devided in non-social and social behavior. RLA and RHA rats were not different in social behavior, but in non-social behavior RHA rats displayed more locomotion and RLA rats more self-grooming.
In HAB and LAB rats the difference in behavior between them was also mainly in locomotion, LAB rats moving more than HAB rats (Henniger et al., 2000).
Krishnan et al. divided a group of mice (C57Bl/6) in a susceptible and unsusceptible group on the basis of the social defeat test. Then they were tested in a

social interaction test. The susceptible mice spend more time in the corners of the arena than the unsusceptible mice and so they avoided the social target. This was the case 11 and 39 days after the social defeat, so the effect of the social defeat was long-lasting. Anhedonia was also tested by the sucrose preference test. On day 11, the susceptible mice had a decreased sucrose preference in comparison with the unsusceptible mice, see figure 9 (Krishnan et al., 2007).

Hormonal

HPA axis

In a social context, introduced as an intruder in the social defeat test, the LAB rats strikingly display a higher HPA axis response while they show less passive behavior than HAB rats (Frank et al., 2006). This also applies to the resident intruder test, when LAB rats were introduced as resident (Veenema et al., 2007).
There was no difference in corticosterone and ACTH response between RLA and RHA rats after exposure to severe stress (Steimer et al., 1997).
When SAL and LAL mice were exposed to a social stressor, sensory contact, LAL mice had a long-lasting increase in plasma corticosterone while SAL mice showed no changes (Veenema et al., 2005-2). Another severe stressor was the procedure whereat the SAL and LAL mice were defeated for 21 consecutive days. After this stressor, LAL mice had higher corticosterone levels compared with SAL mice (Veenema et al., 2003).
Both susceptible and unsusceptible mice (C57Bl/6) had a higher corticosterone level as response to a stressor (Krishnan et al., 2007).

Neurobiological

5-HT system

There are no researches yet which look at the neurobiology in different coping styles after severe stress. However, there are researches in normal lines of rodents. NMRI mice had higher levels of hippocampal 5-HT after an acute social defeat in comparison to baseline levels (Keeney et al., 2006). In another research, Sprague Dawley rats exposed to an inescapable foot shock had also higher 5-HT levels in comparison to the baseline levels (Amat et al., 1998).

Discussion

First the results of the baseline differences between the coping styles will be summarized and then the severe stress results. Subsequently, the baseline differences and severe stress results will be compared. Then an overall conclusion will be drawn and after that some difficulties with this type of research will be discussed.

The baseline differences corresponded with the expectations. On the behavioral level, the reactive coping styles (LAL, RLA and HAB) displayed more passive behavior like immobility and also more anxiety-related behavior. Antidepressants abolished this behavior and changed the behavior more in the direction of the proactive coping style. The HPA axis results corresponded also with the expectations. The reactive coping styles had a higher HPA axis response after exposure to a stressor. Baseline levels were mostly the same between the different coping styles, but not for the ACTH baseline level in the SAL and LAL mice and corticosterone level in RLA and RHA rats. LAL mice had a lower ACTH baseline level than SAL mice and RLA rats had a higher corticosterone baseline level than RHA rats. Nevertheless, the HPA axis response was higher in the reactive coping styles. The 5-HT responses were higher in the proactive coping styles. Antidepressants increased the 5-HT neurotransmission in the reactive coping styles.

The severe stress results were more varied than the baseline differences results. On the behavioral level, the HAB/LAB rats displayed differences in behavior whereat the HAB rats displayed more anxiety-related behavior. The RLA/RHA rats displayed sometimes differences in behavior, whereat the RHA rats were more active. In social behavior there were no differences in HAB/LAB rats and RLA/RHA rats. Susceptible mice were more

passive and displayed more anhedonia than unsusceptible mice. There were no differences in HPA axis results between RLA and RHA rats. LAB rats and LAL mice had a higher HPA axis response after a social stressor. Susceptible and unsusceptible mice had both a higher corticosterone level. There were no data concerning 5-HT levels in different coping styles. 5-HT was higher after severe stress in normal lines of both mice and rats.

Both behavioral tests which investigate baseline differences as tests which investigate the effect of severe stress showed a more passive behavior of the reactive coping style animals. The severe stress tests had also a social component in contrast to the baseline differences tests. But on the social level there were no differences between the coping styles. It seems like there are no differences in behavior between baseline differences and severe stress tests.

The HPA axis results were indeed different between the several tests. The baseline differences tests had as a result a higher HPA axis response in the reactive coping style animals. The severe stress tests had variable results, no differences for RLA and RHA rats and a higher HPA axis response in LAB and LAL. So, in the baseline differences tests (non-social stimuli) HAB rats had a higher HPA axis response, but the LAB rats had a higher response in the severe stress tests (social stimuli). A possible reason for this difference in HPA axis response in LAB rats is that social stimuli are seen as more dangerous than non-social stimuli and therefore they react more aggressively and have as a consequence a higher HPA axis response (Neumann et al., 2010). Some researchers have doubts about the validity of HPA axis as a mark for a coping style. Koolhaas et al. concluded that it is unlikely HPA axis response is causally related with a coping style. The correlations which exist between HPA axis response and coping style can be an effect of individual differences in behavioral activity (Koolhaas et al., 2010). Accordingly it is then also unlikely HPA axis is causally related with vulnerability for depression. It may be only correlated with the behavioral activity and this can be an explanation for the different results. Another idea is that these variable results show that the reactive coping style is not more vulnerable for depression than the proactive coping style, in contrast to the prediction based on baseline differences. After severe stress, they do not have all higher HPA axis responses, as they have after mild stress.

Because the 5-HT levels after severe stress are not investigated in the different coping styles, it is not possible to compare the results with the baseline differences. However, there are results of severe stress on 5-HT in normal lines of rodents and they show that severe stress increases the 5-HT levels. Proactive animals had higher 5-HT levels in the baseline differences tests. The expectation was that stressors would induce low levels of 5-HT, but in the normal lines of rodents the 5-HT levels were higher after severe stress. There is still much confusion whether high or low 5-HT levels are connected with depression, also shown by these results. Neurobiological research in animals of different coping styles after severe stress is needed to bring more clarity.

In this paper, I made a distinction between baseline differences tests and severe stress tests. This is done because the assumption was that the effect of the baseline differences tests is only a mild stress response and that this stress shows what the differences in coping style are, but not really the differences in vulnerability for depression. The severe stress tests are needed to show then what the differences in vulnerability are. In the past, the baseline differences tests were used to make a distinction in vulnerability but now one comes to understand that these tests possibly make a distinction but that severe stress is needed to give clarity (Nestler and Hyman, 2010). But the severe stress results cited in this paper are contradictory and often not different from the baseline differences results. Of course there is much more research needed. But it is also the case that a clear distinction between stress symptoms and depression-like symptoms is difficult to make. In both sort of tests there is stress present to a greater or lesser extent. It is difficult to see where stress symptoms end and depression symptoms begin.

So the question is, is the concept of coping styles capable of representing the depression-like state? Or is het more like a phenotypic copy (phenotype is the same as in

depression but the underlying mechanisms are different)? This is difficult to find out, but best is to compare the different models of depression in animals like knock-out lines, or lines with altered biochemical pathways etcetera (Nestler and Hyman, 2010). Results of different animal models are used in this thesis. This can also be difficult, because they may react differently to the tests and may have a different vulnerability for depression. But because the baseline differences are the same for the different animal models, they also were used to investigate the effect of severe stress. These results were very varied, so a next time it may be better to concentrate on one animal model.

Depression itself is also highly ambivalent, the diagnosis is not very exact because two individuals with different symptoms (either hypophagia or hyperphagia etc.) can both have a depression. But there will be a difference with the control group so a distinction can be made.

Another reason for the varied results after severe stress can be that reactive and proactive coping styles are both vulnerable for depression but on different grounds. In the past, one presumed that the reactive coping style was more vulnerable for the development of depression. They had a higher HPA axis response and displayed more anxiety-related behavior in certain behavioral tests like the forced swim test. But, as said earlier, Nestler and Hyman concluded that this test do not measure symptoms of depression (Nestler and Hyman, 2010). The results of severe stress tests had to bring clarity, but these results are quite varied. The variation might thus be explained by a vulnerability for depression for both the coping styles. Proactive animals, as told in the coping styles part, develop more routine patterns. They expect certain outcomes in certain situations, when the outcomes are different this can be very stressful. This is not yet investigated, so tests have to be developed to do this. One can have proactive animals win for a certain time and then let them lose. The presupposition is that the animals will be very stressed after this loss and will develop a depression. The reactive animals play a waiting game and so for them the social defeat test is likely very stressful. The match-mismatch hypothesis can be a supporting statement. The match-mismatch hypothesis means that there can be a match between the conditions wherein the animal grew up and the conditions in its adult life. But there can also be a mismatch, that happens when the situation in the adult life of an animal is totally different from the situation at a younger age (Gluckman et al., 2009; Schmidt et al., 2011). An important question is when there will be a match or a mismatch in the life of the different coping styles. This can influence the way in which the animals respond to stressors. When there is a mismatch in situations, it is likely the stress response will be increased. In follow-up studies, it is important to investigate this match-mismatch hypothesis in different coping styles.

In conclusion, it is still not clear whether coping style can predict the vulnerability of depression. Depression is a multi-facetted disease and therefore difficult to investigate. Much more research is needed and in follow-up studies the match-mismatch hypothesis should also be taken into account. This can mean coping styles can predict vulnerability for depression in different situations.

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