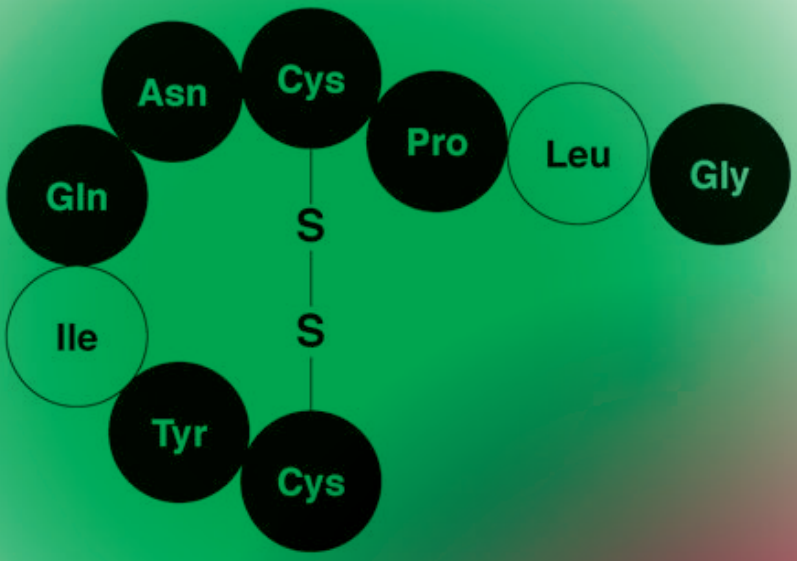
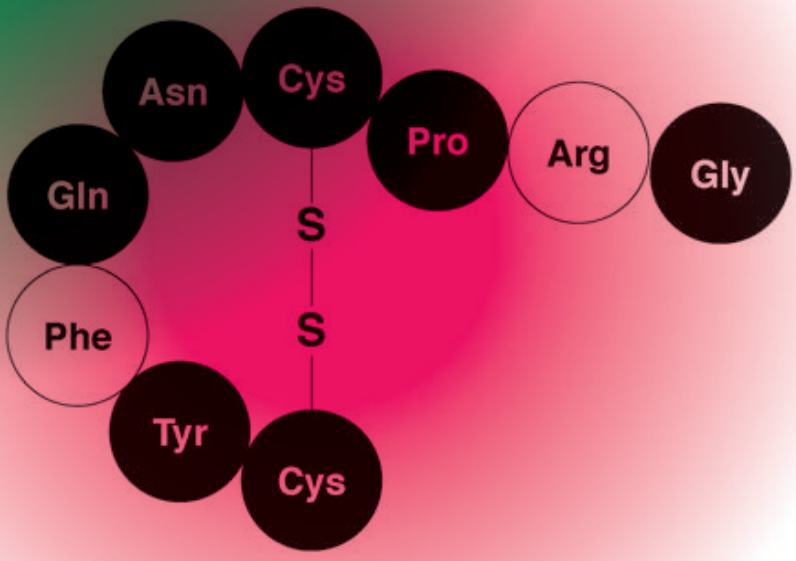
Neuropeptidergic Modulation of Social Behavior in Health and Social Phobia

Bernadette von Dawans



Oxytocin



Vasopressin

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ABSTRACT

Evidence for the key role of oxytocin and vasopressin in social behavior, affiliation, stress, aggression and anxiety has come primarily from studies in animals. Neuropeptides have been shown to cross the blood-brain barrier after intranasal administration, with initial studies reporting direct effects on human behavior. It was recently shown that oxytocin improves trust and the protective effects of social interaction on neuroendocrine responses to social stress.

The theoretical part is devoted to the behavioral effects of oxytocin and vasopressin in animals and humans, and considers their role in stress. Thereafter, social support and social phobia are discussed as different facets of social interaction and these theoretical considerations are rounded off with an integration of the neuropeptidergic effects on health and mental illness.

The empirical section presents data on the role of oxytocin and vasopressin in aggression as well as the role of oxytocin and social support in social phobia. The results of a double-blind placebo-controlled study on the effects of intranasal oxytocin and vasopressin on altruistic punishment in healthy men revealed that vasopressin enhances the readiness to punish unfair behavior. It differed significantly from oxytocin, but oxytocin showed no effects compared to placebo treatment. A second study on the role of oxytocin and social support in social phobia revealed stress-buffering effects for healthy adults as well as social phobic patients. However, both treatments were shown to at most benefit the social phobic patients.

In the final section, the pivotal findings are summarized and directions of future research discussed. Finally, a model of neuropeptidergic modulation of social behavior is proposed that incorporates our results as well as remaining questions. The model should elucidate the complex interactions of oxytocin and vasopressin from a psycho-bio-social perspective and underline its importance for the understanding and treatment of ‘social psychopathology’ in humans.

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‘*Pre-Neanderthal humans developed social skills earlier than thought*’
(comment from www.sciencedaily.com on Richards, Pettitt, Stiner, & Trinkaus, 2001)

1 Introduction

Baruch Spinoza was most likely neither the first nor the last to recognize that man is “a social animal” (cited after Insel, 2002, p. 3). Positive social interaction is one of the most important things in human life. It includes social support and is one crucial aspect in overall quality of life and health (Reblin & Uchino, 2008). Mental disorders mostly affect social life or even impair social interaction. Humans as a highly social species need to have neural mechanisms that reinforce and motivate them to socially engage, interact and bond with others.

The evidence indicates that the neuropeptides oxytocin and vasopressin play a role in these mechanisms. The ancient neuropeptides were conserved through evolution but although all vertebrates have similar peptides, only mammals show the specific receptors for them. Both peptides have important functions in the body (e g. homeostasis, metabolism, growth, sex and reproduction, stress etc.), but most notably they impact strongly on social behavior. Chapter 2 concentrates on these actions and integrates them.

Most impressively, social behavior seems to be as ancient as the neuropeptides themselves. Anthropologists found (by investigating teeth – scientific methods are stunning) that even pre-Neanderthal humans expressed social behavior; in fact much earlier than one might have thought (Richards, Pettitt, Stiner, & Trinkaus, 2001).
The general understanding of the expression ‘social behavior’ seems to be biased towards ‘pro-social’ acts. But ‘social behavior’ includes pro-social aspects, like trust or cooperation, just as it does ‘social aggression’, like altruistic punishment, which has been shown to maintain cooperation (Fehr & Gachter, 2002). The latter must not be equated with antisocial behavior or instrumental aggression. As mentioned above, many psychiatric illnesses show disturbances in social behavior. Social phobia entails pathological anxiety towards most social encounters, and there are other disorders that show exaggerated aggression that can no longer be accounted for as social but rather as anti-social.

Although there is ample evidence on the pro-social effect of oxytocin in healthy humans, it remains unclear whether the peptide helps to reduce symptoms in mental illnesses like social phobia, autism or borderline personality disorder (Heinrichs & Domes, 2008). On the other hand, it needs to be proven that arginine vasopressin can enhance aggression in humans. Animal research and first evidence from human studies point in this direction.

This work reviews the effects of oxytocin (chapter 2.1) and arginine vasopressin (chapter 2.2) on social behavior in animals and humans and integrates their interplay on neuronal circuits (chapter 2.3). This comprises studies on prosocial behavior and also on aggression, and finally stress. The actions exerted by both peptides on the two stress axes are summarized in chapter 3.2. Subsequently, a continuum of social behavior (chapter 4) is proposed that suggests both pro-social and aggressive components in health and links psychopathologies towards biased behavioral expression (either hypersocial, social anxiety or anti-social). The psychobiology of prosocial interaction and social support in healthy humans (chapter 4.1) is followed by the psychobiology of social phobia (chapter 4.2). Thereafter, social behavior and its pathologies is integrated with respect to the relevant neuropeptidergic actions (chapter 5).

In chapter 6, a placebo-controlled double-blind study on the effects of a single-dose intra-nasal application of oxytocin and arginine vasopressin on altruistic punishment in healthy men is presented. The impact of single-dose intranasal oxytocin application combined with social support on stress response in social phobia is subsequently reported in chapter 7. Finally, both empirical studies are discussed in general terms, also with regard to methodological considerations and limitations. The book closes by proposing a model of social behavior (built on the model of Heinrichs & Domes, 2008), which comprises prosocial as well as social aggressive components, bands together oxytocinergic as well as vasopressinergic effects, and tries to explain the share of both peptides in mental disorders that affect the social domain.

2 Neuropeptides and behavior

Oxytocin (OXT) and arginine vasopressin (AVP) are two closely related nonapeptides, synthesized in the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus. They are transcribed from adjacent genes and differ in only two of their nine amino acids (Figure 2-1).

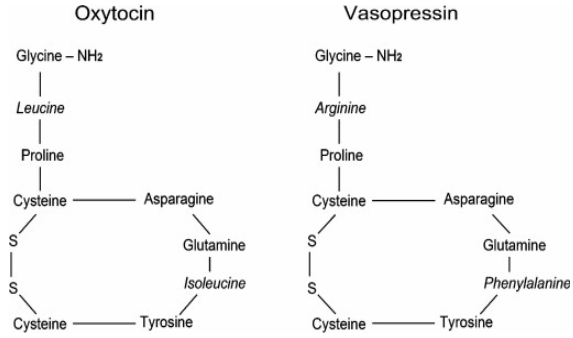

Figure 2-1: Chemical structures of oxytocin and vasopressin (two different amino acids are marked in italics) (Debiec, 2007)

Released into the blood stream via the posterior pituitary, both peptide hormones have important peripheral effects (Figure 2-2). OXT acts on the uterus to induce parturition in late pregnancy and is important for facilitating milk ejection during lactation (Figure 2-3).

AVP, also known as anti-diuretic hormone (ADH), acts on the kidney to facilitate reabsorption of water and regulates vascular tone via action in the blood vessels (Figure 2-4). In addition, OXT and AVP are known for their relevance in the psychobiological stress response as well as multiple social behaviors (Gimpl & Fahrenholz, 2001; Raggenbass, 2008), which will be further explained in Chapter 2 (Neuropeptides and behavior) and Chapter 3 (Stress).

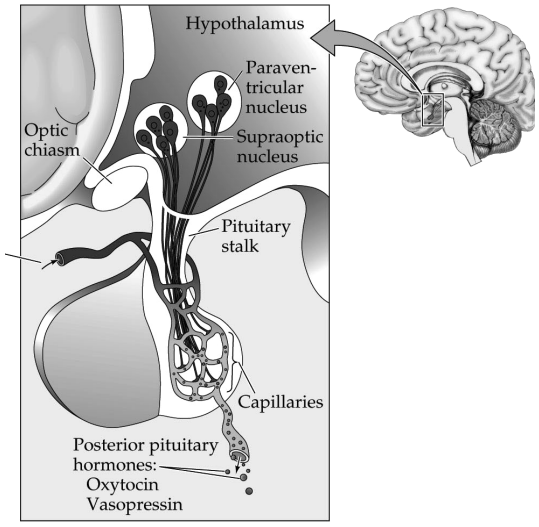

Figure 2-2: Oxytocin and vasopressin production and release in the brain and the body (Rosenzweig, Breedlove, & Watson, 2007)

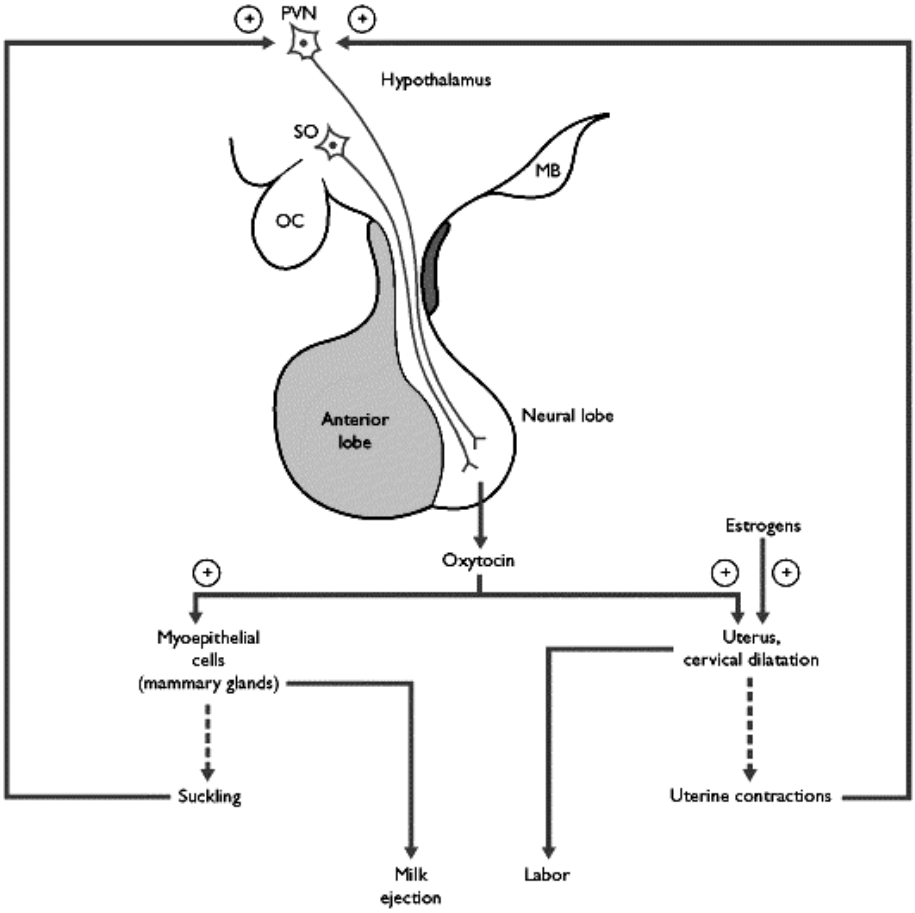

Figure 2-3: Oxytocin - its actions and control;
Abbreviations: MB, mammillary body; OC, optic chiasm; PVN, paraventricular nucleus; SO, supraoptic nucleus (Nussey & Whitehead, 2001)

Whereas for OXT, only one receptor is known, AVP acts on three receptor subtypes: V_{1A}, V_{1B} and V_2 receptor (Raggenbass, 2008). Both peptides act as neuromodulators in the brain, where they influence several regulating functions and behaviors. OXT and AVP (V_{1A}, V_{1B}) receptors are abundant throughout the brain (Barberis & Tribollet, 1996; Young, Li, Wersinger, & Palkovits, 2006). They have been found in the olfactory system, the neocortex, the basal ganglia, the limbic system, the hypothalamus, the thalamus, the circumventricular organs, the brainstem and the spinal cord (for reviews, see Barberis & Tribollet, 1996; Zingg, 1996).

However, not all of these regions are innervated by peptidergic neurons, and since OXT and AVP cannot cross the blood-brain barrier, there must be other ways than only secretion from synapses. How do the peptides exert their actions?

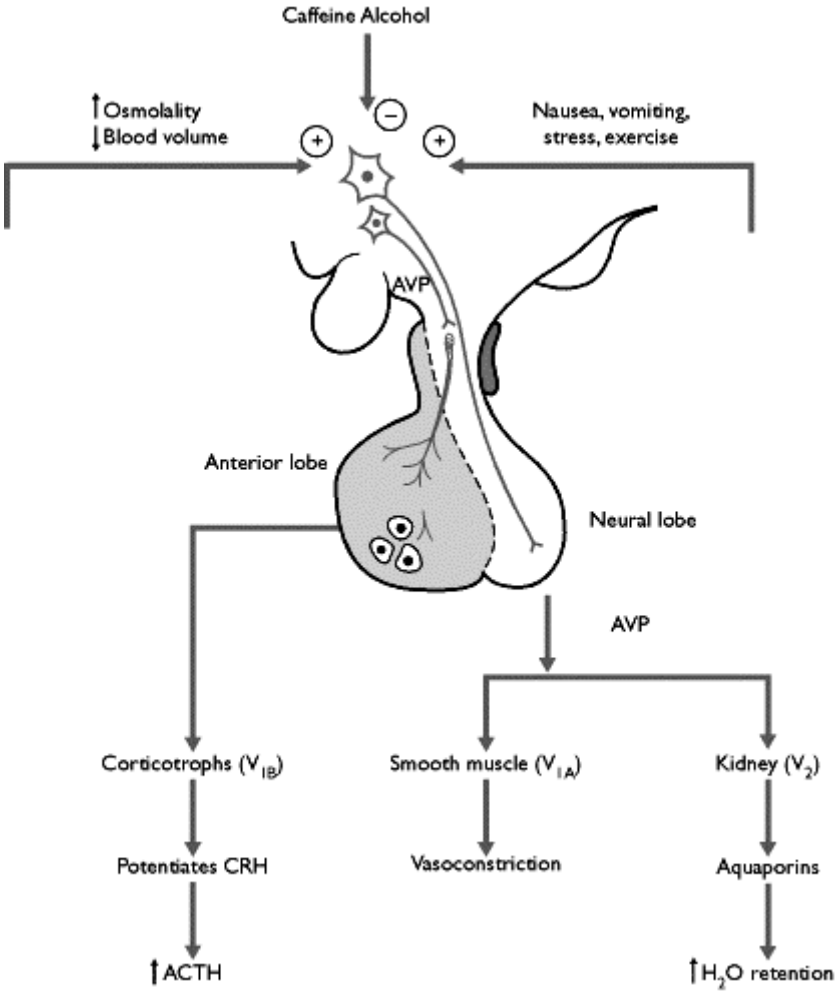

Figure 2-4: The actions of arginine vasopressin (AVP) secretion and mechanisms of control (Nussey & Whitehead, 2001)

Although OXT and AVP neurons signal via synapses, *'[their actions] are not restricted spatially by synaptic wiring, or temporally by rapid degradation'* as is the case for neurotransmitters (Ludwig & Leng, 2006, p. 127). Their effects in the brain are also very different from neurotransmitters. The half-lives of OXT and AVP in the brain are relatively long (~26 and 19 min for AVP and OXT, respectively) compared to a very short half life in the blood (~2 min) (Mens, Witter, & van Wimersma Greidanus, 1983). Interestingly, other neurotransmitters are coexistent on OXT and AVP neurons (which implies multiple neurotransmitter interactions – e.g. with serotonin), and the magnocellular neurons of AVP and OXT from the SON to the pituitary each have one to three dendrites that project to the ventral surface of the brain, where they form a dense plexus.

It has been shown that OXT and AVP concentrations in the extracellular fluid of the SON are 100 to 1,000 times higher than in the blood, indicating strong dendritic release of both neuropeptides throughout the brain. Thus, the dendritic release of the peptides activates self-sustaining, long-lasting excretion as a function of autoregulation (AVP neurons express AVP receptors and OXT neurons OXT receptor). In addition, the dendritic release causes priming effects facilitating later release of the peptides (for review, see Ludwig & Leng, 2006). These paths of action explain why crude diffusion of OXT and AVP exert behavioral modulation and are of relevance besides their local synaptic effects. To summarize their actions:

a) OXT and AVP are not only released from synapses but also in a large amount from dendrites.
b) They act in an autoregulatory manner on their own synapses, thus increasing their own release, and
c) Have priming effects at their receptors, which results in facilitation of activity-dependent dendritic release (not only restricted to the cell of origin).
d) Finally, they diffuse throughout the whole brain to exert actions at various sites that are not directly innervated by OXT or AVP fibers.

Via the depicted mechanism, OXT and AVP have been found to modulate several behaviors. Landgraf and Neumann state in their review (2004):

Taken together *'[t]he capability of responding to and mediating both environmental stimuli and genetic polymorphisms, transducing them into adequate or psychopathological behavior, makes neuropeptide release in distinct brain areas a key process for converging behavioural regulation'*.

2.1 Oxytocin and behavior

OXT modulates mainly social behaviors in animals, but these effects arise in a species-specific manner (the same holds true for AVP), making generalizations across species difficult (the majority of data in animals arises from different rodent species). Of importance is the modulation of OXT receptors by estrogen (Lim & Young, 2006), which underlines its importance for females. However, OXT has also been shown to be crucial to social behavior in males. To provide an overview of the important aspects of oxytocin-relevant behaviors, selected examples from animal and human research will be discussed in this chapter.

2.1.1 Oxytocin and behavior in animals

Social recognition in rodents is a behavioral paradigm for social learning and memory. In the beginning, OXT was hypothesized to attenuate learning and memory (in contrast to AVP), but this was found for physiologically very high doses of OXT resulting in enormous plasma OXT increase (Popik & Vetulani, 1991). Only a few months later, the same authors published facilitatory effects on learning and memory by lower doses of OXT (Popik, Vetulani, & van Ree, 1992). Other studies found an inverted U-shaped curve for OXT action, suggesting an optimal range of OXT in rodents for social recognition. Very high or very low doses impaired social memory. By blocking AVP receptors while applying OXT, the authors were able to prove the specificity of OXT receptors for this effect (Boccia, Kopf, & Baratti, 1998). When an adequate dose of OXT was applied, the animals recognized a previously met conspecific faster, demonstrating facilitation of social memory or social recognition by OXT.

However, OXT was not only shown to make rodents remember their conspecifics better. It also plays an important role in ***positive social interactions*** like maternal behavior (Pedersen, Vadlamudi, Boccia, & Amico, 2006) and is important for pair bond formation in a female rodent species, the prairie vole (Insel, Winslow, Wang, Young, & Hulihan, 1995). A strongly related species, the montane vole, differs to a fairly large degree in their mating behavior: they do not form stable pair bonds and, interestingly, show less OXT receptor density in reward-related brain areas (Young, Lim, Gingrich, & Insel, 2001).

In addition, ***stress-buffering*** effects of OXT as well as ***anxiolytic actions*** (Amico, Mantella, Vollmer, & Li, 2004; Neumann, Wigger, Torner, Holsboer, & Landgraf, 2000) are very well documented in animals, and have been studied in maternal rodents as well as non-maternal and male rodents (for a review, see Slattery & Neumann, 2008).

Given the important regulatory function of OXT in the maternal brain, its role in the offspring is puzzling. Sue Carter states in her review that *'[d]uring development, exposure to peptides and steroids may reprogram the nervous system, altering thresholds for sociality, emotionality and aggression*'. She suggests an ***influence on receptor density and sensitivity*** from '*hormonal imprinting*' (Carter, 2003, p. 390). Mother-reared monkeys showed higher levels of CSF OXT than non-mother-reared monkeys (Winslow, Noble, Lyons, Sterk, & Insel, 2003). Moreover in rodents, lower OXT activity at day one after birth was linked to higher amygdala activation in adulthood. If OXT receptors were blocked on the first day of life in a female prairie vole, she later showed significantly higher central amygdala activation in response to pairing with a male (Kramer, Choe, Carter, & Cushing, 2006). Neonatal manipulation of OXT impacts on the expression of social behavior. Maternal behavior (licking and grooming) was shown to be modulated by OXT via mesolimbic dopamine neurons. Mothers that show high maternal behavior have high dopamine (DA) increase in the nucleus accumbens, and the behavior is reduced by OXT receptor antagonists, indicating a modulatory role for OXT in maternal behavior via reward. If a pup is reared by a low licking and grooming mother, it in turn has reduced levels of OXT receptor binding. Furthermore, there is no upregulation of OXT receptor density by estrogen in these pups in contrast to high licking and grooming pups (for review see Champagne, 2008). Moreover, OXT infusions into the central amygdala reversed social incompetence of prenatally stressed rats (Lee, Brady, Shapiro, Dorsa, & Koenig, 2007).

In summary, animal research provides a strong basis for positive social effects of OXT. OXT increased approach and reduced avoidance behavior, dampened stress and anxiety, and showed important developmental and epigenetic effects.

2.1.2 Oxytocin and behavior in humans

Nearly all the behavioral domains that were found to be regulated by OXT in animals have now also been investigated in humans. However, the techniques used are very different. Endogenous OXT is increased during late pregnancy and lactation (Nussey & Whitehead, 2001) and gentle touch was also found to be associated with increased OXT levels in animals and humans (Carter, 1998; Dunbar, in press; Turner, Altemus, Enos, Cooper, & McGuinness, 1999). To investigate the stress-protective effects of OXT in humans, lactating women were exposed to a psychosocial stressor (Trier Social Stress Test, TSST) (Kirschbaum, Pirke, & Hellhammer, 1993) and prior to the test either breast-fed their baby or only held it in their arms. Breast-feeding resulted in ***lower activation of the hypothalamus-pituitary axis*** (HPA) as well as ***attenuated subjective anxiety*** (Heinrichs et al., 2001). Another study tested the protective effects of touch and social support in women who either received verbal social support or a standardized neck and shoulder massage, before they were confronted with public speech and mental arithmetic stress. A third group came alone to the experiment. When receiving massage before the stress, women showed reduced HPA activity as well as lower heart rate during stress. The authors assume central effects of OXT to be responsible (Ditzen et al., 2007).

Since endogenous stimulation of OXT is always associated with a variety of other biological mechanisms (e. g. endorphins, opiates, serotonin) (Ditzen et al., 2007; Dunbar, in press; Field et al., 2000), more causal manipulation was required. Intranasal application of peptides was found to reach the brain (Born et al., 2002) and provided a possibility to study behavioral effects of oxytocin and vasopressin in humans without exerting negative peripheral side effects.

Intranasal application of 24 I.U. of OXT was found to interact with social support and ***reduced the cortisol reaction to stress as well as anxiety*** in healthy men (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). Anxiety-related effects for OXT were also proven in imaging studies where the peptide was capable of ***decreasing amygdala activation*** to a variety of stimuli (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Domes et al., 2007; Kirsch et al., 2005; Petrovic, Kalisch, Singer, & Dolan, 2008). Petrovic and colleagues (2008) found in addition that oxytocin was not only able to reduce amygdala activity, but also

reduced affective ratings towards aversively conditioned faces. These findings indicate a predominant role for OXT in the down-regulation of psychobiologically relevant fear and anxiety circuits in humans, actions important for overcoming avoidance and initiating social approach behavior.

Animal research has addressed the effects of OXT and its ***developmental consequences***. A study that investigated intranasal effects of OXT also addressed this question in humans. Men with early parental separation showed a lower decrease in cortisol after intranasal OXT application (Meinlschmidt & Heim, 2007), indicating effects of early aversive life events on OXT sensitivity.

Moreover, OXT seems to affect ***social memory*** in humans. Single intranasal administration of oxytocin showed short-term effects of OXT in impairing explicit memory irrespective of the content of the words, whereas the neuropeptide selectively impaired semantic association for words with reproduction-related meaning (Heinrichs, Meinlschmidt, Wippich, Ehlert, & Hellhammer, 2004). Another study investigated long-term effects of single intranasal administration of OXT and found better retrieval of happy faces one day after acquisition (Guastella, Mitchell, & Mathews, 2008). The results indicate that availability of OXT during social interactions prompts a positive bias in memory and thus increases the feasibility of further engaging in social contact.

At the same time, higher levels of OXT in the brain shift the ***gaze*** from less relevant regions to the eyes of one's counterpart (Guastella, Mitchell, & Dadds, 2008) and, moreover, ***improve the ability to infer the mental states*** from the eye-region of the other person. This skill is important for appropriate social interaction and is e. g. impaired in patients suffering from Asperger syndrome (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). In schizophrenic patients, plasma OXT levels were correlated with the ***ability to correctly identify facial emotions*** (Goldman, Marlow-O'Connor, Torres, & Carter, 2008).

Social encounter always assumes that people will bear social risks. One always faces potential threats when trusting another person. But taking this social risk is indispensable for human life. OXT was found to ***increase trust*** in humans, elevating

the willingness to transfer one's own money to another unknown person. All interactions were anonymous and there was no chance of punishing betrayal later on. If participants had more OXT available in the brain, they trusted more strongly (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Another study showed elevation in plasma OXT after trust-related interpersonal interactions. In schizophrenic patients, this elevation was absent. Moreover, this lack of OXT increase was correlated with negative symptoms (social withdrawal, isolation, and flattened affect) in schizophrenic patients (Keri, Kiss, & Kelemen, 2008). Decreased OXT plasma levels have already previously been reported in schizophrenic patients (Goldman, Marlow-O'Connor, Torres, & Carter, 2008).

In summary, OXT in humans was found to decrease stress and anxiety on the psychological and physiological level, to enhance memory of positive social cues, to increase the gaze to the eye region and to improve "mind-reading". Most notably, it increases trust in humans.

2.2 Vasopressin and behavior

AVP is structurally strongly related to OXT and it is suggested that they arose from an ancestral gene-by-gene duplication (Bielsky & Young, 2004). Nevertheless, their behavioral effects differ drastically. As in OXT research, the effects of AVP have been tested using a broad variety of behavioral, pharmacologic and molecular techniques.

2.2.1 Vasopressin and behavior in animals

In the male prairie vole, it is AVP that tightens the bond to the female partner, and again, reward-related brain circuits are of importance (Insel, Winslow, Wang, Young, & Hulihan, 1995; Young, Lim, Gingrich, & Insel, 2001). In social recognition, learning and memory AVP was considered as an improving agent from the very beginning of research in this area. The Brattleboro rat, a laboratory rat species that lacks vasopressin due to a naturally occurring genetic mutation, shows memory and learning deficits (Bohus & de Wied, 1998; de Wied & van Ree, 1982; van Wimersma Greidanus, 1982). Early studies by David de Wied and his group emphasized the ***facilitation of avoidance learning and memory*** (de Wied, 1970; de Wied & van Ree, 1982). Since the 1980s, the experimental evidence has been growing strongly and the data clearly indicate the improvement of social memory and recognition by

AVP (for review, see Bielsky & Young, 2004; Young, 2002). A comparable body of evidence shows ***anxiogenic effects*** of AVP (Frank & Landgraf, 2008; Ring, 2005). Rats bred for high anxiety show an overexpression and release of vasopressin compared to rats bred for low anxiety trait (Landgraf & Wigger, 2003). If mice do not express the V_{1A} receptor for AVP, the animals spend more time in the center of an open field, in the light box or in the open arm of the elevated plus maze. Usually, mice avoid these areas since they resemble endangerment for them in nature. If AVP cannot exert its action via the V_{1A} receptor, the animals show considerably less anxiety. The same animals showed worse performance in social recognition, which was interpreted as an animal variant of autistic-like behavior indicating the V_{1A} receptor function as a prerequisite for adequate social behavior (Bielsky, Hu, Szegda, Westphal, & Young, 2004). Variation in the V_{1A} receptor gene further strengthens the role of AVP in regulating anxiety and anxiety-related behaviors (Hammock, Lim, Nair, & Young, 2005).

AVP also ***increases aggression*** in animals (for a review, see Caldwell, Lee, Macbeth, & Young, 2008; Ferris, 2005). Rodents attack intruders faster and stronger if they have more AVP available in their brains. When the V_{1B} receptors were blocked in hamsters, there was a reduced duration of offensive sideways and chase behaviors of the resident animal towards the intruder (Blanchard et al., 2005). Another overt aggressive behavior in hamsters is flank marking, which determines dominant vs. subordinate relationships in these rodents. Flank marking is enhanced by AVP and can virtually be ‘switched on and off’ by AVP (Ferris & Delville, 1994). It is important to note that testosterone modulates AVP receptor sensitivity and that they both interact in enforcing aggression in rodents. Serotonin plays also a critical role in this interaction (Delville, Mansour, & Ferris, 1996; Young, Wang, Cooper, & Albers, 2000).

As with OXT, AVP is suggested to be important in early development of social behavior. Due to its importance in stress (see chapter 3.2), AVP is discussed as a mediator in early life stress and consequently triggered psychopathologies (depression, anxiety and many others) (Charmandari, Kino, Souvatzoglou, & Chrousos, 2003). In rats, early life stress (separation from the mother) was shown to increase not only depression-like behavior: When these animals grew up, they

showed more aggression and increased AVP as well as reduced serotonin excretion in adulthood (Veenema, Reber, Selch, Obermeier, & Neumann, 2008). These results underline the connection from AVP to aggression and the behavioral relevance of early development.

In sum, there is broad evidence from animal data that AVP facilitates avoidance learning, improves social memory, raises anxiety and increases aggression.

2.2.2 Vasopressin and behavior in humans

In humans, quite similar results have been found to the findings from animal research, although the research approaches need to be very different (see chapter 2.3). Some studies revealed memory-enhancing effects for an AVP analogue as well as AVP (Beckwith, Petros, Bergloff, & Staebler, 1987; Beckwith, Till, Reno, & Poland, 1990; Beckwith, Till, & Schneider, 1984; Pietrowsky, Fehm-Wolfsdorf, Born, & Fehm, 1988; Till & Beckwith, 1985). Researchers suspected that AVP more directly ***improves attention and enhances arousal***, which might then lead to its learning and memory effects. Indeed, there is evidence for a change of event-related potentials (ERP) associated with stimulus processing and attention (for a review, see Born, Pietrowsky, & Fehm, 1998; Dodt et al., 1994; Pietrowsky, Struben, Molle, Fehm, & Born, 1996). These results further strengthen the 'nose-to-brain pathway' and document the central nervous system effects of nasal peptide application.

Besides these cognitive effects, AVP was repeatedly shown to be involved in the hormonal response to ***stress*** (see chapter 3.2) and has now been under scrutiny for over a decade for its relevance in several ***stress-related disorders*** (see chapter 5). In humans, like in animal research, it was shown that AVP is related to ***anxiety***. In healthy subjects, intranasal application of AVP ***elevated skin conductance and heart rate*** towards angry faces and increased state anxiety (Thompson, George, Walton, Orr, & Benson, 2006). Pharmacological AVP stimulation (pentagastrin) increases panic symptoms and anxious distress in healthy adults (Abelson, Le Melledo, & Bichet, 2001). In clinical studies, AVP was found to be related to post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) (elevated CSF AVP levels in OCD; Altemus et al., 1992; elevated plasma AVP in veterans with PTSD; de Kloet, Vermetten, Geuze, Wiegant, & Westenberg, 2008).

Moreover, many researchers discuss a role for AVP in ***autistic spectrum disorder***, known for its impairment in social interaction and social communication as well as restricted and repetitive behavioral patterns. Genetic approaches found relationships between genetic variants of AVP receptor (V_{1A}) and autism. Two polymorphic microsatellite repeats (RS1 with 9 different alleles & RS3 with 16 different alleles in the population – each allele consisting of different numbers of base pairs (bp)) showed a significant transmission disequilibrium in autism. Studies found overtransmission for the 334bp and 340bp alleles of the RS3 and undertransmission of the 312bp allele of the RS1 in autism. In addition, there was upregulation of the 320bp of the RS1 in autistic patients who were still skilled in language (for review, see Israel et al., 2008). Using an imaging genetics approach, Meyer-Lindenberg and colleagues (2008) recently revealed a relationship between these different microsatellites of the $AVPR_{1A}$ gene and their different alleles to ***amygdala activation***. Taken together, these findings ascribe importance to AVP in the regulation of social behaviors that occur in specific psychopathologies and highlight the role of the amygdala in social interaction (see 2.3). They further point to the genetic diversity in AVP-related genetic background, which may account for a proportion of inter-individual differences in behavior and psychopathological predisposition.

AVP in humans is not only related to restricted social skills as they occur in autism; it has also been shown to be related to ***aggression***. The intranasal application of AVP in humans increased adverse motor response patterns towards neutral faces. The authors interpreted this finding as a shift towards a negativity bias in the perception of neutral ambiguous cues that results in aggressive mimic expression and signaling (Thompson, Gupta, Miller, Mills, & Orr, 2004). In another study, they were able to replicate this finding and found that male participants with AVP perceived happy faces as less friendly and approachable compared to placebo (Thompson, George, Walton, Orr, & Benson, 2006).

Aggression and ***reduced prosocial behavior*** in human psychopathology has also been shown to be related to AVP. A subcategory of depression with above-normal levels of AVP showed lower cooperativeness and reward-dependency in a questionnaire compared to normal controls and depressed subjects with below-

normal AVP (Goekoop et al., 2008). Measured in CSF, AVP was positively associated with lifetime history of ***aggression in personality-disordered subjects***. Aggressive subjects showed higher CSF AVP than non-aggressive subjects. These results were controlled for serotonin function and appeared stronger in male patients, pointing to the role of testosterone in AVP function in aggression, as it has been previously reported in animals (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998) (see chapter 2.2.1).

Taken together, in humans one can ascribe effects of AVP on social memory and learning, stress, anxiety, impaired social functioning, and finally aggression.

To contrast the two neuropeptides once again, '[o]*xytocin is {…] considered the calming mothering and relationship peptide, whereas vasopressin promotes aggression and responses to stress' (Pittman & Spencer, 2005).* Do OXT and AVP interact in the brain to exert their opposing effects on social behavior, and if so, how?

2.3 The 'ying and yang': Interactions of oxytocin and vasopressin

The behavioral effects of OXT and AVP discussed above are results of actions in the central nervous system. Although peripheral levels (measured in the blood or in urine) of the peptide have been shown to be related to several behavioral aspects, they are only a proxy for the centrally available amount of the peptides (Landgraf & Neumann, 2004). Human research does not have as many different methodological approaches available as animal research, making assessment and manipulation of central nervous system aspects more complicated. Lumbar puncture is a more straightforward approach to measure levels of the peptides (Born et al., 2002) compared to plasma measurement, but even that method is accompanied by a level of invasiveness that is not justified in every investigation. Causal investigation by application of the peptides represents an obvious approach. Again, the impermeability of the blood-brain barrier hinders peripheral administration and requires large amounts of peptides that in reverse bear the risk of side effects (e. g. cardiovascular effects). A remedy to this problem was found thanks to intranasal application, which allows elevation of peptide levels in the brain with low increase in peripheral levels and hence low peripheral side effects (Born et al., 2002; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Heinrichs & Domes, 2008)

The close relatedness and the described behavioral results from animal and human research lead to the assumption that the OXT and AVP systems are tightly interwoven, and this is in fact what was found in animal and recently also in human research. Actions of both peptides seem to antagonize each other in behaviorally important brain circuits (via gabaergic modulation or reciprocal regulation, autoregulation or priming effects; see chapter 2 & Figure 2-5). They show crosstalk at their receptors, but the existence of a third receptor system has even been hypothesized that recognizes both peptides (Carter, 1998). Taken together, this explains why the two peptides show opposing effects (prosocial for OXT and aggression for AVP) but also share actions on affiliative behaviors.

OXT and AVP have been referred to as 'ying yang' hormones at the level of the HPA axis, where OXT acts as buffer peptide and AVP kicks off the system by triggering ACTH release synergistically with CRH (for review, see Legros, 2001). This shifts the attention towards the states of ergotropy and trophotropy. Activation of the HPA axis and sympathetic adrenal medullary (SAM) system (AVP dominance) follows threat and is associated with ergotropy, mobilization of energy for 'fight or flight' and through this cuts resources for social interaction that one might ascribe to trophotropy under safety conditions and resting hypothalamus pituitary axis (HPA) and SAM system (OXT dominance). Dominance of the OXT in turn extenuates AVP action, and here 'the wheel has come full circle'.

Important for the detection of threat and thereby activation of the HPA axis, the SAM system and for the modulation of behavior is the limbic system. One crucial structure of this system is the amygdala. Animal research was able to reveal OXT and AVP actions on the amygdala and detected separate areas of receptor density for both peptides in the central nucleus of the amygdala as well as contrary actions. The amygdala consists of functionally distinct nuclei. The lateral and basolateral parts of the amygdala are important for fear-learning, building up associations between fearful and neutral stimuli and project to the central amygdala. The central amygdala then signals to the brainstem and hypothalamus, triggering autonomic and endocrine stress and fear responses. Modulation of the central amygdala signal can therefore increase or dampen the fear or stress response. In the central amygdala, the lateral and capsuled parts receive inputs from cortical and subcortical regions and project to

the medial part of the central amygdala. This lateral/capsuled part was found to be dense in OXT receptors. Conversely, AVP receptor density is high in the medial part of the central amygdala and activation was found to increase signal to the brain stem and heighten fear response. As part of an inhibitory network, excitation of OXT receptors reduces activity of AVP neurons and thereby the output to the brain stem via gabaergic fibers (for a review, see Debiec, 2005; Huber, Veinante, & Stoop, 2005) (Figure 2-5).

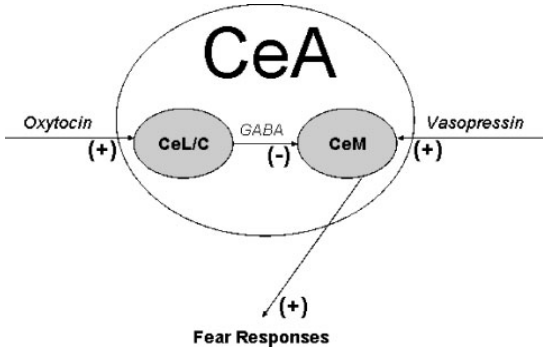

Figure 2-5: Oxytocin and vasopressin modulate activity of the central nucleus of the amygdala (CeA)

Oxytocin excites (+) neurons in the lateral and capsular division of the CeA (CeL/C). Vasopressin excites (+) neurons in the medial part of the CeA (CeM), which plausibly stimulates fear responses. Excitation of CeL/C neurons inhibits (-) CeM activation through GABA-ergic (GABA) projections (Debiec, 2005).

OXT in humans has now been repeatedly shown to reduce amygdala activation as well as a reduction of output from amygdala to brainstem (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Domes et al., 2007; Kirsch et al., 2005). For AVP, a genetic imaging study revealed differential modulation of amygdala activation by AVP receptor gene polymorphisms (Meyer-Lindenberg et al., 2008). In addition, both neuropeptides are assumed to be interrelated within the mesocorticolimbic pathway, important for reward-related behavior (Insel, 2003).

'*Disrupted inhibitory inputs from the medial prefrontal cortex could be compensated for by stimulation of the lateral/capsular central amygdala oxytocin receptors to ultimately inhibit central amygdala output and overly anxious behavioural responses'* (Pittman & Spencer, 2005).

Taken together, these mechanisms were the first to be detected and are very likely not the only pathways through which OXT and AVP modulate behavior and their reciprocal actions. Nevertheless, they provide important impulses and explanations for peptidergic mechanisms and their implication for psychopathology.

‘Stress begins in the brain and affects the brain, as well as the rest of the body’

(McEwen, 2008)

3 Stress

A review entitled stress as ‘*the modern day hidden epidemic*’ and reports that the World Health Organization (WHO) Global Burden of Disease Survey estimates that mental disease, including stress-related disorders, will be the second leading cause of disabilities by the year 2020 (Kalia, 2002). The first prominent contribution to the field of ‘stress research’ was made by Walter B. Cannon, who established the concept of ‘*fight or flight*’ response (Cannon, 1914), emphasizing the sympathetic regulation in response to stress. He was the first to ascribe importance to psychological aspects: emotions, such as anxiety, can serve as modulators of the stress response, explaining similar endocrine responses to different stressors. Moreover, Cannon was also the first to introduce the term ‘homeostasis’ to describe the ‘*coordinated physiological processes which maintain most of the steady states in the organism*’ (cited following Pacak & Palkovits, 2001, p. 503). Cannon pointed towards a specificity of the stress response, since a lack of oxygen requires completely different bodily responses to the exposure, for instance, to cold, but he actually never used the term ‘stress’ (Pacak & Palkovits, 2001).

Another prominent researcher in the field of stress was Selye, who described stress as ’*the nonspecific response of the body to any demand*’ (Selye, 1976). This includes physical stressors like illness, heat, cold, starvation etc. but also emotional threats. According to Selye, the stress response is unspecific, revealing the same reaction for any given stressor. He describes stressors as agents that activate stress, and finally introduces the general adaptation syndrome that represents response to prolonged stressors in a three-stage model:

1) Following the alarm stage,
2) The stage of resistance emerges,
3) Finally ending in the stage of exhaustion.

In his work, the HPA axis and cortisol were already accentuated and linked to stress. Although the unspecificity of the stress response has recently been partly contradicted (Mason, 1971; Sapolsky, Romero, & Munck, 2000), Selye`s suggestion of a multiphasic bodily reaction as well as the role of the HPA axis as a crucial stress axis is still state of the art.

The different regulatory actions of bodily systems towards changing demands was then combined in McEwen's concept of '***allostasis***' (process of maintaing stability or homeostasis), which refers to the mechanism of keeping the body alive and functioning. Allostasis is meant as a network of flexible reactions providing '*stability through change*' (McEwen, 2000). The '***allostatic load***' (the wearing of the body and brain caused by allostasis) (McEwen, 2007) shifts the attention towards health risks of stress and reflects the chronic burden of stress:

'*The perception of stress is influenced by one's experiences, genetics, and behavior. When the brain perceives an experience as stressful, physiologic and behavioral responses are initiated, leading to allostasis and adaptation. Over time, allostatic load can accumulate, and the overexposure to mediators of neural, endocrine, and immune stress can have adverse effects on various organ systems, leading to disease*' (McEwen, 1998).

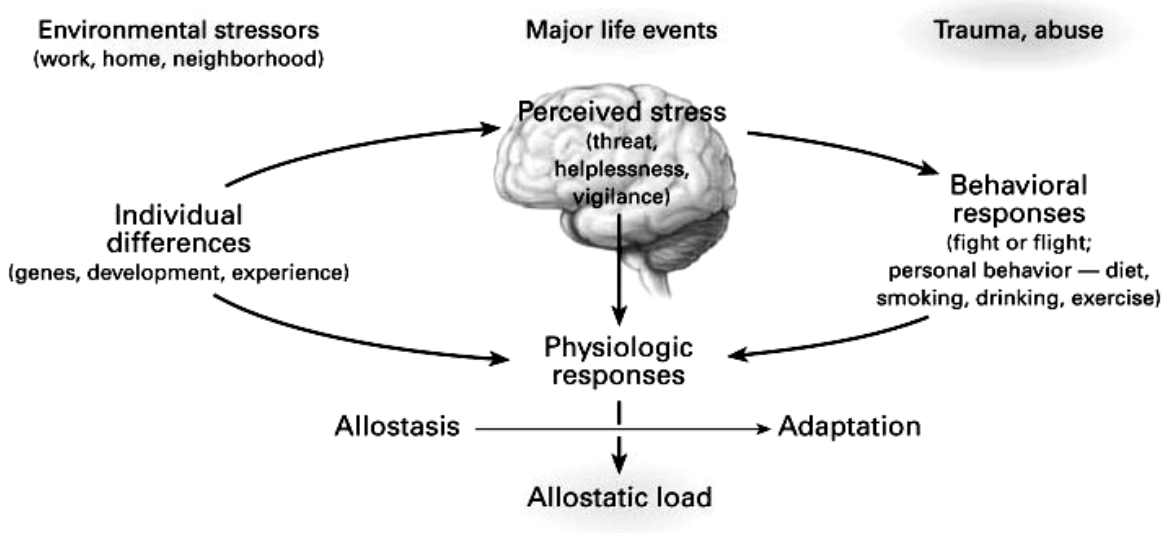

Figure 3-1: The Stress Response and Development of Allostatic Load (McEwen, 1998)

The biologically anchored concepts where complemented by psychological theories that underline the intra- and interinduvidual differences in stress experience where one stressor elicits different reactions among persons simultaneously and even gives rise to different reactions within one person at different time points (Folkman, 1997; Lazarus, 1984).

3.1 The psychological stress reaction

The term ‘stress’ refers both to the stimulus and to the (psychological and biological) reaction to the stimulus, which might cause some confusion. On the side of the stimulus, or the stressor, it is most notably not possible to quantify objective properties that account for initiation of stress in every situation and every person, but Dickerson and Kemeny (2004) reviewed the literature on the cortisol response to a variety of stressors and found earlier works stating that effective stressors need to be:

- Novel,
- Unpredictable,
- Uncontrollable, and
- Threatening with the potential for harm or loss.

After conducting a meta-analysis of stress research data, they came up with dimensions that serve overall as characteristics of truly effective stressors:

- Uncontrollability and
- Social evaluation

However, even these dimensions carry a great deal of individual variation, leading to the assumption that there must be a subjective psychological component to stress. The work of Lazarus finally shed some light on this aspect, introducing the concept of appraisal and states:

‘*Psychological stress is a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being*’ (Lazarus, 1984, p. 19).

Thus, Lazarus conceives of stress as a threat to one's own resources that triggers dysregulation, comprising both psychological and biological responses to stress. In his transactional stress model, he integrates cognitions that include ***primary and secondary appraisal*** as important evaluative functions in stress. In primary appraisal, a person asks 'What is this situation about and what can happen?' That implies an evaluation of the stressor itself and what the threatening outcome might be: 'Might I embarrass myself, loose my reputation or even my job position, will I gain something etc.?' The person will come to a conclusion and rate the situation as either irrelevant, positive or as a stressor that means potential harm, loss, threat or challenge. In secondary appraisal, the person's concern is 'What are my skills to cope with the situation? Do I have experience with such encounters? How will observers rate my actions?' The answers influence the kinds of coping strategies that will be used to manage the demands of the situation. The transaction of situation and the estimation of one`s own resources is never static. A transaction might influence later interpretations and the interpretation of a stressor can change over time.

But why are some people not stressed or even happy if the outcome of a situation is negative or at least not as they wanted it to be? Susan Folkman expanded on Lazarus' model and came up with positive psychological states like reappraisal (Folkman, 1997). In so doing, she introduced ***positive coping strategies*****,** which are important factors for stress-related disorders and for health.

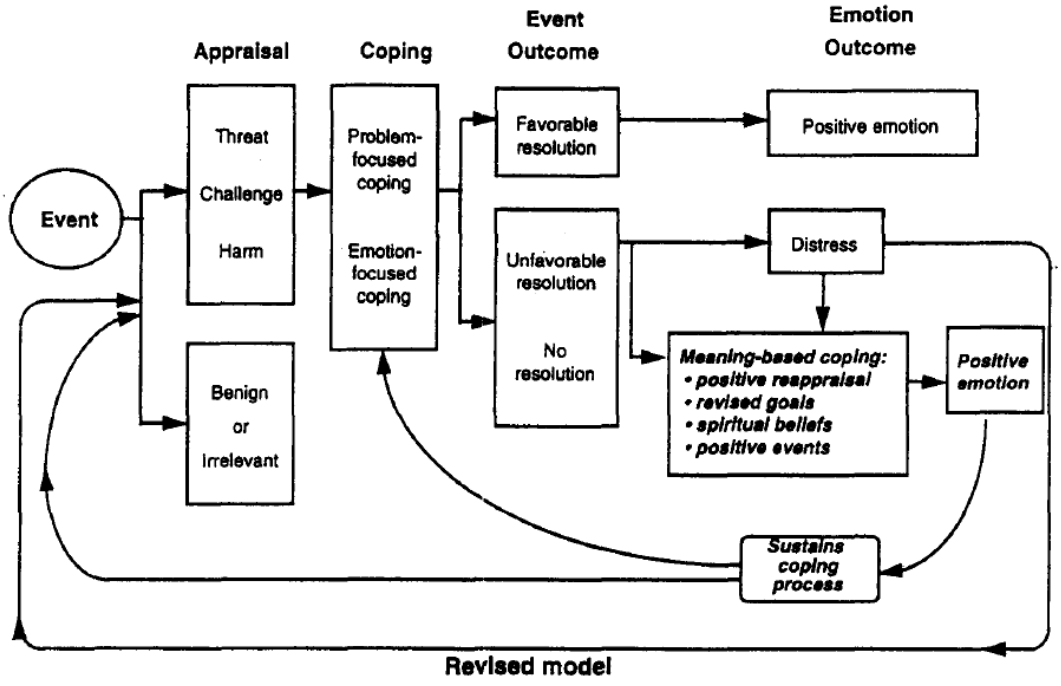

Figure 3-2: Modified theoretical model of the coping process (Folkman, 1997)

3.2 The biological stress reaction

Stress is a prominent example of mind-body interaction. The psychological processes described above are accompanied by distinct physiological phenomena that link stress to its tremendous effects on health. The underlying biological mechanisms form a clever and delicately balanced system that is very keen to maintain homeostasis in the body by adjusting its functions to the requirements of everyday life. This implies that actually, the reactions to stress are adaptive and nothing 'evil' per se. In general, the stress response is meant to be of short or limited duration. Only chronic overload or inappropriate reactions entail physical and mental health risks. The ***hypothalamus-pituitary-adrenal axis (HPA)*** and the autonomic nervous system, or particularly the ***sympathetic-adrenal-medullary system (SAM)***, are the prominent regulatory interfaces in the body that exert the stress response. Whereas the SAM is referred to as the fast axis in mobilizing energy immediately, the HPA acts in a slower and more prolonged manner. This is partly due to the different mechanisms (visceral vs. humoral). The central components of the stress system are the ***hypothalamus*** for the HPA axis and ***brainstem areas*** (locus coeruleus and noradrenergic cell groups in the medulla and pons) for the SAM system (Charmandari, Tsigos, & Chrousos, 2005).

3.2.1 The hypothalamic-pituitary-adrenal (HPA) axis

Corticotropin-releasing hormone (***CRH***) is the principal regulator of the HPA axis (it also acts on the SAM). It triggers the release of adrenocorticotropic hormone (***ACTH***) from the anterior pituitary, which is released into the blood stream. CRH action is assisted by ***AVP***. Under non-stressful conditions, both are released in a circadian, pulsatile and concurrent manner. AVP holds also a prime role in the central networks regulating the stress responses. It has itself the capability of triggering ACTH release, but under stress, the excretion of AVP and CRH from the PVN increase in amplitude and synchronization. AVP and CRH are released immediately after a stressor has occurred. AVP is thereby able to amplify the secretatory force of CRH on ACTH that is released approximately 5-10 seconds after the stressor. ACTH subsequently reaches the adrenal glands and initiates glucocorticoid (in humans: ***cortisol***) release from the adrenal cortex. The cortisol peak is observed between 20 to 60 min. after the stressor, which marks out the ***HPA as the 'slow' stress axis***. Cortisol acts in a catabolic, lipogenic, antireproductive, and immunosuppressive manner, and is

coupled with negative feedback mechanisms to inhibit further CRH and ACTH release, thereby limiting the exposure of the body to its own influence (Carrasco & Van de Kar, 2003; Charmandari, Tsigos, & Chrousos, 2005).

3.2.2 The sympathetic-adrenal-medullary (SAM) system

The ***autonomous nervous system*** consists of the ***sympathetic*** and the ***parasympathetic*** (***vagal***) part. Both regulate nearly every part of the body, including cardiovascular, respiratory, gastrointestinal, renal, endocrine and many other functions. Under resting conditions, both branches act in a ***functionally synergistic*** manner, meaning assistance or antagonization. The parasympathetic nervous system exerts an inhibitory regulating function in allostatic processes protecting the organism against the wear and tear of allostatic load (Thayer & Sternberg, 2006). Under stress, the influence of the parasympathetic nervous system is withdrawn towards a dominance of the sympathetic nervous system, which results in adaptive metabolism of the body (mobilization of energy, oxygen, etc.) and is subjectively experienced in sweating, tachycardia, breathlessness, cold hands and so forth.

The fast visceral activation of the sympathetic nervous system is triggered by inputs from the amygdala as well as CRH from the hypothalamus and norepinephrine (***NE***), resulting in direct action on several peripheral organs (e.g. the heart) and in the release of epinephrine and norepinephrine from the adrenal medulla into the blood, which in turn negatively feeds back to the brain (Carrasco & Van de Kar, 2003). Figure 3-3 gives a schematic overview of the HPA axis as well as the SAM system.

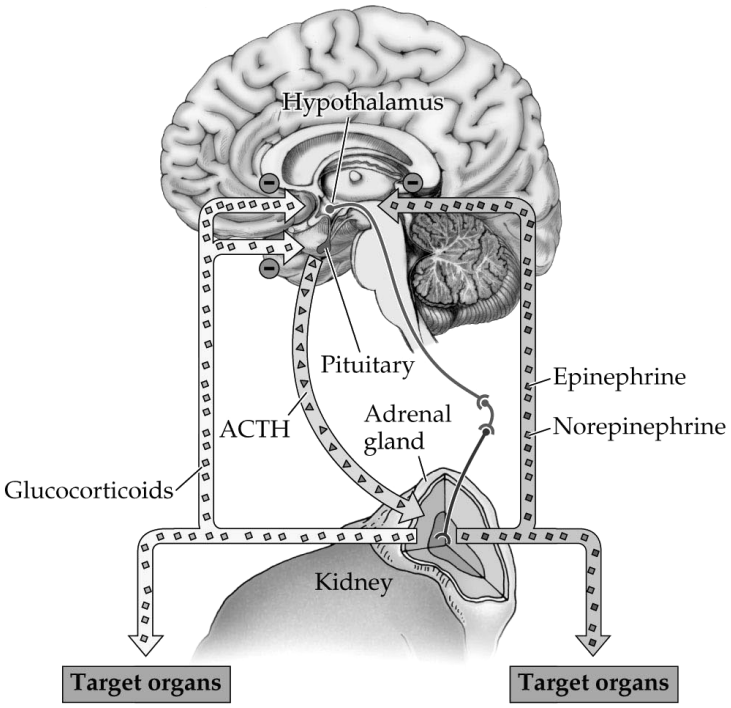

Figure 3-3: The hypothalamic-pituitary-system (HPA) (left) and the sympathetic andrenal medullary system (SAM) (right) (Rosenzweig, Breedlove, & Watson, 2007)

The psychobiological stress reaction influences, via the SAM and the HPA, many aspects of the human organism and delicately balances the needs in fast-changing demands. This implies central nervous system interactions of the stress system that include the POMC neuronal system (pro-opiomelanocortin: a precursor of ACTH, ß-endorphine, α-MSH neuronal system) that inhibits the central components of the stress response and suppresses pain sensation, hence inducing analgesia and modulating temperature and appetite under stress. Acute stressful situations are usually associated with the onset of anorexia and subsequent restriction of food consumption (via α-MSH release) (Richard, Lin, & Timofeeva, 2002).

More interesting to behavioral aspects, the ***amygdala-hippocampus complex*** and the ***mesocorticolimbic dopaminergic reward system*** are also involved in stress.
The mesocorticolimbic dopaminergic system is implicated in anticipatory phenomena and cognitive functions and is densely innervated by both PVN CRH neurons and the LC / NE sympathetic noradrenergic system. In a state of stress catecholamines, CRH and glucocorticoids strongly activate the reward system. From the mesocortical region, fibers project to the prefrontal cortex, where they suppress the activity of the stress system (Roth, Tam, Ida, Yang, & Deutch, 1988). In addition, the nucleus accumbens is stimulated by the dopaminergic neurons of the mesolimbic system.

This connection is assumed to be responsible for the motivational, reinforcement reward phenomena and in the formation of the central dopaminergic 'reward' system. It modulates euphoria and dysphoria and is the main target of several addictive substances, but most interestingly, it is assumed to mediate crucial sensitization processes associated with various stressors (Tsigos & Chrousos, 2002).

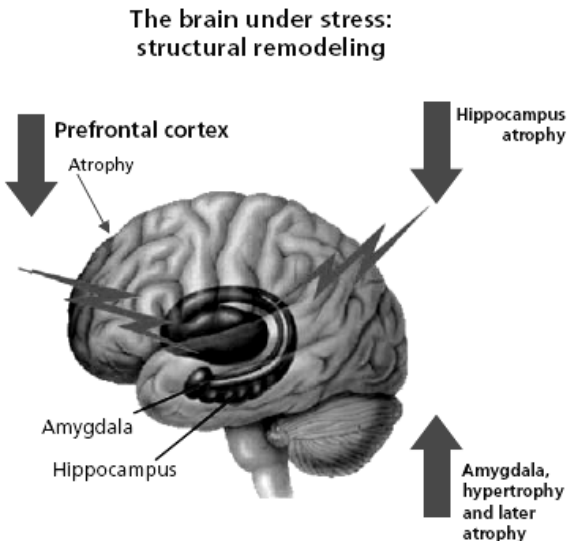

Figure 3-4: Brain regions that are involved in perception and response to stress, and which show structural remodeling as a result of stress (McEwen, 2006)

The amygdala-hippocampal complex is innervated by ascending catecholaminergic neurons from the brainstem, by glucocorticoids (from HPA axis) and finally by internal emotional states such as fear, which are generated in the amygdala. For retrieval, emotional analysis and weighting of any given stressor, activation of the amygdala is crucial. The ***amygdala*** for its part can innervate the central components of the stress system as well as the mesocorticolimbic dopaminergic system in response to emotional stressors. It informs a ***variety of integrative centers*** responsible for the somatic and visceral motor expression of emotion, and for modifying behavior relevant to seeking rewards and avoiding punishment. The hippocampus exerts tonic and stimulated inhibition on the activity of the amygdala and many other central stress network components (Charmandari, Tsigos, & Chrousos, 2005). Moreover, under conditions of stress, dendrites in the amygdala and orbitofrontal cortex grow, whereas dendritic loss has been found in the medial prefrontal cortex. Chronic stress also has a tremendous effect on the hippocampus (for review, see Fuchs, Flugge, & Czeh, 2006; McEwen, 2006). A schematic overview of structural changes under stress is depicted in Figure 3-4.

There is also evidence documenting not only ***structural*** but also ***functional alterations*** in these areas under acute and chronic stress in health (Kern et al., 2008) and psychopathology (Bremner, 2004; Drevets, 2003; Etkin & Wager, 2007).

Regarding the crucial role of the amygdala in stress response, it should be mentioned that this structure is decisive at all stages of ***fear conditioning*** and learning and thereby resembles a key structure in many psychiatric disorders, e.g. ***anxiety disorders*** (Delgado, Olsson, & Phelps, 2006). Recently, a neuroimaging study revealed that psychosocial resources moderate the brain stress response and cortisol secretion in a threat regulation task. Individuals with high resources (measured via questionnaire) showed stronger activation in right ventrolateral prefrontal areas and less activation in the amygdala, which was linked to lower cortisol excretion (Taylor et al., 2008).

Overall, the phenomenon of 'stress' includes both psychological and biological reactions and exerts important effects on the central nervous system. One key hormone is cortisol. If the impact of stress grows chronically, the wear and tear on the organism increases and the 'allostatic load' can lead to ***severe physical and mental illness*** (McEwen, 2008). Moreover, stress includes activation of distinct brain circuits that play a crucial role in mental disorders like anxiety disorders, and finally, psychosocial resources have even been shown to modulate the stress response on the brain level.

4 From health to mental illness: A continuum of social behavior

Severe or chronic illness often comprises the interpersonal domain and is a burden for social relationships. However, whereas stress exerts all of the negative effects on human life, it is the social domain, social contact and social interaction that represents a main opportunity and resource for well-being. There are many variations in social interaction, and impairment in social functioning is a key feature of nearly any mental illness. Indeed, there are even mental disorders in which the primary symptomatology is characterized by severe disturbances in social interaction. Patients with Williams syndrome (a heritable developmental disorder) show hypersociability, social phobia is characterized by deep fear of social encounters, whereas antisocial personality disorder comprises a neglect of social aspects. It is possible to assume a span of social behavior and arrange the different social phenomena on a social continuum. Health-beneficial social interactions form the center. Moving in the direction of positive sociability, one would cross high traits of empathy, compassion or social intuition and finish with disorders like the Williams syndrome. Following the axis into the negative social dimension, one would cross social phobia, then perhaps autism, and finally reach antisocial personality disorder and even psychopathy. This assumption of the course of social behavior is only a rough categorization, but it does enable a 'social focus' on human interaction and its importance in health and psychopathology.

4.1 Psychobiology of pro-social interaction and social support

It does not take a scientific study to point out that positive social interactions have beneficial effects for a person's well-being, but there is a huge body of evidence that indeed proves this. Today, there is no doubt that pro-social interaction and social support are ***important factors in human health*** that influence cardiovascular, neuroendocrine, and immune function as well as subjective well-being (Uchino, 2006). Social support can be regarded as a '[…] *social 'fund' from which people may draw when handling stressors*' (Thoits, 1995). But the concept of social support does not only have positive aspects in terms of '***salutogenesis***'. If the provided support does not fit to the needs of the recipient or if the providing person even lacks an overall positive intention, social support can become a social strain.

The research on social support began in the 1970s (Caplan, Cobb, & French, 1975; Cobb, 1976) and shows a tremendous diversity of research focuses and operationalizations of the construct. Social support can be conceptualized by:

1) ***Structural components***: social networks, social integration, network size and frequency
2) ***Functional components***:
    - Received support
    - Perceived support (received or available), or a
    - Discrepancy between perceived support and received support

Moreover, social support can be divided into different functional dimensions like ***instrumental support*** (practical help like lending money or helping with children) or ***emotional support*** (receiving love and empathy). The characteristics of the relationship as well as the situation might demand different sorts of support (Reblin & Uchino, 2008).

Marriage or ***long-term romantic relationships*** provide a vast resource for long-lasting social support (Thoits, 1995). Social support in partnership differs from other social support in a variety of aspects: the support lasts longer, is more easily accessible, the spouse has a different standing compared to friends and therefore his or her support is more valuable, and, in addition, non-verbal support (physical contact, holding hands or embrace) is more common among partners than friends. This list of differences could, of course, go on and on.

Marital status was repeatedly found to be an important health-promoting aspect. Many studies found the quality and satisfaction with the marriage to be a moderating variable (Coyne et al., 2001) and repeated conflicts in unhappy relationships can serve as chronic stressors (Kiecolt-Glaser & Newton, 2001). On the other hand, however, a huge body of evidence indicates that married persons are better off than single or widowed persons, regardless of the quality of their relationship. Patients with cancer, for example, were found to live longer if they were married (Goodwin, Hunt, Key, & Samet, 1987). The connections between marital satisfaction, marital status, social support and health are, of course, very complex and cannot be

resolved and characterized sufficiently here. Interestingly, one study found that marital support and its quality is of particular importance to persons who do not have best friends (Birditt & Antonucci, 2007). The relationship to one's spouse becomes essential if a person lacks other social networks and resources. This should already point in the direction of social phobia where a poor social network puts weight on the partner.

What are the biological mechanisms that mediate the health-promoting effects of social support? Social support might lead to healthy behavior or act directly on physical aspects on a general level or especially ***buffer the stress response*** (Cohen & Hoberman, 1983). Social support was repeatedly found to buffer stress. It reduced cortisol reactivity to stress in animals (for a review, see DeVries, Craft, Glasper, Neigh, & Alexander, 2007; DeVries, Glasper, & Detillion, 2003) and humans (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirschbaum, Klauer, Filipp, & Hellhammer, 1995). A metaanalysis of 22 studies with laboratory stressors found that social support was able to ***reduce the cardiovascular as well as cortisol response*** to stress (Thorsteinsson & James, 1999).

The above-discussed neuropeptide ***OXT*** is assumed to be involved in the biological health-promoting effects of social support (Heinrichs & Domes, 2008; Ozbay et al., 2007; Uvnäs-Moberg, 1998). As described earlier, ***OXT in combination with social support*** buffered the subjective and biological stress response in men (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003) and is ***associated with touch*** in humans and animals (Carter, 1998; Dunbar; Turner, Altemus, Enos, Cooper, & McGuinness, 1999). In this way, touch was able to reduce the cardiovascular and cortisol response to stress in women (Ditzen et al., 2007). One could assume that social support itself triggers OXT release and OXT release makes people seek and engage more in positive social contact and interaction.

The important health-promoting effects of social interaction underline the meaningfulness of the social domain in humans. As mentioned above, there are disorders that show severe impairment in precisely this domain. Tom Insel stated in his editorial to a special issue on social anxiety in *Biological Psychiatry*:

'*We are, by nature, a highly affiliative species craving social contact. When social experience becomes a source of anxiety rather than a source of comfort, we have lost something fundamental—whatever we call it*.' (Insel, 2002). Exactly this is what strikes patients with social phobia.

4.2 Psychobiology of social phobia

Patients with social phobia lose their ability to positively socially interact with others. If they do interact socially, it causes them tremendous stress, leading to more and more avoidance of such encounters. This, in turn, accentuates the effect that social phobia has on nearly all areas of everyday life, particularly social relationships, romantic relationships and also education and career (Wittchen, Fuetsch, Sonntag, Müller, & Liebowitz, 2000). The ***quality of life is tremendously impaired*** in social phobic patients (Eng, Coles, Heimberg, & Safren, 2005; Safren, Heimberg, Brown, & Holle, 1996; Thevos, Thomas, & Randall, 1999). Finding a spouse represents a great challenge, but then elevates quality of live and overall social functioning significantly (Safren, Heimberg, Brown, & Holle, 1996). Social phobic patients are more than simply shy.

4.2.1 Diagnostic criteria, comorbidity, etiology and epidemiology

Social phobia or social anxiety disorder is characterized by a ***marked and persistent fear of social situations*** in which there is a fear of embarrassing oneself under scrutiny by others. Sufferers not only fear social interaction but also performance situations. A list of such events would be endless, but includes (always in the presence of other people) eating, signing a paper or check, small talk at parties, public speaking or even walking or standing in a public place where one could be observed by others. Social phobics exhibit obvious ***physical symptoms*** (like sweating, trembling, blushing, tachycardia) and when confronted with a feared social situation, they react with immediate anxiety symptoms. They know that their fear is not appropriate, but the anxiety nevertheless leads to ***avoidance*** of social encounters and situations. The diagnosis of 'social phobia' requires, for persons

below 18 years, a duration of at least six months. The DSM IV, moreover, differentiates between ***generalized*** (the disorder comprises all social areas of life) and ***non-generalized*** social phobia (American Psychiatric Association, 1994). The complications include educational and occupational underachievement, isolation, substance abuse, depression, and an increased risk of suicide (Coupland, 2001)

In 1994, the most common disorder in the USA was found to be major depression, followed by alcohol dependence but then, ranking on third place, social phobia (Kessler et al., 1994) with 13.3 % lifetime prevalence. A review of the European studies on social phobia confirmed these results. Although early studies found very low estimates of prevalence, the later studies using revised diagnostic instruments ranged between 4.1 % (France) and 16 % (Switzerland-Basel). The authors underline that in Europe, the interest in and study of social phobia overall did not exist in every country (Wittchen & Fehm, 2003).

Social phobia is ***highly comorbid***. Lifetime comorbidity was found to be between 69 % and 92 %. The comorbidity strongly increases with the number of fears (62.9 % for 1-4 fears and 90.2 % for more than 11 fears) (Ruscio et al., 2008). Depression, other anxiety disorders, avoidant personality disorder as well as alcohol and substance abuse are the most common comorbid disorders. Alcohol and other substance abuse is highly prevalent in the attempt to reduce symptoms in social encounters and can develop into a full picture of pathological dependency (American Psychiatric Association, 1994; Wittchen & Fehm, 2003).

Patients with social phobia are strongly impaired. They show ***poor social support networks***, are less often married or in stable relationship and report a strong influence of their disorder on everyday life, including worklife and career (Kessler, Stang, Wittchen, Stein, & Walters, 1999; Ruscio et al., 2008; Safren, Heimberg, Brown, & Holle, 1996; Vriends et al., 2007; Wittchen, Fuetsch, Sonntag, Müller, & Liebowitz, 2000).

Moreover, regarded as a ***chronic condition,*** social phobia has a quite early onset in early adolescence between 12 and 16.6 years (Wittchen & Fehm, 2003). If loaded with a large number of social fears, the onset was found to be in early childhood and mid-adolescence. For a group with 1-4 fears, the onset was most pronounced in the mid-20s (Ruscio et al., 2008). ***Behavioral inhibition*** (BI) in early childhood was found to represent an early risk factor for the development of social phobia. Children who were regarded as BI before the age of three were followed to the age of 13. BI predicted adolescent social phobia in these children (Kagan & Snidman, 1999; Schwartz, Snidman, & Kagan, 1999).

Another risk factor for social phobia is ***early social trauma*****,** which every social phobic has usually exhibited at some time. Early traumatic life events were found to be more common in social phobic patients than in controls (12 % of the social phobics compared to 5.2 % of the healthy controls). Other studies reported events like separation from parents, parents` marital discord, sexual abuse, violence or childhood illness (Bandelow et al., 2004). Bandelow and colleagues report a series of studies in anxiety disorder that found similar results, but the results were mostly not reported for social phobia separately. Interestingly, it was hypothesized that social ***traumatic conditioning*** leads to the onset of social phobia, which would align the disorder with posttraumatic stress disorder. The patients mostly report one triggering (conditioning) event before the onset of their disorder (Stemberger, Turner, Beidel, & Calhoun, 1995). Nevertheless, this event does not always involve direct personal experience of actual or threatened death or serious injury or another threat to one's physical integrity, which clearly distinguishes the disorder from PTSD (criterion A for diagnosing PTSD, American Psychiatric Association, 1994). Another study investigated re-experiencing, avoidance, and hyperarousal symptoms (associated with PTSD) in social phobics. Although they did not meet criterion A, more than a third of the patients with social phobia met all other criteria for PTSD-like symptom patterns (Erwin, Heimberg, Marx, & Franklin, 2006).

Genetic studies revealed a ***heritable risk*** for social phobia and its underlying traits. First-degree relatives had 10-fold higher risk for development of social phobia (Stein et al., 1998). These results were confirmed by twin studies (Rose & Ditto, 1983; Stein, Jang, & Livesley, 2002). Heritability was also found for behavioral inhibition in

a longitudinal twin study (Robinson, Kagan, Reznick, & Corley, 1992) and for shyness (Daniels & Plomin, 1985). Shyness and low sociability of the biological mother was correlated with these traits in adopted infants. Moreover, social phobia and avoidant personality disorder were shown to have a common genetic vulnerability (Reichborn-Kjennerud et al., 2007). First-degree relatives of people suffering from ***autism*** and ***fragile X syndrome*** have also been shown to have a higher risk to establish social phobia. Men with fragile X syndrome showed marked social anxiety but are less socially impaired than autistic patients (Reiss & Freund, 1990; Smalley, McCracken, & Tanguay, 1995). Nevertheless, genetic factors account for only one third of the variance, while two thirds were attributed to environmental factors (Fyer, 1993).

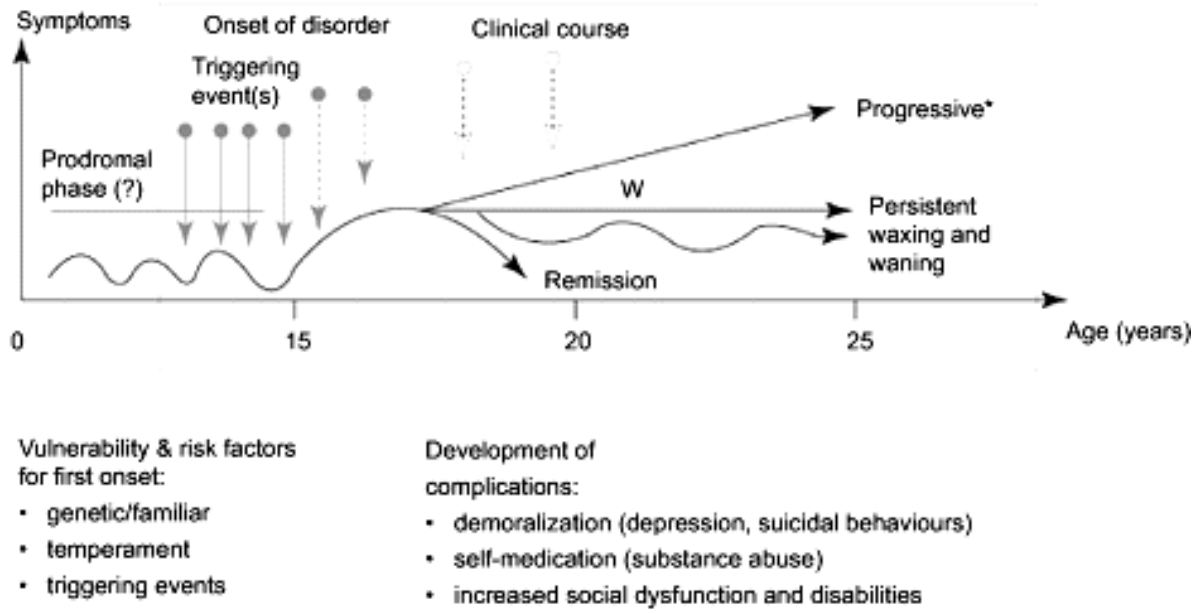

Figure 4-1: Developmental framework of onset and natural course of social phobia (SP)

SP emerges in the early teens and is followed by progressive worsening or a persistent course by the age of 19 years. A waxing and waning course characterizes the late adolescent age group. A persistent and stable course of SP occurs after the age of 24, with few patients experiencing stable and spontaneous remission (Wittchen & Fehm, 2003).

4.2.2 Neurobiology of social phobia

From the viewpoint of an integrated psycho-bio-social model of mental illness, the understanding of the neurobiological underpinnings of social phobia can help to improve the diagnostic process (depicting subtypes of social phobia based on

biological measures) as well as behavioral or pharmacological treatment of the disorder. Recent review articles have addressed this topic (Coupland, 2001; Marcin & Nemeroff, 2003) and discussed neurobiological differences in social phobia, but as Dewar and Stravinsky (2001) stated in their review, '*so far biological correlates of social phobia remain elusive*' and more research is called for in this area.

4.2.2.1 HPA axis and SAM system in social phobia

Stress has been shown to be reliably induced by psychosocial evaluative paradigms such as public speaking or mental arithmetic in front of evaluators (Dickerson & Kemeny, 2004). These paradigms have now come to resemble a social phobic stimulus to patients suffering from social phobia. A series of studies tried to depict the differences in stress response and the underlying biological systems in social phobia and its relevance for the pathophysiology and treatment of the disorder.

Experimental studies on HPA activity revealed both ***hyperactivity*** (Condren, O'Neill, Ryan, Barrett, & Thakore, 2002; Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001) and ***hypoactivity*** (Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001). Condren and colleagues compared healthy control subjects and social phobics on a mental stress paradigm (serial subtraction and digit span test). They repeatedly measured cortisol and ACTH from plasma and found higher delta max cortisol in social phobics (Condren, O'Neill, Ryan, Barrett, & Thakore, 2002). Another study compared acute psychological and physical stress and showed one group of patients responding very strongly to the psychological stressor (90% increase compared to 50 % increase in the control group), but on the other hand a second group of phobic patients did not respond to the psychological stress (32 % decrease compared to 17 % decrease for the controls). The response to the physical stress was comparable between social phobics and healthy controls (Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001).

The SAM system was shown to be more activated in social phobics when they were embarrassed. Accompanied by evaluators, they had to listen to their own singing voice and showed a higher heart rate during this confrontation (Gerlach, Wilhelm, & Roth, 2003). Moreover, phobic patients show a higher QT dispersion. QT dispersion represents a risk factor for sudden cardiac death and develops by ***increased sympathetic tone*** (and also decreased parasympathetic tone). The QT dispersion was highly correlated with social phobic symptoms (Nahshoni et al., 2004). When

confronted with events that they usually avoid, social phobics seem to respond with increased cardiac output. Wieser and colleagues screened 145 college students on social anxiety and included the lowest and highest 20 % as well as the 40-60 % group in their study, resulting in low, high and medium social anxiety groups. Participants had to watch clips of animated faces with either direct or averted gaze. The authors found ***pronounced cardiac acceleration*** in the high socially anxious group towards direct gaze (Wieser, Pauli, Alpers, & Mühlberger). When subjects scoring high on social phobia inventory were confronted with a happy or fearful masked stimulus (subliminal presentation), they showed a greater difference in ***skin conductance response*****,** resulting in a higher response to the fearful face (Tsunoda et al., 2008). One EEG and one PET study investigated the ***anticipatory reaction*** of the social phobic towards a threatening stressor and revealed higher heart rate during anticipation (Davidson, Marshall, Tomarken, & Henriques, 2000). Some researchers even propose endoscopic sympathetic blockade for patients with social phobia who are non-responders to the available psychotherapeutic and pharmacological treatments (Pohjavaara, Telaranta, & Vaisanen, 2001, 2003; Sciuchetti et al., 2006). Although this procedure is reversible and the authors propose it only for treatment-resistant social phobia, it is invasive and brushes aside the behavioral and psychobiological interplay in social phobia.

4.2.2.2 Relevant neurotransmitter systems

Besides cardiovascular and HPA axis alternations, several neurotransmitter systems are discussed to be involved in the pathophysiology of social phobia. Studies with pharmacological agents, imaging techniques and dopamine-deficient disorders found a share of ***dopamine, serotonin, norepinephrine and GABA***.

Social phobia was found to be very common among Parkinson's patients (Richard, 2005). Pharmacological agents for depression that affect the dopamine system (MAO inhibitors: they prevent dopamine from intraneural degradation) have been found to be more effective in social phobia than tricyclic antidepressants. The authors assume that ***social phobics lack the rewarding experience of the social encounter*** because of impairment in brain reward signaling (Liebowitz, Campeas, & Hollander, 1987). This hypothesis was confirmed by imaging studies that found ***lower D2 receptor binding in the striatum*** in social phobia (Schneier et al., 2000) and in OCD patients with comorbid social phobia (Schneier et al., 2008) as well as ***striatal***

dysfunctioning in fMRI data (Sareen et al., 2007). The efficacy of selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (NSRI) shows the involvement of both neurotransmitters in social phobia (Ipser, Kariuki, & Stein, 2008). Both neurotransmitters participate in the stress response and are thought to be crucial to the pathologies of this system in social phobia. While norepinephrine from the locus coeruleus activates the amygdala, the brain stem, triggers CRF release from the PVN and acts on the hippocampus, it is the ***serotonin system*** (raphe nuclei) that bridles these actions and prevents an overflow of the whole system (for a review, see Marcin & Nemeroff, 2003).

GABA is the most prominent inhibitory neurotransmitter in the brain. Agonists at specific GABA receptors ($GABA_A$) act in an anxiolytic or even sedative manner. The $GABA_A$ (subunits α & δ) receptor is the target of benzodiazepines such as diazepam and has been repeatedly been shown to reduce symptoms in social phobia and other anxiety disorders (Nardi & Perna, 2006).

4.2.2.3 Neural foundations of social phobia

PET, fMRI and EEG studies investigated the ***neural correlates of anticipatory anxiety*** in social phobic patients prior to performing a public speech task as well as the relevant networks while experiencing such events directly or viewing negative emotional faces.

Anticipatory social anxiety was related to increased cerebral blood flow in the right dorsolateral prefrontal cortex, left inferior temporal cortex, and the left amygdaloid-hippocampal region. The authors assume that the higher dorsolateral prefrontal activation indicates greater working memory through extensive worry (Tillfors, Furmark, Marteinsdottir, & Fredrikson, 2002). An EEG study was able to replicate the elevated right-sided activation in the anterior temporal and lateral prefrontal scalp regions (Davidson, Marshall, Tomarken, & Henriques, 2000). Whereas an fMRI study revealed lower prefrontal activation, they replicated findings on stronger activated subcortical regions including the amygdala (Lorberbaum et al., 2004). Taken together, the studies revealed ***increased activation of regions associated with emotion processing*** such as the amygdala, prefrontal cortex, and insula compared with control subjects. Indeed, higher amygdala and also insula activation was

repeatedly found with different imaging methods (Birbaumer et al., 1998; Phan et al., 2005; Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein, Simmons, Feinstein, & Paulus, 2007; Tillfors et al., 2001; Tillfors, Furmark, Marteinsdottir, & Fredrikson, 2002) but for prefrontal regions, hypo- as well as hyperactivation was found. In a recent meta-analysis on functional imaging data of PTSD, social phobia and specific phobia, Etkin and Wagner (2007) reported ***higher activity for amygdalae, para-hippocampal gyrus, fusiform gyrus, globus pallidus, insula, inferior frontal gyrus, and superior temporal gyrus***. They did not report any hypoactivation for social phobia in comparison to healthy controls.

Regarding the above-mentioned dopaminergic deficits, functional imaging studies looked more closely at the functioning of reward-related areas. Social phobics and healthy controls had to perform an implicit learning task (the serial reaction time task), which has been shown to reliably activate striatal regions (putamen and caudate), and no behavioral differences were found, but an impairment in striatal functioning was detected. The investigators hypothesize in the discussion '[…] *that abnormal left caudate function may contribute to the information biases observed in GSP [generalized social phobia], wherein GSP subjects are unable to maintain the information of behaviors that led to socially rewarding outcomes or the recollection of these outcomes*.' (Sareen et al., 2007).

Social phobic patients show exactly the opposite: they are ***biased towards negative interpretation of social events***, recognize almost only negative responses from other people and most ***strongly remember the negative aspects*** of an event (Clark & McManus, 2002). Taken to extremes, they appear as highly 'socially' pessimistic. Alterations in reward-related areas appear to be of relevance.

4.2.3 Cognitive theories and treatment of social phobia

The above-mentioned 'socially pessimistic negativity bias' of social phobic patients is crucial to cognitive and behavioral theories and treatment of the disorder.

4.2.3.1 Cognitive behavioral theories

As reported earlier, most social phobics remember clear-cut events that initiated their fear. To many, these events return to their mind over and over and bring about the same embarrassment, stress and fear that they might have exhibited earlier.

Previously summarized risk factors might lead to conditioning of social phobia. Cognitive models assume that self-consciousness, self-directed attention and negative interpretation biases are involved in social phobia. The cognitive models of Clark and Wells (1995) and Rapee and Heimberg (1997) share the assumption regarding ***dysfunctional beliefs*** about oneself and a ***negative bias*** of the interpretation of social events. Figure 4-2 gives an overview of Rapee and Heimberg`s model. First, it is important to note that social phobics assume that others are critical and that they will evaluate them negatively (as described above). When confronted with social encounters and perceiving an audience, dysfunctional mental representations about one's own person as seen by the audience are directly activated. Attentional capacity will be directed towards these distorted self-images and towards any external indicator of negative evaluation and both will become highly salient. In addition to monitoring one's mental representation about one's own appearance, the social phobic patient forms assumptions of what the audience expects from him. The greater the difference between what is expected and what the phobic ascribes towards himself, the higher the threat. Usually, social phobics assume high expectancies from the audience. Finally, the phobic estimates the probability of negative evaluation and negative consequences from the audience. Not surprisingly, social phobics have been shown to estimate this probability as fairly high. This will ultimately lead to anxiety, which is exhibited on a behavioral, cognitive and physical level. In turn, these internal cues again reinforce the negative mental representations and are perceived as internal indicators of negative evaluation from others. The reported negativity bias in perception leads to a masking of positive experience and an overvaluation of probable negative cues. After the social situation, social phobics strongly ruminate negatively about the past event (Dannahy & Stopa, 2007).

The cognitive models of social phobia reflect, once established, a vicious circle. In terms of the negative assumptions about oneself and the pessimistic negativity bias, social phobics do not exhibit positive corrections. On the contrary, they show high avoidance as a common dysfunctional coping mechanism leading to even higher perceived fear and lower possibility of positive encounters.

While some authors assume two cognitive biases (negative image of oneself and negative pessimistic interpretation of external social information) (Hirsch, Clark, & Mathews, 2006), others elaborate a comprehensive model of cognitive factors that are important in the cognitive models of social phobia (Hofmann, 2007):

- High perceived social standards
- Poorly defined social goals
- Heightened self-focused attention
- Negative self-perception
- High estimated social costs
- Low perceived emotional control
- Poor perceived social skills
- Avoidance and use of safety behaviors
- Post-event rumination

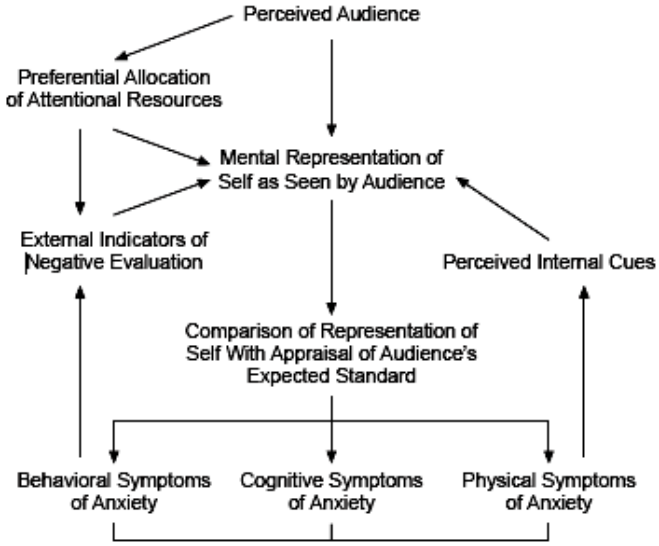

Figure 4-2: Cognitive model of social phobia following Rapee & Heimberg (1997) (reprinted from Coupland, 2001)

4.2.3.2 Therapy of social phobia

A combination of cognitive behavioral therapy (CBT) and pharmacotherapy is the common treatment for social phobia. CBT approaches have been proven to constitute an effective treatment for social phobia (Butler, Chapman, Forman, & Beck, 2006). Important interventions for social phobia comprise exposure, cognitive restructuring, relaxation training, social skills training and group setting (Deacon & Abramowitz, 2004; Heimberg, 2001; Ponniah & Hollon, 2008). Although mentalization-based stress reduction (MBSR) was found to be able to reduce symptoms in one study, the cognitive behavioral control group improved more strongly (Koszycki, Benger, Shlik, & Bradwejn, 2007).

Pharmacotherapeutic agents for social phobia include serotonin reuptake inhibitors (***SSRI and MAO-inhibitors***) as well as ***SNRI*** (serotonin-norepinephrine reuptake inhibitors), drugs that target the serotonin and norepinephrine system. If further treatment is needed, ***benzodiazepines*** come into play, although they have a high potential for addiction. Drugs such as buspirone, tricyclics and beta-blockers are of

limited use or even ineffective (Davidson, 2003, 2006; Liebowitz, Gelenberg, & Munjack, 2005). Recent studies suggest ***glucocorticoid application*** as promising in anxiety disorders including social phobia. It is hypothesized that retrieval of aversive memory is impaired by glucocorticoid application (de Quervain & Margraf, 2008) and it was able to reduce stress induction in social phobia and spider phobia (Soravia et al., 2006).

Although both psychological and pharmacological treatments are effective, they are far from satisfactory. In their recent review in *The Lancet*, Stein and Stein (2008) report 30-40 % non-responders. Other studies report between 35-60 % non-responders (Davidson, 2003), leaving a huge proportion of the patients with a chronic highly disabling mental illness. Effective treatment for social phobia needs to bring under control fear, avoidance and physiological symptoms, restore self-esteem and social functioning (improve quality of life) and treat the associated comorbidity.

5 Integration: Neuropeptidergic modulation on the continuum of social behavior

On a continuum of social interaction and social disorder, the neuropeptides OXT and AVP can both be attributed to several modulating aspects. Recent reviews provide insights into the modulatory effects of both neuropeptides on a range of mental disorders in the social domain (Bartz & Hollander, 2006b; Heinrichs & Domes, 2008).

On the hypersociability side, the Williams syndrome was mentioned above. This rare genetic disorder leads to unconditional trust in any person and spontaneous positive approach towards anybody. '*Might their high level of trust be due to excessive oxytocin release?*' speculated Antonio Damasio in Nature (Damasio, 2005) as he commented on the study by Kosfeld, Heinrichs and colleagues (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). The study found increased trust in humans after intranasal OXT application. In humans, increased ability to read the emotions from other people`s eyes is increased by OXT (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007) and healthy adults better remember the positive social encounters (Guastella, Mitchell, & Mathews, 2008). Humans even seem to 'forget' about negative events, continuing to trust even though they were previously betrayed (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008), and they show no negative affect towards faces that have been aversively conditioned earlier (Petrovic, Kalisch, Singer, & Dolan, 2008).

If we cross the normal healthy range of social behavior and move onto the less prosocial side, we come across anxiety or social anxiety, where patients show disabilities in the aforementioned social domains and have abnormal brain alterations that have been shown to be modulated by OXT and AVP (amygdala, reward circuits).

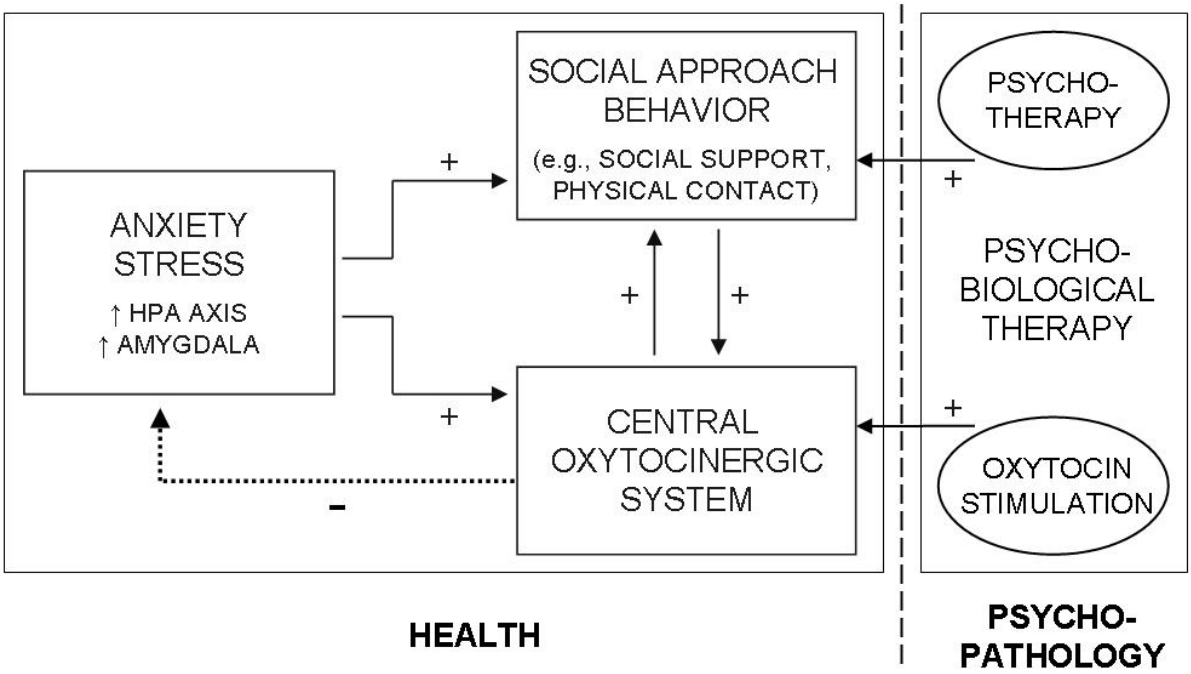

Figure 5-1: Interactions between anxiety and stress, social approach behavior, and the oxytocinergic system (Heinrichs & Domes, 2008)

In their model (Figure 2-3), Heinrichs and Domes propose that ***anxiety and stress encourage social approach behavior*** and ***stimulate oxytocin release*** in healthy individuals. Positive social encounters (e.g., physical contact) are associated with oxytocin release, and in turn, ***oxytocin promotes social approach behavior***. We have already discussed the reduction of HPA axis activity and the amygdala by OXT, which exerts the important stress and anxiety-reducing effects. For mental and developmental disorders that are associated with severe deficits in social interactions (e.g., autism, social phobia, borderline personality disorder), Heinrichs and Domes propose novel therapeutic approaches combining effective psychotherapy methods with oxytocin, which they call ***'psychobiological therapy'***.

Following the social continuum further, we come across autism, which has been repeatedly linked to OXT and AVP (Bartz & Hollander, 2006b; Carter, 2007; Heinrichs & Domes, 2008; Hollander et al., 2007; Meyer-Lindenberg et al., 2008), and finally end up at aggression. Aggressive behavior is to a certain extent part of everyday live in healthy humans. Healthy and pathological aggression has been related to AVP in humans (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998; Thompson, Gupta, Miller, Mills, & Orr, 2004; Thompson, George, Walton, Orr, & Benson, 2006) and animals.

Taken together, both neuropeptides have been shown to modulate a variety of social behaviors, including psychiatric disorders. However, the picture is far from complete. Several questions need to be answered to further understand the neuropeptidergic mechanisms and to clarify their ability to support psychotherapeutic treatments.

Anxiety disorders have been related to increased AVP release (especially as a key aspect of hyerreactivity of the HPA axis) (Holmes, Heilig, Rupniak, Steckler, & Griebel, 2003) and ***AVP antagonists*** are discussed as pharmacological treatments. But although peripheral AVP antagonists are available (Lemmens-Gruber & Kamyar, 2006), centrally targeting agents are still lacking. The two areas that are investigated in this thesis are:

Is prosocial aggressive behavior (altruistic punishment) in healthy humans increased by vasopressin and reduced by oxytocin?

Do oxytocin and social support reduce the psychosocial stress response in social phobia?

6 Empirical study I: Vasopressin enhances altruistic punishment in humans[1]

6.1 Introduction

Cooperation is indispensable in human societies. Even genetically unrelated human beings cooperate and are tempted to abide by this behavior. They care about social norms and sanction defectors even if sanctioning is costly for them and does not promise any material future gain. They punish unfair behavior altruistically (Fehr & Gachter, 2002). The 'Janus face' of altruistic punishment unifies a prosocial gift to the community and an aggressive component in the proximate behavior by the punisher. Altruistic punishment perpetuates cooperation from the collective`s point of view and on the individual`s level activates neural structures related to reward processing (de Quervain et al., 2004). The involved biological principles leading to altruistic punishment are not yet known. Here, we show how arginine vasopressin and oxytocin modulate altruistic punishment oppositionally. The two neuropeptides are structurally closely related and have been shown to modulate important social behaviors in animals and humans (Bartz & Hollander, 2006b; Bielsky, Hu, Szegda, Westphal, & Young, 2004; Carter, 1998; Carter, 2007; Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998; Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Ferris et al., 2006; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Arginine vasopressin enhances the readiness to punish unfair behavior. This effect holds true for social interactions and vanishes in unintentional random situations.

However, arginine vasopressin modulates prosocial aggressive behavior in humans only if untrustworthiness occurs deliberately by another human being. Our results are in line with animal and human studies and allocate a share of the responsibility for the modulation of basic social interaction to the two neuropeptides arginine vasopressin and oxytocin.

[1] von Dawans, B., Fischbacher, U., Fehr, E. & Heinrichs, M. (2008). Vasopressin but not oxytocin increases altruistic punishment in humans, *submitted.*

The physiological functions of the nonapeptides oxytocin and arginine vasopressin have long been known. Oxytocin plays an important role in lactation and labor, whereas arginine vasopressin is involved in fluid balance of the body. Underpinning the dampening effect of oxytocin on the HPA axis and consequently on the HPA-triggering effect of arginine vasopressin, the two of them are referred to as “ying yang hormones” in matters of stress response (Legros, 2001). Such antithetic consequences also occur regarding anxiety, where oxytocin reduces anxiety in humans (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003) and arginine vasopressin enhances anxiety in rodents (Bielsky, Hu, Szegda, Westphal, & Young, 2004; Keck, 2006; Landgraf, 2001; Murgatroyd et al., 2004; Ring, 2005) and humans (Abelson, Le Melledo, & Bichet, 2001). On a molecular level, Huber and colleagues (2005) were able to identify in vitro distinct populations of arginine vasopressin and oxytocin neurons in the amygdala proving gabaergic restraint of arginine vasopressin neurons by oxytocin. However, non-human and recently also human research suggests further important functions of oxytocin and arginine vasopressin on behavior. These two related hypophyseal hormones are involved in the modulation of many different social behaviors in non-human mammals and in humans, as their receptors are distributed in brain areas of behavioral relevance (Landgraf & Neumann, 2004). Both peptides are involved in the modulation of social behavior and its disorders (Heinrichs & Domes, 2008).

Oxytocin is associated with pair bonding, maternal care, the ability to engage in close social interaction (Carter, 1998), and reduces amygdala activation (Domes et al., 2007; Kirsch et al., 2005; Petrovic, Kalisch, Singer, & Dolan, 2008), increases gaze towards the eye region (Guastella, Mitchell, & Dadds, 2008) and improves the ability of ‘mind-reading’ (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). Moreover, OXT increases trust in humans (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) as well as the encoding of positive social memories (Guastella, Mitchell, & Mathews, 2008) and has been proposed as a crucial piece of the puzzle in the pathology of mental disorders of the social domain (e.g. autism) (Bartz & Hollander, 2006b; Carter, 2007; Heinrichs & Domes, 2008; Lim & Young, 2006).

Besides the effects on cognitive functions (Born, Pietrowsky, & Fehm, 1998; Pietrowsky, Struben, Molle, Fehm, & Born, 1996), arginine vasopressin - like oxytocin - modulates pair bonding in male monogamous animals (Nair & Young, 2006; Young, 2002). Moreover, it enhances aggressive and anxiety-like behavior in rodents (Ferris et al., 1996; Ferris et al., 2006; Gobrogge, Liu, Jia, & Wang, 2007; Veenema, Blume, Niederle, Buwalda, & Neumann, 2006; Young & Wang, 2004). Coherent with these findings, first studies in humans have already established a link between arginine vasopressin and aggression (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998; Thompson, Gupta, Miller, Mills, & Orr, 2004; Thompson, George, Walton, Orr, & Benson, 2006). The proximate effect of arginine vasopressin (in direct comparison to oxytocin) on human social behavior has not yet been documented in humans. Given their role in social approach and avoidance behavior and the effects on aggression, both neuropeptides should be involved in the modulation of prosocial aggression – such as the sanctioning of unfair behavior as it occurs in altruistic punishment.

We used a standardized trust game with an altruistic punishment condition with real monetary stakes to analyze the effects of arginine vasopressin and oxytocin on individuals` decision making. The subjects interacted anonymously and played either the role of an investor or a trustee. First, the investor decides either to trust the trustee by transferring his endowment or not. Via a transfer of his endowment, the total amount available for distribution between the two players increases, but initially, the trustee takes the whole asset. If a trustee is fair, he will repay half of the asset subsequently to a transfer and both players will end up with a higher and above all equal monetary payoff. On the other hand, a trustee has the option to keep all the monetary increase for himself, violating the investor`s trust and behaving unfairly, i.e. in an untrustworthy manner. Afterwards, the truster has the possibility to sanction unfair behavior by applying deduction points to the trustee. These deduction points are costly for the truster, and since the interactions are anonymous and one-shot, he has no future material advantage.

To disentangle the relevant social components of the neuropeptidergic mechanism in the game, in 6 out of the 12 interactions the decision on the back transfer is not made by the trustee intentionally. Instead, a die is thrown and dictates the decision (non-intentional).

Since cheating is economically favorable for the trustee, a certain amount of unfair behavior should be apparent by means of no back transfer in the intentional condition, enabling us to study the influences of oxytocin and arginine vasopressin on altruistic punishment behavior. From the empirical evidence, we derived the hypothesis that arginine vasopressin should increase the aggressive component of altruistic punishment in comparison to both placebo and oxytocin. The antipodal effects of arginine vasopressin and oxytocin should emerge in higher punishment for arginine vasopressin in comparison to oxytocin. Oxytocin should, in relation to placebo, reduce punishing behavior in terms of stress protection or reduction of anxiety (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003).

6.2 Methods

6.2.1 Participants

A total of 288 healthy male students (mean age +/- s.d., 22.5 +/- 2.5 yrs) from different universities in Zurich participated in the study. Exclusion criteria for participation were significant medical or psychiatric illness, medication, smoking more than 5 cigarettes per day, and drug or alcohol abuse. Subjects were instructed not to drink more than 2 liters before the experiment and to abstain from food 3 hours before the experiment as well as from alcohol or any other medication 24 hours before the experiment. During recruitment, participants were told that the experiment would evaluate the effects of two different hormones on social interaction and decision making. In total, 50 individuals out of the original sample of 288 were excluded because of incorrect substance administration (1 participant), insufficient knowledge of the German language (2 participants), high blood pressure and therefore no substance administration (1 participant), high psychological strain (1 participant) or stated disbelief that the opponent in the altruistic punishment game was actually a human being (45 participants, 19 Player A, 13 Player B intentional, 13 Player B non-intentional). Another 15 Player A subjects were not included in the calculation of punishment behavior because they either did not transfer their endowment (5 in the arginine vasopressin group, 3 in the placebo group and 2 in the oxytocin group) or were never betrayed throughout the experiment (1 in the arginine vasopressin group, 2 in the placebo group, 2 in the oxytocin group). From the analysis of cortisol and testosterone data, two subjects were excluded for each hormone because they showed baseline levels two standard deviations above the

mean. The study protocol was approved by the ethics committee of the University of Zurich. All subjects gave written, informed consent before participation.

6.2.2 Procedure

On the day of the study, all participants were asked to eat regular meals, refrain from nicotine and caffeine 2 hours before the experiment, and to desist from taking any medication, alcohol and physical exercise 24 hours prior to the session. The experiment took place between 4 p.m. and 6.30 p.m. in order to control for diurnal variation of saliva cortisol (Pruessner et al., 1997) and lasted approximately 2.5 hours. Groups of 20 or 24 participants were invited for one experimental run. All participants were randomly assigned to one of nine conditions [three treatment conditions (vasopressin, oxytocin or placebo) and three player conditions (player A, player B intentional and player B non-intentional)]. After arrival at the laboratory, the experimental procedure and the use of the salicaps for collection of the cortisol and testosterone samples as well as the nasal spray and the blood pressure device were explained. Throughout the experiment, there were four saliva samples and blood pressure and heart rate were measured three times. The experiment was built on five sequenced parts: The baseline period for introduction, assessing psychological and physiological measures (30 minutes), followed by a brief 'social priming' period (10 minutes) and a training period where participants received written instructions and had to fill out test questions to check for full comprehension (35 minutes). Following this, the actual social interaction took place (25 minutes) and the experiment was completed by a resting and debriefing period (30 minutes) (see Figure 6-1).

After participants were welcomed to the laboratory, they were informed about the whole procedure and completed baseline questionnaires on a computer to measure psychological characteristics as well as anxiety, anger and mood. Thereafter, the nasal spray was applied synchronously to the whole group, ensuring a standardized substance uptake in all participants. Application was closely supervised by trained experimenter personnel. Due to the crucial role of social environment in triggering behavioral effects of oxytocin and arginine vasopressin (as shown in animal research), subjects were afterwards asked to wait in the rest area while the next part of the experiment was prepared. During this 10-min waiting period, participants were seated at different tables.

Subjects at the same table could talk to each other, but in the experiment they would not be interacting with those who sat at their table. When subjects reentered the laboratory, they received written instructions (available from the authors on request) explaining the payoff structure of the experiment and the private payment procedure at the end of the experiment. Participants had to answer test questions to check whether they fully understood the paradigm. These questions were checked by the experimenters individually. At 45 minutes after spray application, the social interaction experiment started and was finished after 25 minutes. Again, questionnaires had to be answered and biological measures were obtained. Finally, the debriefing and payment took place individually.

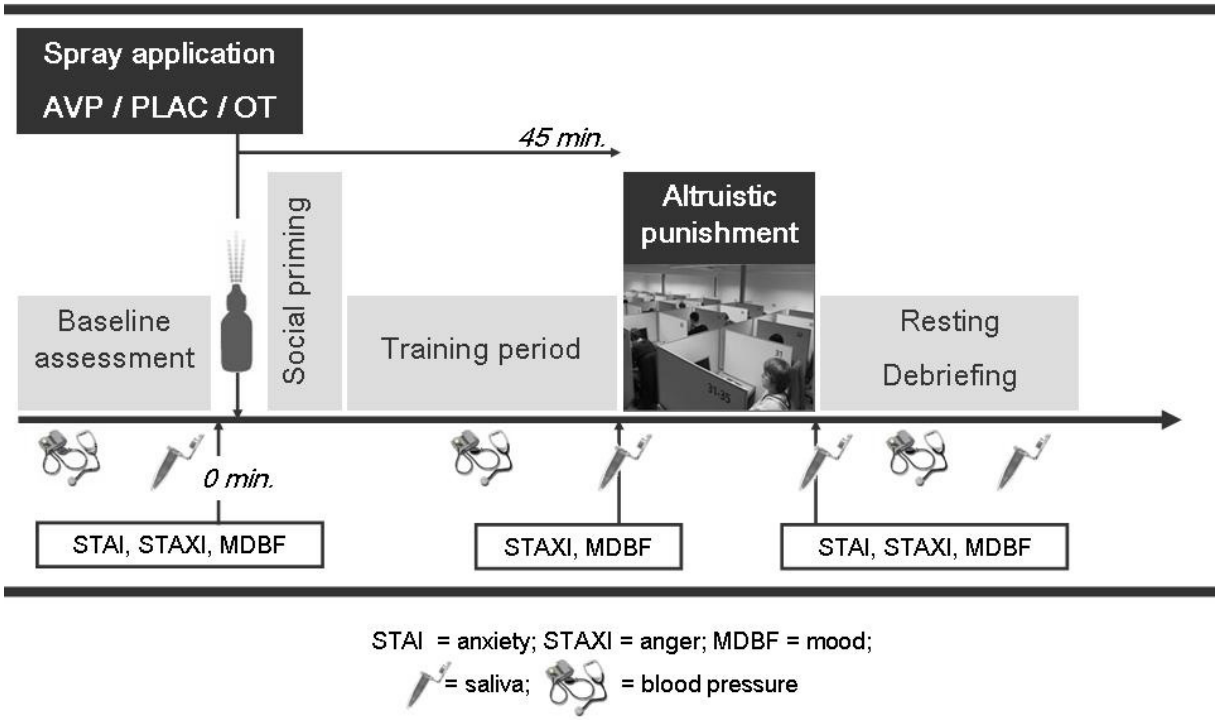

Figure 6-1: Study protocol: Vasopressin enhances altruistic punishment in humans

6.2.3 Social interaction: altruistic punishment

Subjects were randomly and anonymously assigned to the role of an investor, a trustee who could decide by himself (intentional) or a trustee whose decisions were assigned by a random algorithm by a die (non-intentional). Participants did not know the identity of the persons with whom they were matched. All subjects stayed in the same role for the whole experiment. After the subjects had read the instructions, we checked whether they understood the payoff structure by means of several

hypothetical examples. All subjects (with two exceptions) answered the control questions correctly. The two subjects who did not answer the questions correctly because of insufficient knowledge of the German language were excluded from the data set. In addition, subjects received an oral summary of the instructions.

Each investor decided once if he wanted to transfer his endowment to the second mover. This decision held for all 12 periods. In six of the periods, an investor was paired with six trustees, who could decide intentionally whether they wanted to give back half of their points to the investor or not (intentional). In the other six periods, the investor was paired with trustees who were not able to decide by themselves (non-intentional). Instead, a die was thrown and the decisions were therefore set by a probability of 50 %. Each subject stayed in the same condition for 3 periods in a counterbalanced design. After the back-transfer of the trustees, the investors had the possibility to apply deduction points (punishment) between 0 and 20 MU. One deduction point cost one point and reduced the payoff of the second mover by three MUs. All decisions in the experiment and the answers to the questionnaires were entered into a computer using z-Tree software (Fischbacher, 2007). Subjects received a flat fee of 70 Swiss francs for participation in the experiment; each MU earned in the altruistic punishment game was worth 0.06 Swiss francs.

6.2.4 Psychological measures

Before substance administration, participants completed standardized questionnaires on a computer to measure psychological characteristics (BSI; Brief Symptom Inventory) (Franke, 2000) as well as state anxiety (STAI; State-Trait-Anxiety Inventory) (Laux, Glanzmann, Schaffner, & Spielberger, 1981), anger (STAXI; State-Trait-Anger-Expression Inventory) (Schwenkmezger, Hodapp, & Spielberger, 1992) and mood (MDBF) (Steyer, Schwenkmezger, Notz, & Eid, 1997). Repeated measurements (anxiety: before substance administration, end of experiment; anger: before substance administration, before interaction, end of experiment; mood: before substance administration, before interaction, end of experiment). Trait anxiety and anger were assessed by the STAI (Laux, Glanzmann, Schaffner, & Spielberger, 1981) and STAXI (Schwenkmezger, Hodapp, & Spielberger, 1992) trait version at the end of the whole experiment.

6.2.5 Physiological measures and laboratory analysis

Salivary cortisol and testosterone were collected four times using Salicaps® (IBL, Hamburg, Germany). They were collected immediately before substance administration (minute -5), before the altruistic punishment interaction (minute 40), immediately after the interaction (minute 70) and the last sample was collected at minute 90. They were stored at -80° C until required for later analysis by chemiluminescence immunoassay (CLIA; IBL Hamburg, Germany; inter- and intraassay coefficients of variation < 10%) for cortisol and luminescence immunoassay (LIA, IBL Hamburg, Germany; inter- and intraassay coefficients of variation < 10%) for testosterone. Heart rate and blood pressure were assessed repeatedly (at the beginning of the experiment, after substance administration, and at the end of the experiment) using a fully automatic upper-arm blood pressure monitor (M7, Omron®, Mannheim, Germany).

6.2.6 Substance administration

Since neuropeptides cross the blood-brain barrier after intranasal application (Born et al., 2002; Pietrowsky, Struben, Molle, Fehm, & Born, 1996), the study of central nervous system effects of oxytocin and arginine vasopressin is possible, and diminishes risks for peripheral side effects to a minimum.

Participants received a single intranasal dose of 24 I.U. oxytocin (Syntocinon-Spray, Novartis; 3 puffs per nostril, each with 4 I.U. oxytocin), arginine vasopressin (Sigma-Aldrich; 3 puffs per nostril, each with 4 I.U. arginine-vasopressin) or placebo 45 minutes before the start of the altruistic punishment experiment. Subjects were randomly assigned to the oxytocin, arginine vasopressin or placebo group (double-blind, placebo-controlled study design). In order to avoid any subjective substance effects (for example, olfactory effects) other than those caused by oxytocin or arginine vasopressin, the arginine vasopressin and placebo sprays contained all of the inactive ingredients of the syntocinon® spray (except for the oxytocin).

6.2.7 Data analysis

To analyze punishment, only the A-players who transferred and were betrayed by a player B at least once were included. For these players, the average number of punishments was counted and then divided by the number of betrayals. This resulted in the punishment frequency index. An index of 1 (or 100 %) means that player A

punished every single betrayal. An index of 0 (or 0 %) indicates that player A never punished when he was betrayed. The mean of punishment points was also counted in the betrayal rounds and standardized by the number of betrayals. The same procedure was conducted for the maximum punishment.

To test for homogeneity of variance and normal distribution, the Levene test and the Kolmogorov-Smirnov test were computed for dependent variables. Since punishment was not normally distributed, non-parametric testing was obtained using Kruskal-Wallis test and Mann-Whitney U test. With questionnaire data and biological measures, analysis of variance (ANOVAs) were calculated, with substance (vasopressin, placebo, oxytocin) and repeated measure (time). Fisher`s LSD was computed for post-hoc comparisons. If the Mauchly test of sphericity indicated heterogeneity of covariance, repeated-measurement results were verified with Greenhouse–Geisser corrections. Since all hypotheses were unidirectional, statistical tests were one-tailed and conducted at the .05 level of significance.

6.3 Results

The arginine vasopressin group (n = 33) punished betrayal by the trustees more often. In the arginine-vasopressin group, investors punished on average in 71.21 % of betrayal cases, whereas in the placebo (n = 36) group, the investors punished only in 50.23 % of the betrayal cases. The frequency of punishment was 20.98 % higher in the arginine vasopressin group in comparison to the placebo group (Mann-Whitney U test; z = -1.884, p = 0.030).

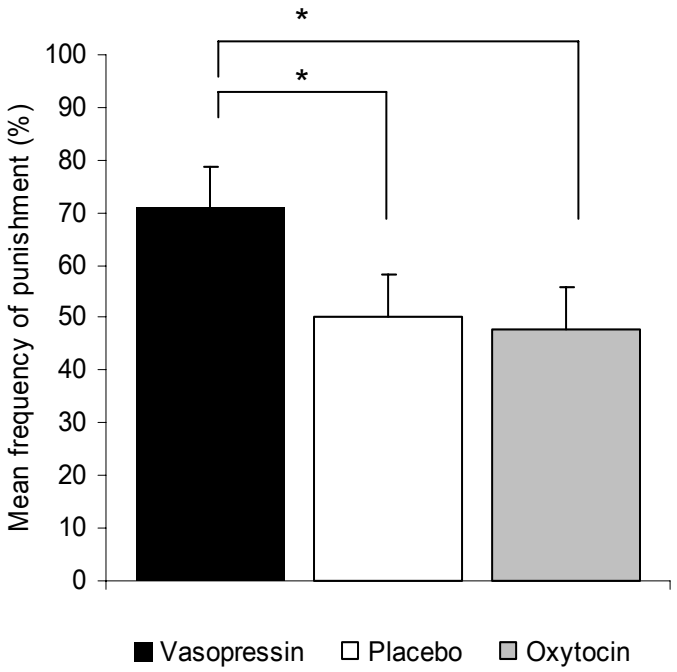

Figure 6-2: Mean (+SEM) frequency of punishment (intentional) (* = p<0.05)

The effect of arginine vasopressin was even more pronounced in comparison to the oxytocin group. Thus, the punishment frequency in the arginine vasopressin group was 23.29% higher than in the oxytocin (n = 36) group, in which the investors punished on average only 47.92% of the betrayal cases (Mann-Whitney U test; z = -2.175, p = 0.015). Although oxytocin slightly decreased the readiness to punish unfair behavior, the placebo and oxytocin group did not differ significantly (Mann-Whitney U test; z = -0.234, p = 0.406) (Figure 6-2).

Table 6-1: Mean and median average of punishment points in the intentional condition

	Vasopressin	Placebo	Oxytocin
Mean average punishment in points (SEM)	10.21 (1.46)	8.15 (1.44)	6.62 (1.26)
Median average punishment (points)	10	7	3
	n=33	n=36	n=36

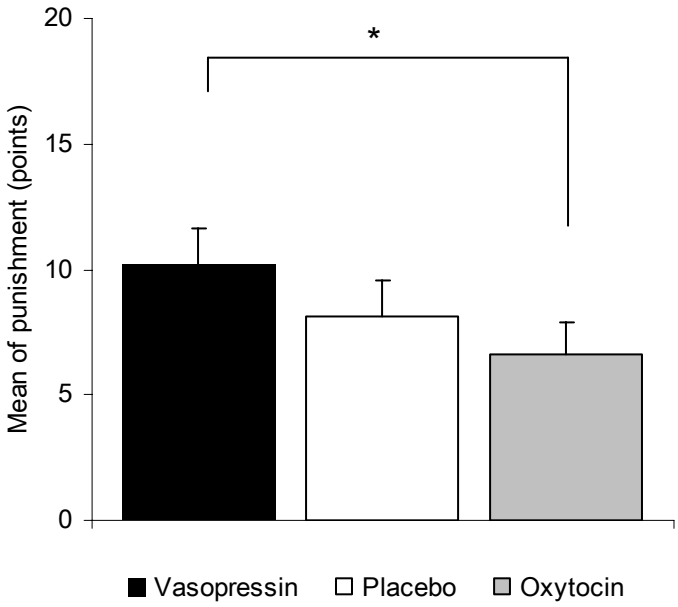

Figure 6-3: Mean (+SEM) of punishment points (intentional) (* = p<0.05)

The mean of punishment points was 10.21 (median = 10) in the arginine vasopressin group, 8.15 (median = 7) in the placebo group and 6.62 (median = 3) in the oxytocin group (Table 6-1). Interestingly, the arginine vasopressin and the oxytocin group differed not only in their readiness to punish betrayal but also in their strength of punishment (Mann-Whitney U test; z = -1.940, p = 0.026) (Figure 6-3).

Consequently, the frequency of maximum punishment (20 points) underpins the counterbalancing effects of the two neuropeptides. In the arginine vasopressin group, investors punished with maximum punishment in 36.4% of the betrayal cases, whereas in the oxytocin group the investors only punished with the maximum amount of 20 points in 17.6% of the cases (Mann-Whitney U test; z = -1.870, p = 0.030) (Figure 6-4).

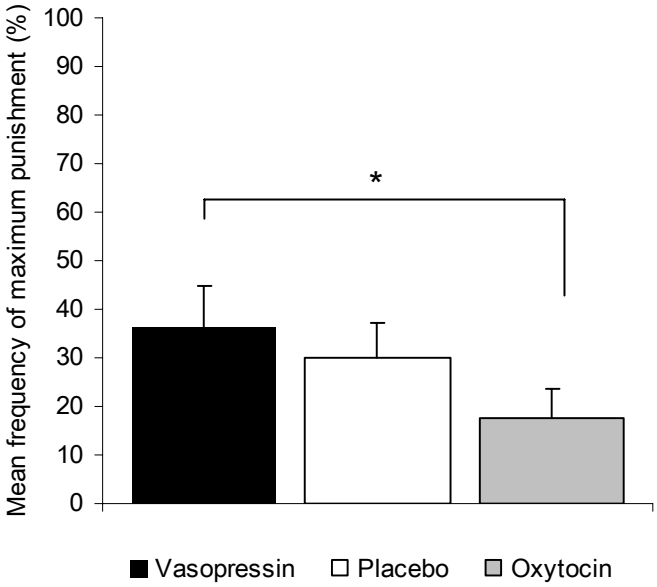

Figure 6-4: Mean (+SEM) frequency of maximum punishment (intentional) (* = p<0.05)

In addition, there was no neuropeptidergic effect in the non-intentional condition, proving the social context dependency of neuropeptidergic mechanisms (Kruskal-Wallis test; chi^2=0.823, df=2, p=0.663) (Figure 6-5). The mean transfer is 1.10 in the arginine vasopressin group, 1.21 in the placebo group and 1.25 in the oxytocin group, with an overall median of zero (Table 6-2).

Table 6-2: Mean and median average punishment in the non-intentional condition

	Vasopressin	Placebo	Oxytocin
Mean average punishment in points (SEM)	1.10 (.53)	1.21 (.60)	1.25 (.62)
Median average punishment in points	0	0	0
	n=34	n=38	n=38

The distribution of punishment points in the intentional condition is shown in Figure 6-6, and the distribution of the non-intentional condition is displayed in Figure 6-7.

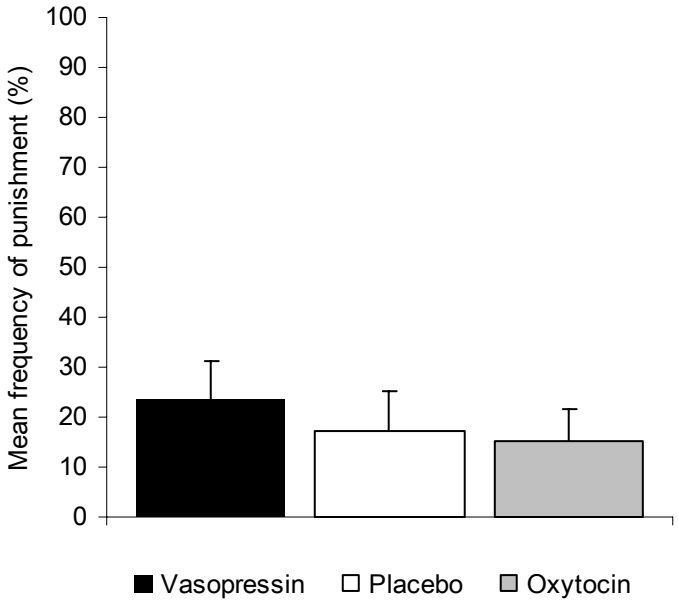

Figure 6-5: Mean (+SEM) frequency of punishment (non-intentional)

Two-way ANOVAs with repeated measurement revealed a significant time effect for cortisol (time: $F_{(1.281,\ 128.143)}$=174.273; p<.001; ε^2=.635) and testosterone (time: $F_{(2.326,\ 232.627.143)}$=17.477; p<.001; ε^2=.149). The ANOVAs and post-hoc comparisons

revealed no differences for cortisol and testosterone for oxytocin or vasopressin compared to placebo. Moreover, there was a significant increase in heart rate (time: $F_{(1.878, 191.574)}$=17.467; p<.001; ε^2=.146) and blood pressure (time: $F_{(1.991, 203.772)}$=8.739; p<.001; ε^2=.079) over the experiment.

Again, neither the ANOVAs nor post-hoc comparisons revealed any differences in heart rate or blood pressure for vasopressin and oxytocin. The endocrine and autonomic values at the beginning of the social interaction are presented in Table 6-3. Finally, there was no effect of vasopressin or oxytocin on untrustworthiness of the B players (Kruskal Wallis test; $chi^{2=}$1.045 df=2, p =0.593).

Table 6-3: Mean levels of endocrine and autonomic markers before the social interaction (45 minutes after substance administration)

	Vasopressin	Placebo	Oxytocin
Cortisol (nmol/l)	5.56 (.36)	5.16 (.48)	5.24 (.39)
Testosterone (pg/ml)	73.10 (4.30)	69.31 (3.95)	69.24 (4.43)
Blood pressure (systolic/diastolic)	121/75 (1.71/1.31)	119/71 (1.80/1.25)	121/71 (2.02/1.62)
Heart rate (beats per minute)	69.67 (1.87)	65.28 (1.82)	67.92 (1.66)

Data are expressed as mean (SEM).

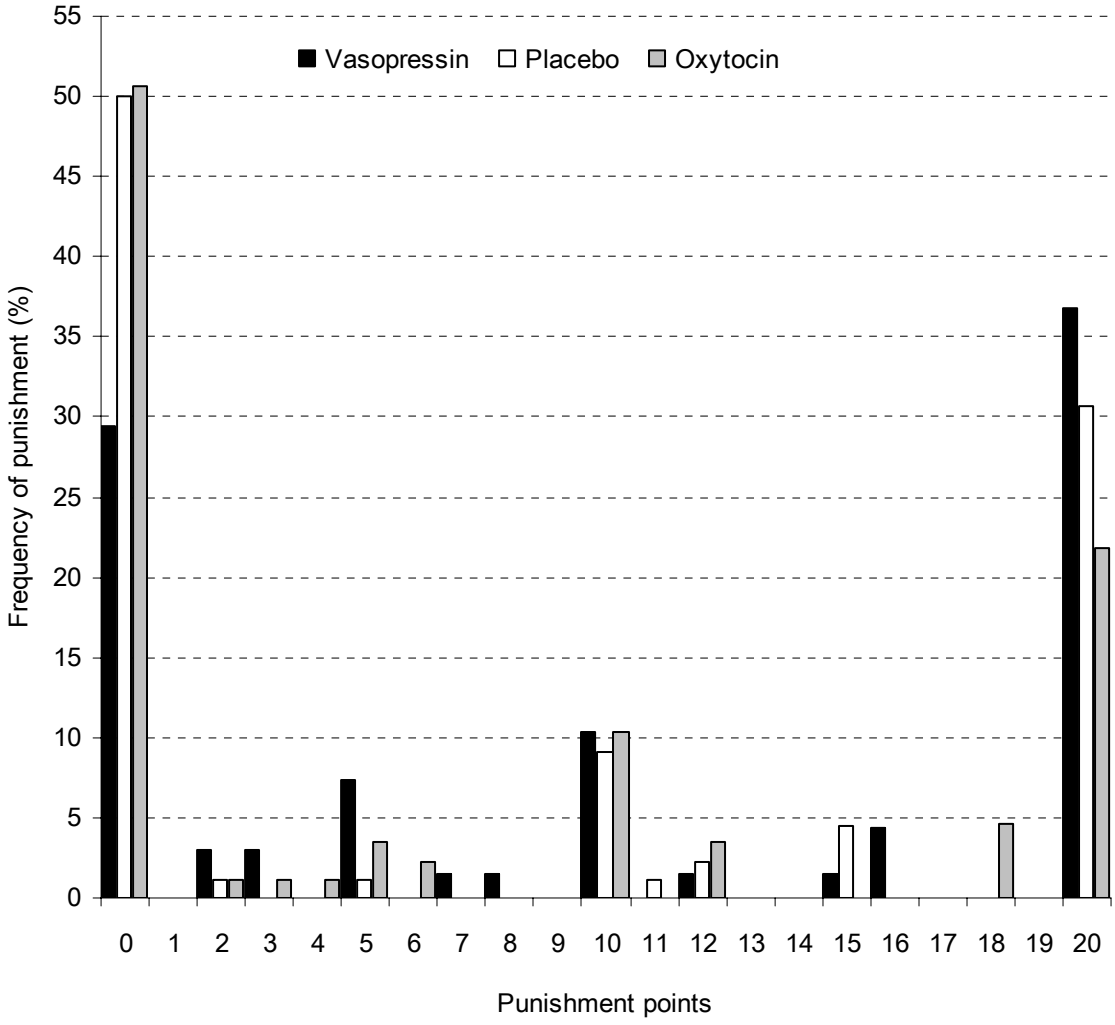

Figure 6-6: Distribution of punishment points after intentional betrayal by human (intentional)

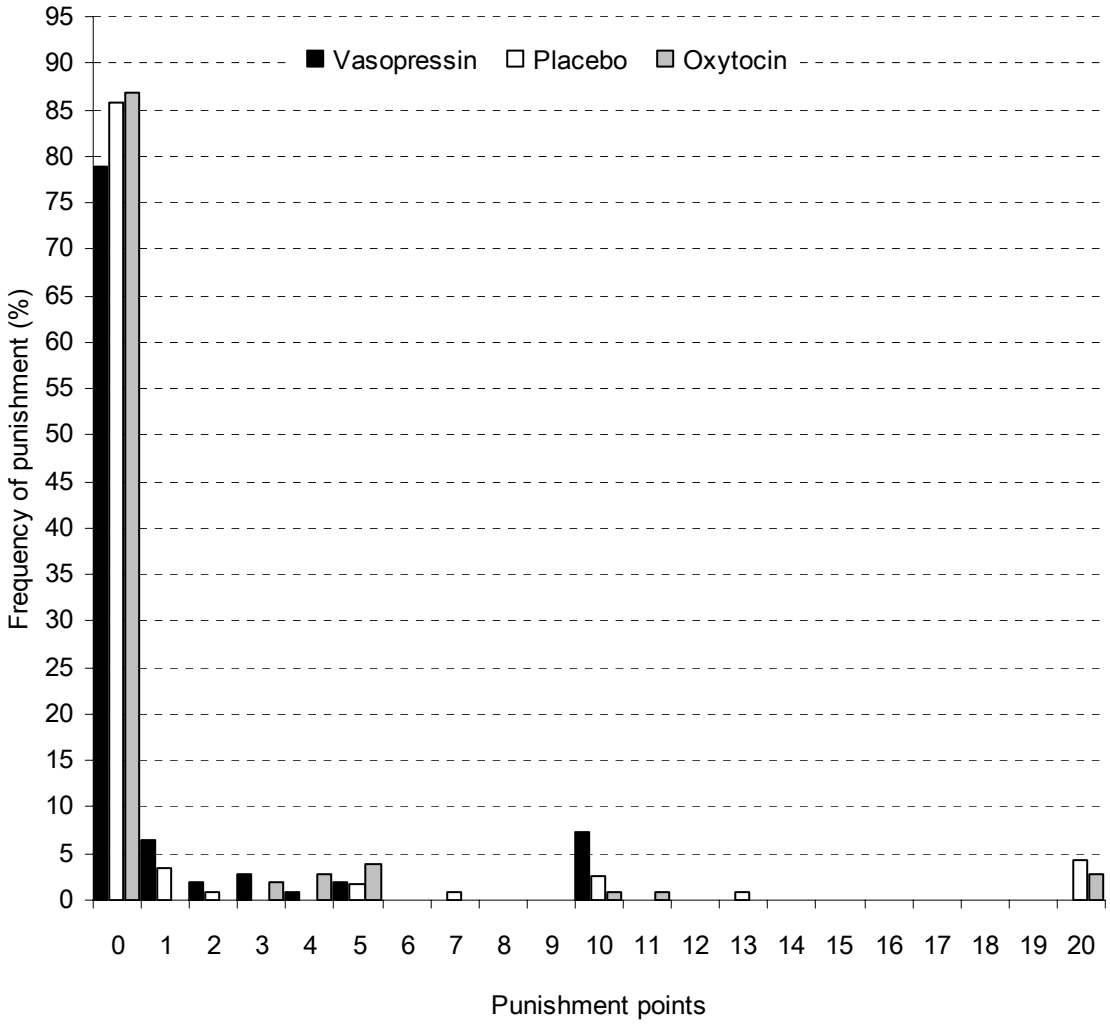

Figure 6-7: Distribution of punishment points when non-intentional betrayal was dictated by a die (non-intentional)

6.4 Discussion

To put our results in a nutshell: arginine vasopressin significantly enhances the readiness to punish unfair behavior compared to both placebo and oxytocin. Furthermore, arginine vasopressin is in significant contrast to the effect of oxytocin in terms of the readiness to punish, average punishment points and maximum punishment, pointing in the direction of higher social aggressive behavior for vasopressin compared to oxytocin. These effects occur only in a genuine prosocial interaction and do not emerge with regard to antisocial untrustworthiness. Furthermore, these behavioral changes are not driven by unspecific effects of the neuropeptides on mental state, physiological arousal or other hormonal influences.

The results are all in line with previous animal and human research and for the first time verify the causal impact of vasopressin on social aggression in humans.
Humans voluntarily punish violations of social norms even if it is costly and does not promise material future benefit. Previous findings (de Quervain et al., 2004) already provided evidence for the activation of reward-related brain circuits by altruistic punishment. However, so far there is no correlate that generates this behavior on a molecular level. Since arginine vasopressin receptors are located in reward-related areas (Insel, Winslow, Wang, & Young, 1998), one could hypothesize that the action of arginine vasopressin on behavior is partially mediated by reward-related mechanisms, although we cannot report subjective feelings of reward by vasopressin in our study.

The altruistic act of punishment incorporates prosocial as well as aggressive components and in our study is even strengthened by arginine vasopressin. Arginine vasopressin is responsible for pair bonding in male monogamous species (Young & Wang, 2004) and on the other hand enhances territorial aggression (Gobrogge, Liu, Jia, & Wang, 2007), such as biting attacks in resident intruder paradigms (Ferris et al., 2006) or flank marking behavior (Ferris et al., 1996). In humans, plasma levels of AVP were found to be correlated with trait measure of cooperation in depressed subjects (Goekoop et al., 2008). Most interestingly, a recent study showed that reduced serotonin levels lead to higher punishment of unfair behavior in the ultimatum game (Crockett, Clark, Tabibnia, Lieberman, & Robbins, 2008). Low serotonin is in turn associated with high AVP levels in animals (Ferris & Delville,

1994) and humans (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998). This might lead to the assumption that rejection in the ultimatum game was driven by AVP. Our results indicate involvement of arginine vasopressin in the facilitation of prosocially oriented aggression in humans as well.

A slight increase of centrally available arginine vasopressin elevates altruistic punishment. Studies in healthy males have already shown that arginine vasopressin shifts the perception of neutral faces towards threatening as it facilitates agonistic facial motor patterns for neutral cues (Thompson, Gupta, Miller, Mills, & Orr, 2004). Moreover, men with arginine vasopressin rate happy faces as less approachable than men with placebo (Thompson, George, Walton, Orr, & Benson, 2006). Taken together, this speaks in favor of the argument that arginine vasopressin amplifies negative social cues and alerts humans in social encounters.

This alertness could then lower the threshold for sanctioning unfair antisocial behavior of the trustees on a subconscious level. This negativity bias is indeed part of mental disorders that are linked to increased aggression, like borderline personality disorder (Domes et al., 2008). It was found that in personality disorder, the level of CSF AVP was positively correlated with lifetime history of aggression (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998). Our results on the causal manipulation of aggression by AVP in humans link these findings and strengthen the importance of this peptide in aggressive behavior in healthy humans and mental disorders. Pathologically heightened arginine vasopressin levels or hypersensitivity of arginine vasopressin receptors could even result in excessive sanctioning, impulsive aggression or, more generally, inappropriate social interaction. There is some evidence corroborating this link.

Early life stress (maternal separation), as a developmental factor, induced an increase in intermale aggression in rats (Veenema, Blume, Niederle, Buwalda, & Neumann, 2006) and human CSF levels of arginine vasopressin correlate with lifetime history of aggression in patients with personality disorders (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998). In conjunction with this, negative early childhood experiences heighten the risk for the development of, for example, personality disorders in humans (van der Kolk, 2003).

In addition, both vasopressin and oxytocin are pulled together with other pathologies of the social domain, namely autism, anxiety disorders or obsessive compulsive disorder (Bartz & Hollander, 2006a; Carter, 2007; Hollander et al., 2007). Taken together, the empirical evidence for the arginine vasopressin system suggests it to be a delicately balanced and fine-tuned distributing center that plays a key role in human social interaction and pathology in this domain.

The amygdala can be seen as a decisive relay in this system which is modulated by oxytocin and arginine vasopressin in an inverse manner (Huber, Veinante, & Stoop, 2005). Arginine-vasopressin switches the amygdala on, enhances anxiety and channels amygdala brainstem connectivity (Huber, Veinante, & Stoop, 2005), whereas oxytocin was found to reduce amygdala activity (Domes et al., 2007; Huber, Veinante, & Stoop, 2005; Kirsch et al., 2005). In humans, AVP receptor gene polymorphisms were able to either up-regulate or down-regulate the amygdala and were linked to autism (Meyer-Lindenberg et al., 2008). One could assume that direct actions of AVP might have increased amygdala activation and ultimately the readiness to punish unfair behavior. Aggression basically encompasses two important factors: hyper-responsivity of the amygdala and other limbic regions and at the same time reduced prefrontal inhibition or 'top-down' control (Siever, 2008). In other words, if an anger-provoking stimulus (like betrayal) is accompanied by a peptide that further activates the amygdala (AVP), a misbalance in this modulation might occur towards increased amygdala and decreased top-down control and aggression (punishment) increases. Our results show, however, effects of central arginine vasopressin that could of course be driven by the amygdala but neither result in subjective experience nor in physiological arousal. It is of vital importance that only slightly increased levels of the neuropeptides arginine vasopressin and oxytocin already foster social behavior in humans.

OXT differed clearly from AVP but did not influence altruistic punishment compared to placebo. OXT was found to improve positive social encounters like trust and decrease anxiety and stress. It could be that its actions cannot take hold of central modulation since our paradigm neither increased stress nor anxiety. On the first level of trust, we did not have enough observations to clearly test the effects (only one decision per investor, which held for 12 subsequent periods) but found the

distribution of highest trust in OXT and lowest trust in AVP. Moreover, one could hypothesize that the altruistic punishment paradigm simply does not represent an OXT-specific behavior. It might be the case that OXT rather modulates altruistic rewarding. This leads to a very interesting question that needs to be investigated further. The behavior of the B Player in the current study as well as in the study of Kosfeld et al. (2005) could not confirm this hypothesis.

Further studies should disentangle the neural correlates of the neuropeptidergic system in humans and, moreover, further elucidate the share of arginine vasopressin and oxytocin in the pathology of mental disorders in the social domain.

7 Empirical study II: Oxytocin and social support buffer the psychobiological stress response in social phobia[2]

7.1 Introduction

Social phobia ranks as the third most common mental health disorder. Besides marked and persistent fear of social interactions, patients report avoidance and various physical symptoms including sweating or tachycardia, which in turn reinforce phobic fear. Treatment of the disorder includes psychotherapeutic as well as pharmacological approaches but shows a high rate of non-responders. The disorder is highly comorbid and impacts strongly on quality of life. The patients are deeply impaired in social functioning, show weak social networks and struggle in finding a partner (Wittchen & Fehm, 2003).

Patients lack an important factor for health and well-being, namely social support. Ample evidence proves the effectiveness of social support in improving and maintaining quality of life and mental as well as physical health (chapter 4.1). Social support was found to reduce stress in humans (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirschbaum, Klauer, Filipp, & Hellhammer, 1995). Although the biological mechanisms of social support are still not fully evident, the neuropeptide OXT has been repeatedly discussed to be involved in the biological framework of social support (Ditzen et al., 2007; Heinrichs & Gaab, 2007; Uvnäs-Moberg, 1998). It has been previously reported to decrease stress and anxiety and encourage social encounter in animals and humans (see chapter 2.1). In healthy adults, OXT was shown to reduce amygdala activity (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Domes et al., 2007), subjective anxiety (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003) and to increase positive social behaviors like trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Moreover, the combination of OXT and social support revealed significantly lower cortisol response towards a psychosocial stressor.

[2] von Dawans, B., Soravia, L. M., Neumann, I. D., Carter, C. S., de Quervain, D., Ehlert, U. & Heinrichs, M. (2008). Oxytocin buffers the psychobiological stress response in social phobia, submitted in part.

Given the evidence, we hypothesized that social phobic patients would profit strongly from OXT and the combination of OXT and social support. The present study compared the effects of both treatments in social phobia and healthy controls.

7.2 Methods

7.2.1 Participants

Sixty-five male patients with social phobia and 79 healthy male control subjects where recruited via advertisement. Four out of the original 71 patients with social phobia were unable to comply with the study rules (they were asked to bring their spouse with them but were not able to) and two took cortisone medication, resulting in six excluded subjects in the patient group. Two out of the original 81 control subjects were excluded because of cortisone medication. After a telephone screening to determine suitability for the study, patients where diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994) using a computer-based structured clinical interview (DIA-X) (Wittchen & Pfister, 1997) administered by one clinical rater in order to guarantee a high rate of reliability. The healthy control subjects answered questionnaires on important psychometric variables. Exclusion criteria for all subjects were smoking more than five cigarettes per day, neurological or physical problems, pharmacological treatment and relationship duration less than 1 year. They were also excluded if they had already participated in a stress task. Healthy control subjects were required to not meet the criteria for any axis I or II disorder and have no liftetime history of psychiatric illness. Patients with social phobia were excluded if they showed axis I comorbidity or a personality disorder other than insecure, dependent or compulsive disorder, assessed via SCID II (Fydrich, Renneberg, Schmitz, & Wittchen, 1997) or if they had experience with cognitive-behavioral therapy. Since female subjects might have created additional gender effects due to estradiol influences on cortisol secretion, an all-male population was chosen (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). The study was approved by the Swiss Ethics Committee at the University of Zurich, Switzerland. After the study was explained to them in detail, all participants gave written informed consent and were informed of their right to discontinue their participation at any time. Patients where interviewed prior to their confirmation.

Eligible control subjects and patients were assigned to a double-blind placebo-controlled design. All participants received 150 Swiss francs and the patients could additionally participate in a subsequent cognitive-behavioral group therapy program if desired.

7.2.2 Procedure

On the day of the study, all participants were asked to eat regular meals, refrain from nicotine and caffeine 2 hours before the experiment, and to desist from taking any medication, alcohol and physical exercise 24 hours prior the session. The experiment took place between 2 p.m. and 6 p.m. in order to control for diurnal variation of saliva cortisol (Pruessner et al., 1997) and lasted approximately 3 hours. The basic design used was a two (social phobia or healthy control) by two (oxytocin or placebo) by two (social support or no social support) design. All phobic patients and healthy controls were randomly assigned to one of four treatment conditions at the beginning of the telephone screening. They were given either placebo or oxytocin after the baseline period and were asked to bring their spouse with them (social support) or come alone (no social support).

After arrival at the laboratory, the experimental procedure and use of the salivettes for collection of the cortisol samples was explained in detail and a venous catheter was inserted in the non-dominant arm by the study nurse. Throughout the experiment, there were six blood samples, six saliva samples (cortisol) and continuous recording of heart rate. The experiment was built on four sequenced parts: The baseline period for assessing psychological and physiological measures (30 minutes) was followed by an intervention (social support or no social support) and socio-evaluative stress (60 minutes), and the experiment ended with a resting recovery and debriefing period (90 minutes) (see Figure 7-1). The ‘Trier Social Stress Test’ (TSST) (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirschbaum, Pirke, & Hellhammer, 1993) was applied as a standardized socio-evaluative stressor. The test has repeatedly proven its ability to elicit the bio-psychological stress response (Dickerson & Kemeny, 2004) and consists of a five-minute mock job interview followed by an unprepared mental arithmetic task (subtraction of 17 from 2043) in front of an evaluating two-person audience and a video camera. Prior to the ten-minute stress task, the participants had a ten-minute preparation phase.

In the “social support condition” (SS), the subjects where supported by their spouse during these 10 minutes. The partner was told to help the participant to come up with arguments for the job application, i.e. by identifying positive characteristics that he could later tell to the committee. The partners were told that they would know best what to say to support the subjects’ individual coping preferences, as described elsewhere (Kirschbaum et al., 1995; Heinrichs et al., 2003). If participants were in the “no social support condition” (NoSS), they had to prepare alone for the test. After this preparation period, the spouse had to leave the laboratory and was not present when the participant left the TSST room. In the debriefing, the participants were finally informed extensively about the aims of the whole study as well as their own performance and were told that their individual performance was not important for the goal of the study.

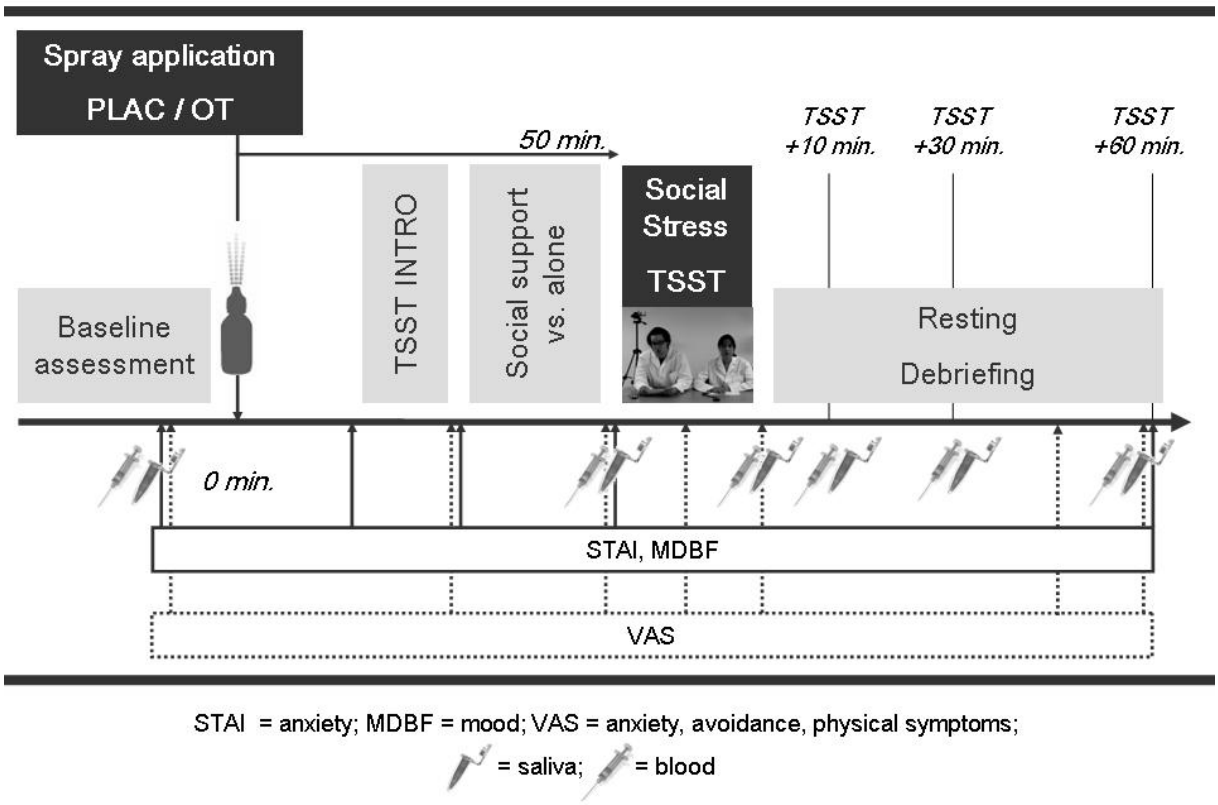

Figure 7-1: Study protocol: Oxytocin and social support buffer the psychobiological stress response in social phobia

7.2.3 Psychological measures

Prior to the experiment, all participants filled out the German version of the Liebowitz Social Anxiety Scale (LSAS) (Stangier & Heidenreich, 2003) and the German trait version of the State-Trait Anxiety Inventory (STAI) (Laux, Glanzmann, Schaffner, & Spielberger, 1981). In addition, the social phobic patients completed the Social Phobia Inventory (SPIN) (Connor et al., 2000) and the Beck Depression Inventory (BDI) (Hautzinger, Bailer, Worall, & Keller, 1994), whereas healthy subjects filled out the Symptom Checklist (SCL-90-R) (Franke, 2002) to control for psychiatric symptomatology.

At the beginning of the experiment, all subjects rated their baseline anxiety using the STAI state questionnaire (Laux, Glanzmann, Schaffner, & Spielberger, 1981) as well as mood using a standardized questionnaire (MDBF) (Steyer, Schwenkmezger, Notz, & Eid, 1997). The visual analogue scale (VAS) was assed to rate actual anxiety, physical reaction symptoms and avoidance at baseline. On the VAS scales, subjects rated feeling states by marking a line along a 100 mm visual analog line. The scale ranged from ‘not at all’ to ‘very strong’. Repeated measures of anxiety (STAI state: 5 times), mood, wakefulness and calmness (MDBF: 5 times) and the three VAS (anxiety, physiological symptoms and avoidance: 7 times) were applied throughout the experiment.
In addition, participants rated their relationship satisfaction (PFB) (Hahlweg, Klann, & Hank, 1992) and social support (BSSS) (Schulz & Schwarzer, 2003).

7.2.4 Physiological measures and laboratory analysis

Participants were connected to a heart rate monitor (Polar® S810) and the data were aggregated in 1-min intervals (beats/min) from beat-to-beat analyses from -2 to +2 minutes relative to the stressor (14 units) and a five-minute baseline mean (beats/min) aggregation.

To measure saliva cortisol, six saliva samples were taken (at baseline, before TSST, +0 min., +10 min., +45 min. and +90 min. after TSST) using salivettes (Sarstedt, Sevelen, Switzerland). After the experimental session, devices were stored at –20°C until required for later analysis by chemiluminescence immunoassay (CLIA; IBL Hamburg, Germany; inter- and intraassay coefficients of variation < 10%). Blood

samples were taken six times (at baseline, after substance administration, before TSST, +0 min., +45 min. and +90min. after TSST) via a venous catheter and stored at -80°C until required for later analysis by enzyme immunoassay (ELISA; IBL Hamburg, Germany; inter- and intraassay coefficients of variation < 10%). From these samples, plasma cortisol was analyzed.

7.2.5 Substance administration

Since neuropeptides cross the blood-brain barrier after intranasal application (Born et al., 2002; Pietrowsky, Struben, Molle, Fehm, & Born, 1996), the study of central nervous system effects of oxytocin is possible and diminishes risks for peripheral side effects to a minimum.

Participants received a single intranasal dose of 24 I.U. oxytocin (Syntocinon® Spray, Novartis; 3 puffs per nostril, each with 4 I.U. oxytocin), or placebo 50 minutes before the start of the TSST. In order to avoid any subjective substance effects (for example, olfactory effects) other than those caused by oxytocin, the placebo spray contained all inactive ingredients of the syntocinon® spray (except for the peptide).

7.2.6 Data analysis

To test for homogeneity of variance and normal distribution, the Levene test and the Kolmogorov-Smirnov test were computed for dependent variables. Baseline differences were computed with one-way analysis of variance (ANOVAs). If baseline measures differed significantly, three-way analysis of covariance (ANCOVAs) were computed [social phobia (healthy control vs. social phobia) by oxytocin (placebo vs. oxytocin) by social support (no social support vs. social support)] for single measures or four-way ANCOVAs with repeated measurement [social phobia (healthy control vs. social phobia) by oxytocin (placebo vs. oxytocin) by social support (no social support vs. social support) by time (repeated measurement: five for endocrine measures, 14 for heart rate measures, four for anxiety and mood and six for visual analogue scales)].

Post-hoc comparisons between groups were obtained by Fisher`s LSD. A Kruskal-Wallis test was computed to test for differences in duration of the disorder, severity and degree of generalization between the four phobic groups. The individual response curves (area under the curve with respect to the ground (AUC_G)) and area

under the curve with respect to increase (AUC_I) were calculated using the trapezoid formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) aggregating the repeated measures (five for endocrine measures, 14 for heart rate measures, four for anxiety and mood and six for visual analogue scales). If the Mauchly test of sphericity indicated heterogeneity of covariance, repeated-measurement results were verified with Greenhouse-Geisser corrections. Statistical tests were two-tailed and conducted at the .05 level of significance.

7.3 Results

7.3.1 Sample characteristics

Three-way (social phobia, social support, oxytocin) ANOVAS showed that social phobic patients were less satisfied with their relationship (social phobia: $F_{(1, 136)}$=5.698; p=.018; ε^2=.040), with the perceived emotional support (social phobia: $F_{(1, 135)}$=27.416; p<.001; ε^2=.169) and perceived instrumental support (social phobia: $F_{(1, 135)}$=17.155; p<.001; ε^2=.113) provided by their spouse and also sought less social support (social phobia: $F_{(1, 135)}$=32.687; p<.001; ε^2=.195) compared to healthy controls. One significant group difference emerged for age ($F_{(1, 136)}$=8.36; p=.004; ε^2=.058). The phobic patients were older than the healthy controls, but this difference did not appear to be of relevance. The two groups differed clearly in trait anxiety (STAI trait: $F_{(1, 136)}$=232.330; p<.001; ε^2=.631) and social anxiety (LSAS: $F_{(1, 136)}$=284.04; p<.001; ε^2=.676) indicating higher levels for the social phobic patients.

A Kruskal-Wallis test revealed no difference in duration of the disorder, the severity and degree of generalization between the four groups of social phobic patients (with the exception of two subjects, all patients had been diagnosed with generalized social phobia). In addition, the four groups did not differ in their social phobic symptomatology measured by the Social Phobia Inventory (SPIN) (Connor et al., 2000). Pretreatment demographic and psychometric characteristics are presented in Table 7-1 (age, duration of relationship, relationship satisfaction) and Table 7-2 (social anxiety of healthy subjects and subjects with social phobia). The clinical characteristics of the social phobic patients are presented in Table 7-3 (duration of the disorder, generalization, social phobic symptomatology, depression).

Table 7-1: Age, duration of relationship and relationship satisfaction

	Healthy controls (n=79)				Social phobic patients (n=65)				
	Oxytocin (OXT)		Placebo (PLAC)		Oxytocin (OXT)		Placebo (PLAC)		
Characteristic	SS (n=22)	NoSS (n=20)	SS (n=16)	NoSS (n=21)	SS (n=15)	NoSS (n=17)	SS (n=18)	NoSS (n=15)	ANOVA *p*
Age (years)	36.05 (1.39)	38.45 (2.19)	42.00 (2.35)	38.05 (1.807)	41.87 (2.31)	44.12 (2.38)	43.72 (1.78)	42.53 (2.37)	*=.004*** (*Social phobia)*
Duration of relationship (years)	9.18 (1.40)	7.58 (1.54)	14.88 (2.75)	8.69 (1.98)	11.20 (2.77)	13.09 (2.57)	14.39 (2.08)	9.60 (1.99)	*ns*
Relationship Satisfaction	61.32 (2.60)	66.65 (2.10)	58.25 (2.74)	62.81 (2.42)	60.00 (3.5)	58.63 (2.61)	54.67 (2.31)	56.95 (4.03)	*=.018** (*Social phobia)*

Data are expressed as mean (SEM).

Table 7-2: Social anxiety

	Healthy controls (n=79)				Social phobic patients (n=65)				
	Oxytocin (OXT)		Placebo (PLAC)		Oxytocin (OXT)		Placebo (PLAC)		
Characteristic	SS (n=22)	NoSS (n=20)	SS (n=16)	NoSS (n=21)	SS (n=15)	NoSS (n=17)	SS (n=18)	NoSS (n=15)	ANOVA *p*
LSAS	20.05 (1.73)	18.15 (2.22)	22.00 (2.60)	19.10 (2.44)	65.73 (6.53)	75.35 (5.48)	65.50 (5.78)	70.76 (5.67)	*<.001*** (*Social phobia)*
STAI	31.95 (1.41)	28.70 (1.14)	30.86 (.96)	30.29 (.78)	52.13 (2.35)	51.64 (3.37)	49.22 (1.91)	48.47 (2.12)	*<.001*** (*Social phobia)*

Data are expressed as mean (SEM).

Table 7-3: Clinical characteristics

Social phobic patients (n=65)

	Oxytocin (OXT)		Placebo (PLAC)		
Characteristic	SS (n=15)	NoSS (n=17)	SS (n=18)	NoSS (n=15)	ANOVA *p*
SPIN	37.60 (2.98)	40.07 (2.49)	39.17 (2.51)	39.33 (1.67)	*ns*
Generalized social phobia	14	16	18	15	*ns*
Duration of the disorder	26.60 (3.45)	28.94 (2.63)	28.22 (3.04)	25.13 (3.25)	*ns*
BDI (Depression)	11.60 (1.48)	10.76 (2.04)	12.28 (1.43)	10.87 (1.22)	*ns*

Data are expressed as mean (SEM).

7.3.2 Endocrine response to stress

7.3.2.1 Salivary free cortisol

Since a three-way ANOVA revealed significantly higher salivary free cortisol at baseline for social phobic patients (social phobia: $F_{(1,\ 132)}$=4.468; p=.036; ε^2=.033), baseline salivary cortisol served as covariate. The expected salivary free cortisol response to stress in the total group (time effect: $F_{(2.326,\ 304.674)}$=19.478; p<.001; ε^2=.129) was shown by a four-way ANCOVA with repeated measurement. Moreover, social phobic patients showed less response to stress over time than control subjects (time × social phobia: $F_{(2.326,\ 304.674)}$=3.774; p=.019; ε^2=.028) (Figure 7-2) and a three-way ANOVA revealed a significant social phobia by oxytocin interaction for $AUC_{I\ (salivary\ cortisol)}$ (social phobia × oxytocin: $F_{(1,\ 132)}$=4.270; p=.041; ε^2=.031). A Fisher`s LSD post-hoc test revealed a trend towards a lower increase of cortisol in patients with oxytocin compared to patients with placebo and a significantly lower increase for patients with oxytocin compared to healthy controls with (Figure 7-3).

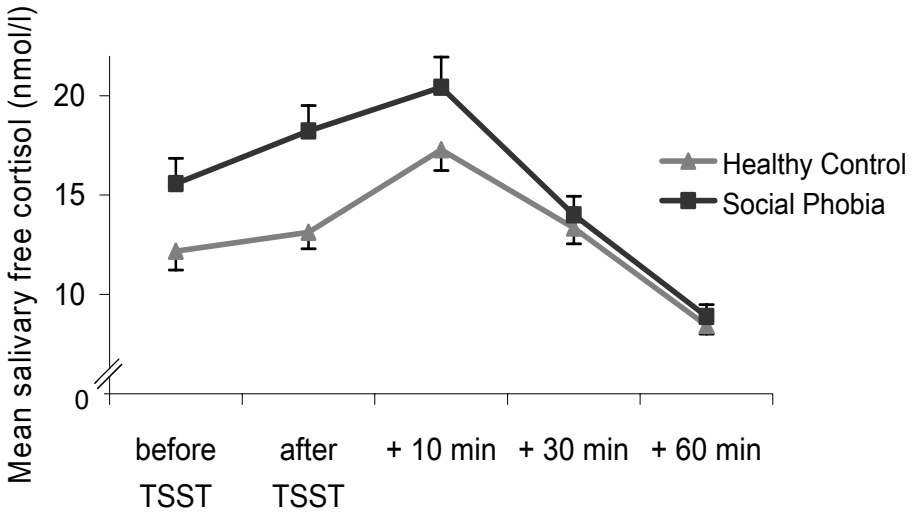

Figure 7-2: Mean (+/-SEM) salivary cortisol in healthy controls and social phobia

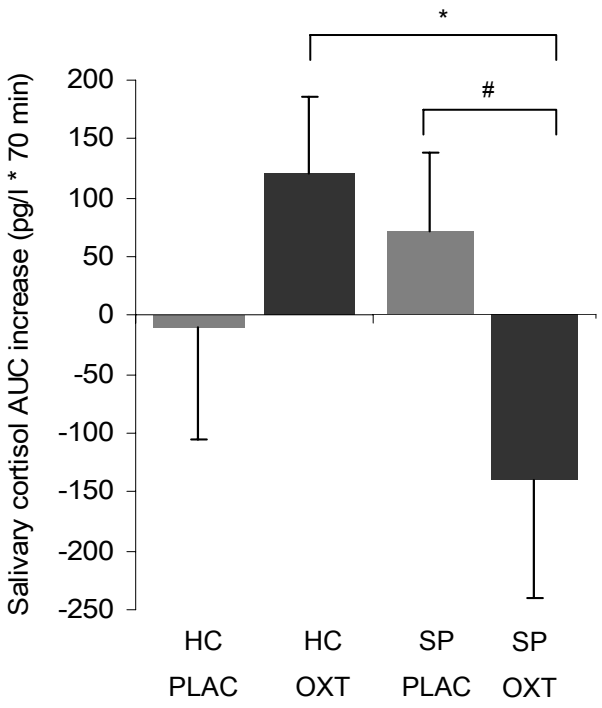

Figure 7-3: AUC increase of salivary cortisol in social phobics (SP) and healthy controls (HC) with placebo (PLAC) or oxytocin (OXT) (**= p<.001; * = p<0.05; # = p<.10)

7.3.2.2 Plasma cortisol

Baseline levels of plasma cortisol also revealed significantly higher levels for social phobic patients (social phobia: $F_{(1,\ 105)}$=4.175; p=.044; ε^2=.038) and were used as covariate in another four-way ANCOVA with repeated measurement. Again, the expected stress response occurred (time effect: $F_{(2.672,\ 277.933)}$=6.627; p<.001; ε^2=.060). There was no significant difference in stress response between patients and controls (time × social phobia: $F_{(2.672,\ 277.933)}$=.724; p=.523; ε^2=.007) but social support treatment showed a lower increase in plasma cortisol (time × social support: $F_{(2.672,\ 277.933)}$=3.276; p=.026; ε^2=.031). Moreover, there was a significant time by social phobia by oxytocin interaction (time × social phobia × oxytocin: $F_{(2.672,\ 277.933)}$=3.289; p=.026; ε^2=.031), documenting a lower increase of cortisol over time for social phobic patients with oxytocin (Figure 7-4).

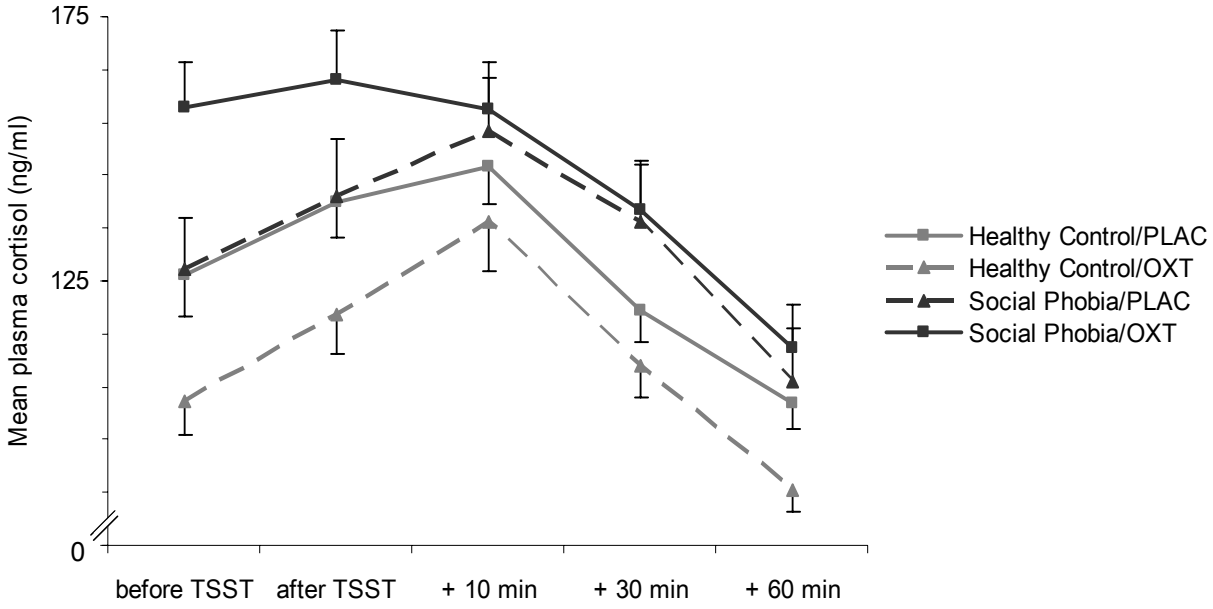

Figure 7-4: Mean plasma cortisol in social phobics (SP) and healthy controls (HC) with placebo (PLAC) or oxytocin (OXT)

In addition, a main effect for social phobia indicated higher overall levels of plasma cortisol in the patients compared to healthy controls ($F_{(1,\ 104)}$=5.342; p=.023; ε^2=.049). Three-way ANOVAs revealed significantly higher $AUC_{G\ (plasma\ cortisol)}$ for social phobia (social phobia: $F_{(1,\ 105)}$=8.550; p=.004; ε^2=.075) and a significant main effect of social interaction for $AUC_{I\ (plasma\ cortisol)}$ (social support: $F_{(1,\ 105)}$=7.456; p=.007; ε^2=.066), with

a lower increase in plasma cortisol in social support groups compared to no social support (Figure 7-5).

The social phobia by oxytocin interaction occurred again regarding the $AUC_{I\ (plasma\ cortisol)}$ (social phobia × oxytocin: $F_{(1,\ 105)}$=8.583; p=.004; ε^2=.076). Fisher`s LSD post-hoc test revealed a significantly lower increase for patients with oxytocin compared to patients with placebo and controls with oxytocin. Moreover, there was a trend towards lower increases in plasma cortisol for social phobic patients with oxytocin compared to controls with placebo (Figure 7-6). Cortisol baseline levels are shown in Table 7-4.

Table 7-4: Cortisol baseline levels

	Healthy controls				Social phobic patients				
	Oxytocin		Placebo		Oxytocin		Placebo		
Characteristic	SS	NoSS	SS	NoSS	SS	NoSS	SS	NoSS	ANOVA *p*
Salivary cortisol (nmol/l)	13.869 (1.34) n=22	14.27 (1.38) n=20	14.23 (1.73) n=16	14.45 (1.38) n=21	18.10 (2.74) n=15	20.44 (2.33) n=17	16.58 (2.41) n=17	13.29 (2.29) n=12	*=.036** (*Social phobia)*
Plasma cortisol (ng/ml)	118.62 (8.77) n=14	122.10 (9.22) n=15	136.53 (9.68) n=13	130.07 (9.00) n=17	158.89 (15.45) n=14	143.50 (13.42) n=17	133.05 (11.63) n=14	140.48 (15.01) n=9	*=.044** (*Social phobia)*

Data are expressed as mean (SEM).

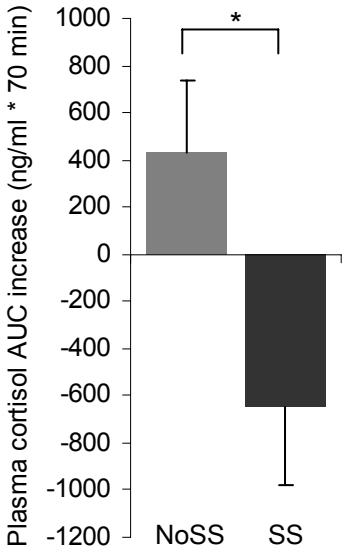

Figure 7-5: AUC increase plasma cortisol in subjects without social support (NoSS) and with social support (SS) (**= p<.001* = p<0.05; # = p<.10)

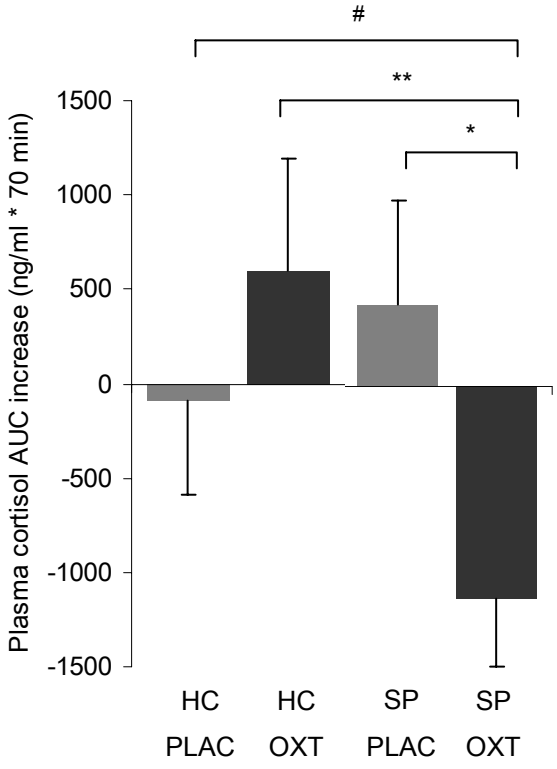

Figure 7-6: AUC increase plasma cortisol in social phobics (SP) and healthy controls (HC) with placebo (PLAC) or oxytocin (OXT) (**= p<.001* = p<0.05; # = p<.10)

7.3.3 Autonomic response to stress

A three-way ANOVA showed significantly higher baseline heart rate in social phobia ($F(1,86)=12.690$; $p=.001$; $\varepsilon 2=.129$) (Table 7-5).

Controlling for this difference, a four-way ANCOVA with repeated measurement revealed no time effect but a significant time by oxytocin interaction (time effect × oxytocin: $F_{(5.267,\ 428.595)}=2.871$; $p=.013$; $\varepsilon^2=.034$), indicating a lower increase in heart rate for oxytocin (most pronounced at the beginning of the TSST). Interestingly, there was a social phobia by oxytocin by social support interaction (social phobia × oxytocin × social support: $F_{(1,\ 81)}=5.373$; $p=.023$; $\varepsilon^2=.062$).

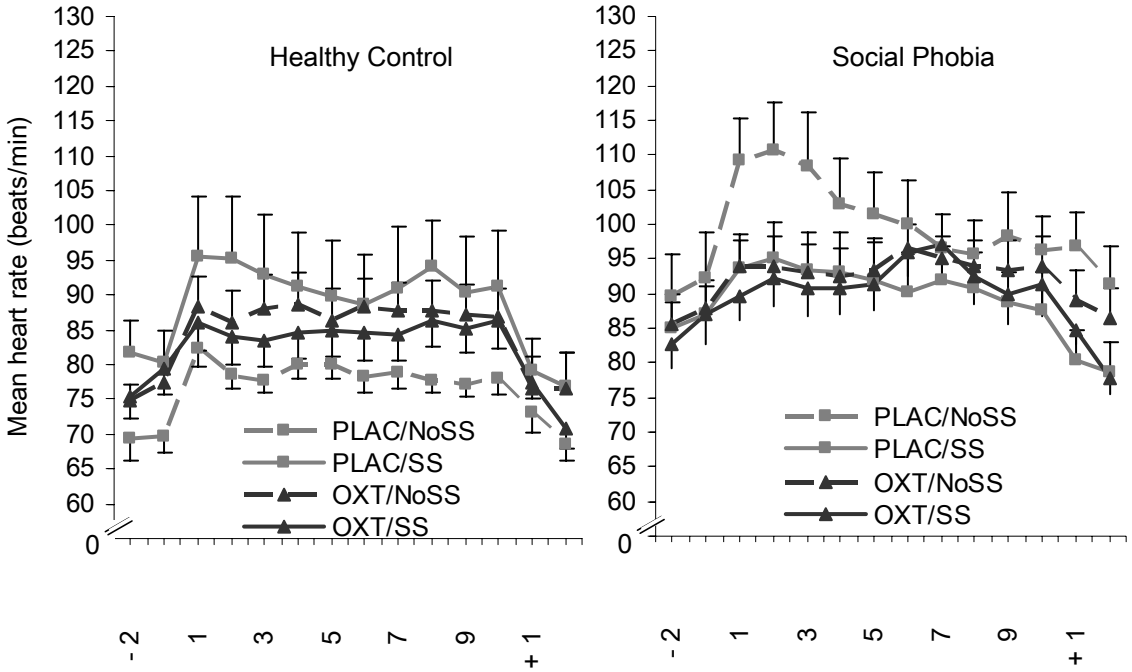

Figure 7-7: Mean (+/-SEM) heart rate during TSST for healthy controls and social phobia subjects without social support (NoSS) and with social support (SS) and placebo (PLAC) or oxytocin (OXT)

This result demonstrates that social phobic patients who received neither social support nor oxytocin show the highest autonomic reactivity to stress (Figure 7-7). The increase from two minutes before the TSST to the first minute is shown in Figure 7-8 and further illustrates this effect.

Table 7-5: Heart rate baseline

	Healthy controls (n=51)				Social phobic patients (n=43)				
	Oxytocin		Placebo		Oxytocin		Placebo		
Characteristic	SS	NoSS	SS	NoSS	SS	NoSS	SS	NoSS	ANOVA *p*
Baseline heart rate (beat/min.)	75.78 (3.10) n=14	73.42 (1.83) n=15	76.84 (3.90) n=10	69.20 (1.96) n=12	79.40 (2.67) n=11	82.03 (3.08) n=12	81.67 (3.35) n=12	81.39 (2.62) n=8	*<.001*** (*Social phobia)*

Data are expressed as mean (SEM).

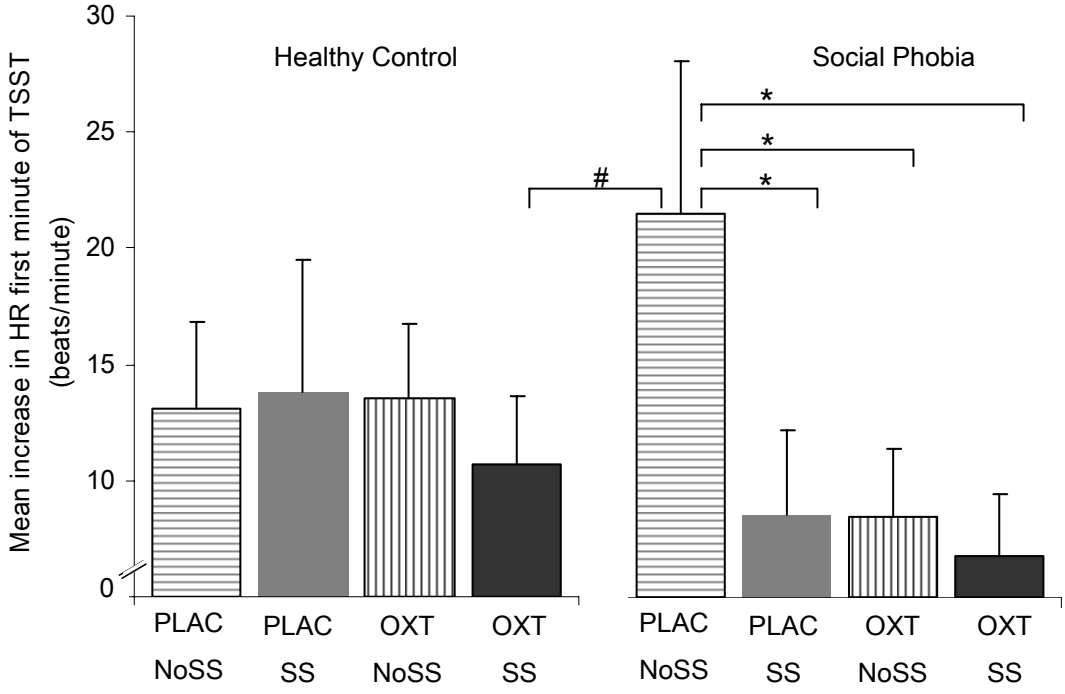

Figure 7-8: Mean (+SEM) increase in heart rate during TSST for healthy controls and social phobia subjects without social support (NoSS) and with social support (SS) and placebo (PLAC) or oxytocin (OXT) (**= p<.001;* = p<0.05; # = p<.10)

7.3.4 Psychological responses to stress

7.3.4.1 Calmness, mood and wakefulness

Calmness, mood and wakefulness were measured at baseline, prior to and after the introduction to the TSST, after the TSST and at the end of the experiment. Three-way ANOVAS showed significantly lower calmness ($F_{(1,136)}$=64.162; p<.001; ε^2=.321), worse mood ($F_{(1,136)}$=65.108; p<.001; ε^2=.324) and lower wakefulness ($F_{(1,136)}$=25.984; p<.001; ε^2=.160) for the social phobic patients at baseline (Figure 7-9).

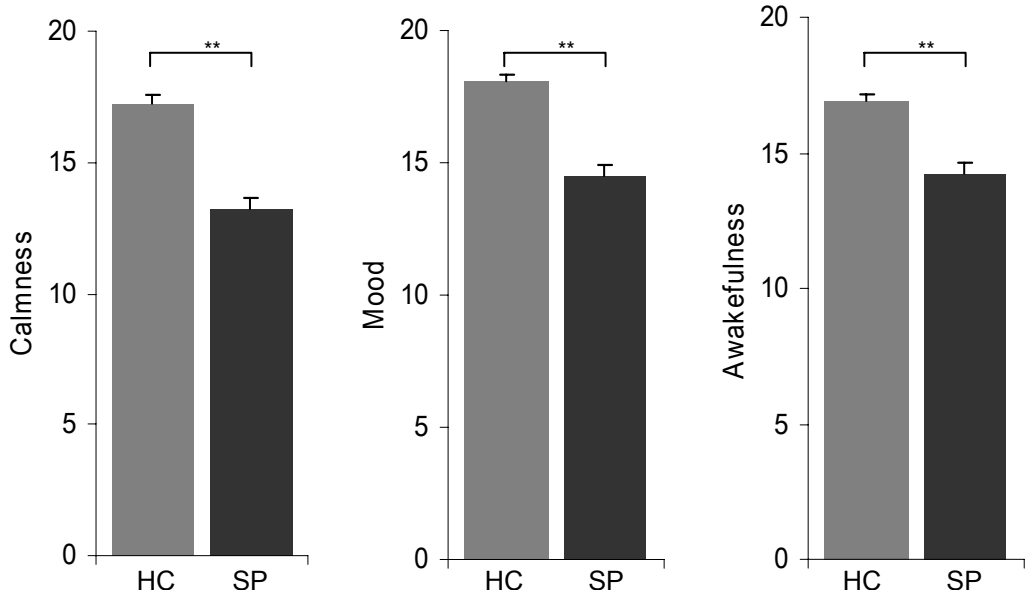

Figure 7-9: Mean (+SEM) baseline levels of calmness, mood and wakefulness (**= p<.001)

Three four-way ANCOVAs (baseline measure as covariate) with repeated measurement were calculated for all three scales.

For *calmness*, there was the expected significant decrease over time in the whole group (time effect: $F_{(2.742,370.224)}$=4.858; p=.003; ε^2=.035). Participants with social phobia (time × social phobia: $F_{(2.742,370.224)}$=7.506; p<.001; ε^2=.053) as well as participants with placebo (time × oxytocin: $F_{(2.742,370.224)}$=3.099; p=.031; ε^2=.022) showed a higher decrease in calmness over time. A three-way ANOVA with the total decrease in mood (difference score: calmness prior to intro – calmness after intro) as dependent measure showed the same result.

A significantly higher decrease in calmness was observed for social phobic patients (social phobia: $F_{(1,136)}$=16.207; p<.001; ε^2=.106) and for the whole placebo group (oxytocin: $F_{(1,136)}$=6.467; p=.012; ε^2=.045).
In addition, there was a significant social phobia by oxytocin interaction (social phobia × oxytocin: $F_{(1,136)}$=4.058; p=.046; ε^2=.029) revealing less decrease in calmness for the oxytocin predominantly in the social phobic patients (Figure 7-10).

Moreover, the study revealed a main effect for social phobia ($F_{(1,135)}$=16.770; p<.001; ε^2=.110), with lower calmness for the patients as well as a significant social phobia by social support interaction (social phobia × social support: $F_{(1,135)}$=6.965; p=.009; ε^2=.049). The latter result reveals overall lower calmness for the control subjects when they where supported by their spouse. The social phobic patients instead showed faster recovery from the TSST-induced drop in calmness if they had been supported by their spouse (Figure 7-11).

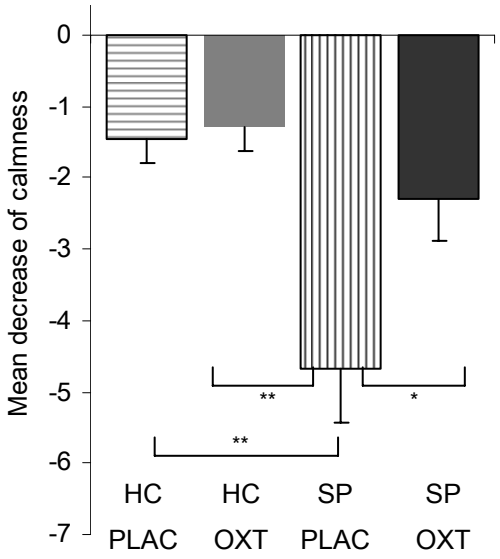

Figure 7-10: Mean (-SEM) decrease in calmness for social phobics (SP) and healthy controls (HC) with placebo (PLAC) or oxytocin (OXT) (**= p<.001* = p<0.05; # = p<.10)

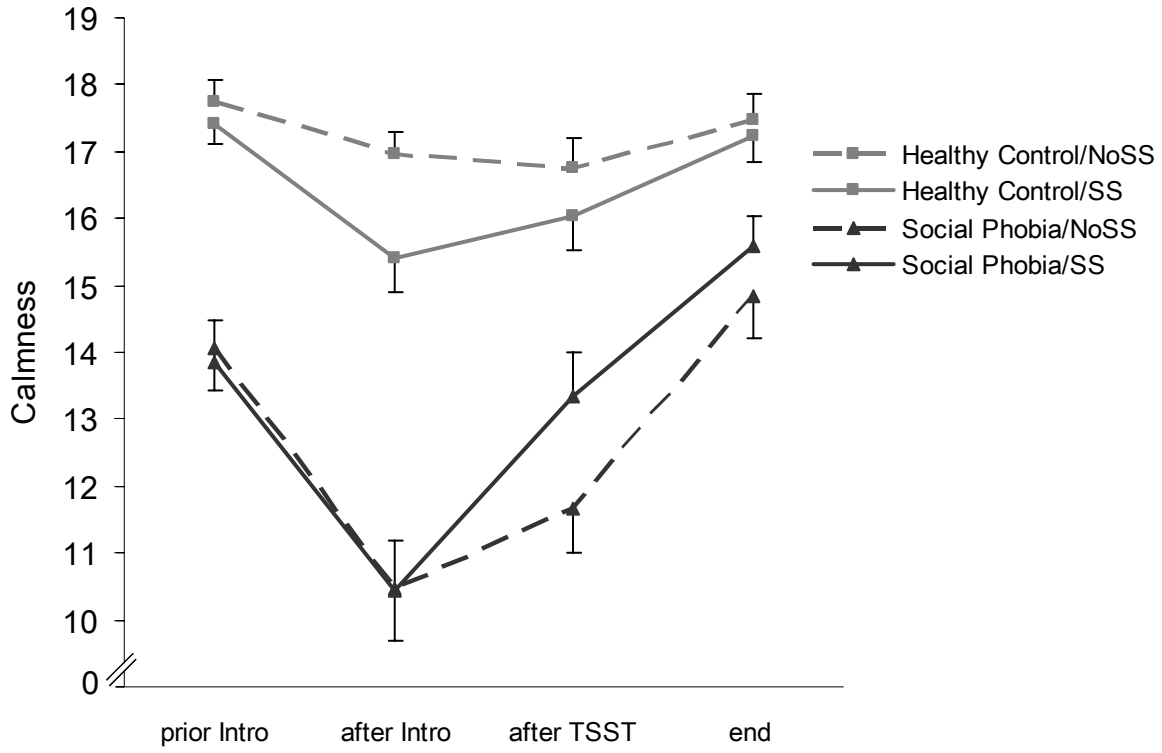

Figure 7-11: Mean (+/-SEM) calmness for healthy controls (HC) and social phobics (SP) without social support (NoSS) and with social support (SS)

For *mood*, there was a significant decrease over time (time effect: $F_{(2.456,331.563)}$=11.028; p<.001; ε^2=.076) and again a stronger decrease in mood over time for the social phobic group (time × social phobia: $F_{(2.456,331.563)}$=11.571; p<.001; ε^2=.079) compared to controls (Figure 7-12). In addition, there was a main effect for social phobia indicating worse mood for patients over the whole experiment compared to controls (social phobia: $F_{(1,135)}$=20.052; p<.001; ε^2=.129).

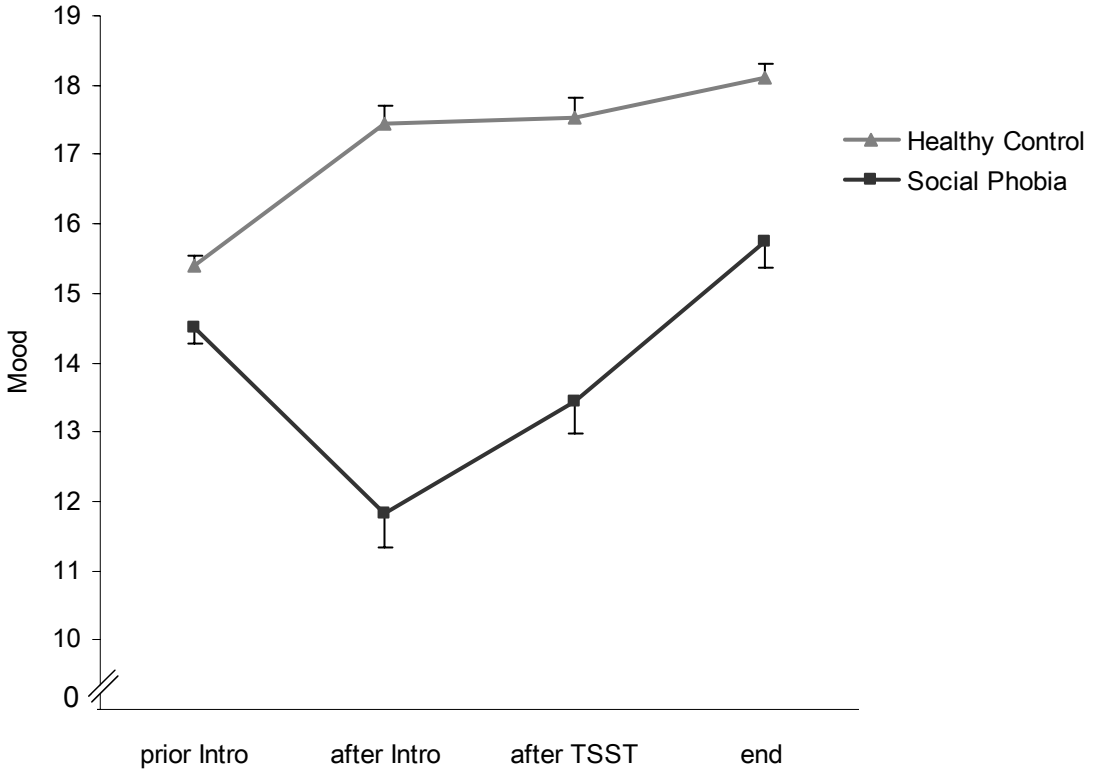

Figure 7-12: Mean (+/-SEM) mood for healthy controls (HC) and social phobics (SP)

Wakefulness showed no main effect of time but a significant time by social phobia interaction, revealing a clear decrease in wakefulness over time for the patients in contrast to the control subjects (time × social phobia: $F_{(2.823,381.075)}$=4.803; p=.003; ε^2=.034) (Figure 7-13).

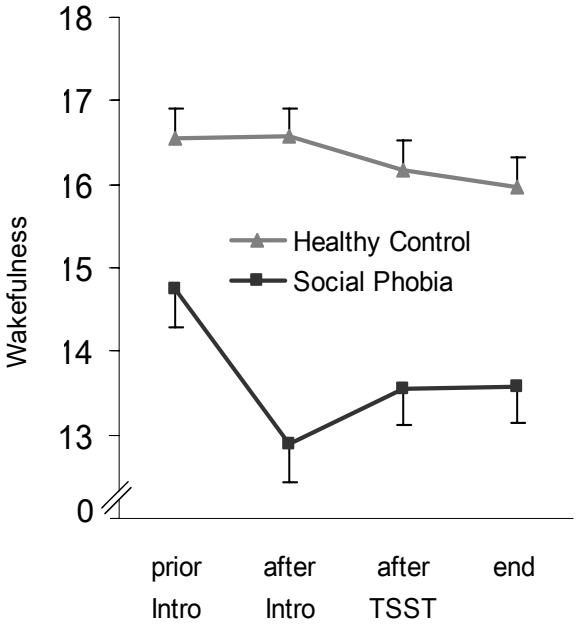

Figure 7-13: Mean (+/-SEM) wakefulness for healthy controls (HC) and social phobics (SP)

7.3.4.2 State anxiety

State anxiety was measured at baseline, prior to and after the introduction to the TSST, after the TSST and at the end of the experiment. A three-way ANOVA revealed significant baseline differences in baseline state anxiety (STAI). As expected, patients showed higher levels than controls (social phobia: $F_{(1,136)}$=73.264; p<.001; ε^2=.350). Moreover, the social support condition revealed higher baseline levels (social support: $F_{(1,136)}$=4.026; p=.047; ε^2=.029) and there was a significant social phobia by oxytocin interaction (social phobia × oxytocin: $F_{(1,136)}$=4.273; p=.041; ε^2=.030) indicating higher levels of baseline state anxiety for social phobic patients who had received oxytocin after baseline measurement. These differences were accounted for in a four-way ANCOVA with repeated measurement in order to investigate the treatment effects on state anxiety over time. The expected stress response again occurred (time effect: $F_{(2.366,319.442)}$=3.356; p=.029; ε^2=.024).

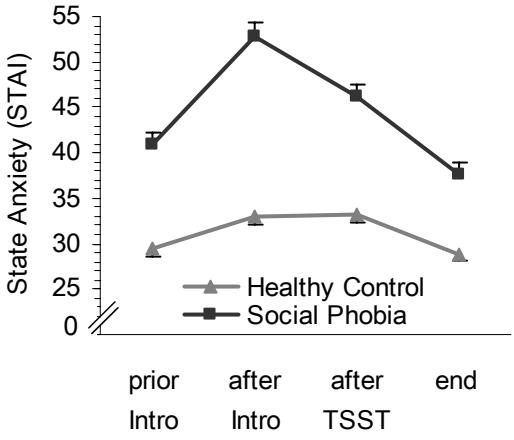

Figure 7-14: Mean (+/-SEM) State anxiety for healthy controls (HC) and social phobics (SP)

There was a stronger increase in anxiety over time for the participants with social phobia (time × social phobia: $F_{(2.366,319.442)}$=6.904; p=.001; ε^2=.049) (Figure 7-14) and a time by oxytocin interaction (time × oxytocin: $F_{(2.366,319.442)}$=3.299; p=.030; ε^2=.024), which represents an attenuated increase in anxiety over time for oxytocin. A three-factor ANOVA with $AUC_{I\ (STAI)}$ as dependent measure also revealed a main effect of oxytocin in lower increases ($F_{(1,136)}$=9.046; p=.003; ε^2=.062) (Figure 7-15).

Moreover, a significant social phobia by oxytocin interaction indicates that the oxytocin effect predominantly occurred in the social phobic patients (social phobia × oxytocin: $F_{(1,136)}$=6.696; p=.011; ε^2=.047). Post-hoc analyses revealed significant differences in anxiety only for the social phobics with placebo. Patients who received oxytocin did not differ from healthy controls (Figure 7-16).

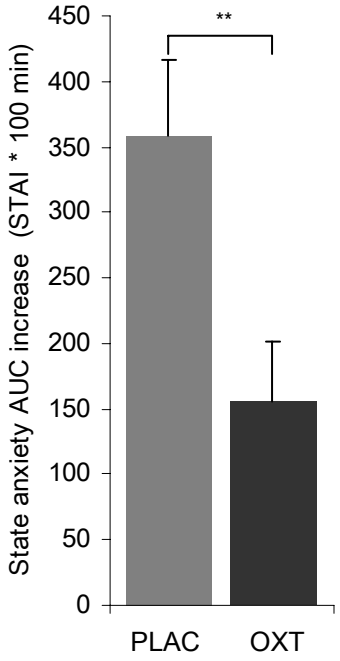

Figure 7-15: Mean (+/-SEM) state anxiety in placebo (PLAC) and oxytocin (OXT) (**= p<.001; * = p<0.05; # = p<.10)

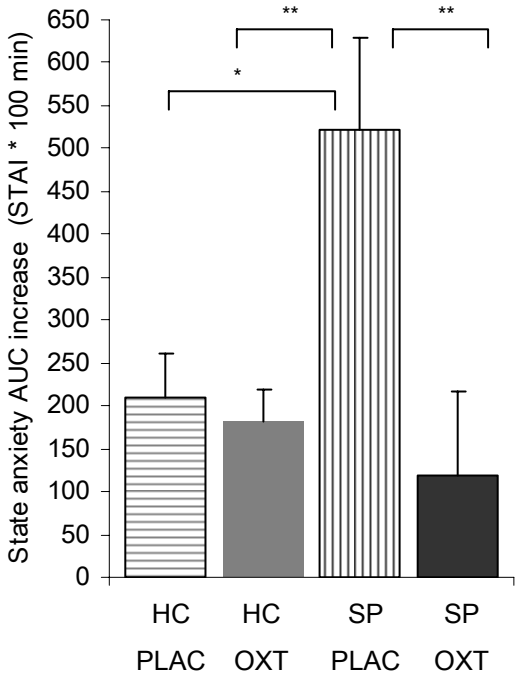

Figure 7-16: Mean (+/-SEM) state anxiety for social phobics (SP) and healthy controls (HC) with placebo (PLAC) or oxytocin (OXT) (**= p<.001; * = p<0.05; # = p<.10)

7.3.4.3 Avoidance, anxiety, physical reaction symptoms

Visual analogue scales were measured seven times: at baseline, after the introduction to the TSST, before, during and directly after the TSST, +30 and +45 minutes after the TSST. Three-way ANOVAS showed higher avoidance ($F_{(1,136)}$=55.294; p<.001; ε^2=.289), anxiety ($F_{(1,136)}$=40.690; p<.001; ε^2=.230) and more physical symptoms ($F_{(1,136)}$=21.836; p<.001; ε^2=.138) at baseline for the social phobic group compared to controls (Figure 7-17). To account for these baseline differences, again three four-way ANCOVAS (baseline measure as covariate) with repeated measurement were calculated for all three scales.

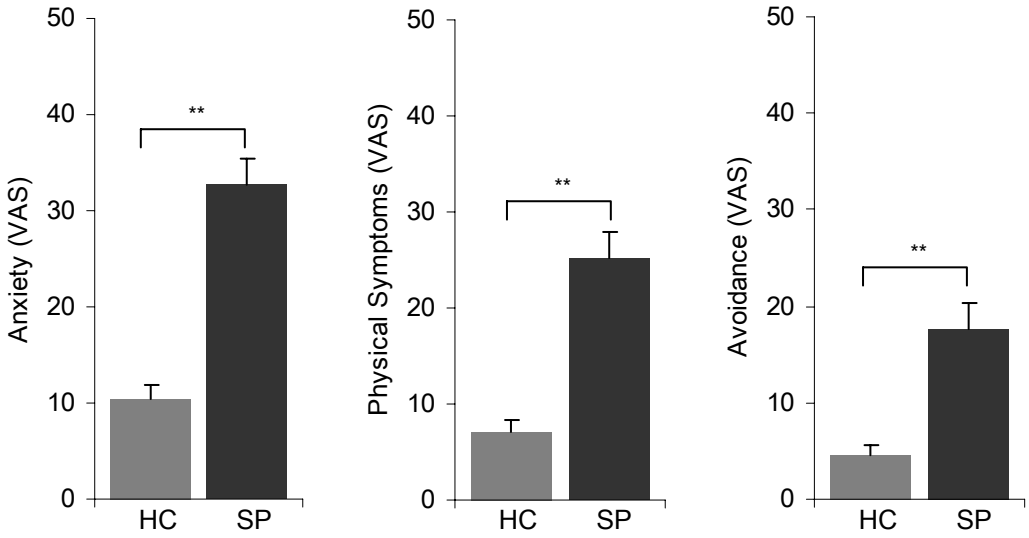

Figure 7-17: Mean (+SEM) baseline levels of visual analogue scales (anxiety, physical symptoms and avoidance for healthy controls (HC) and social phobics (SP) (**= p<.001; * = p<0.05; # = p<.10)

Avoidance increased throughout the experiment (time effect: $F_{(3.309,446.650)}$=16.970; p<.001; ε^2=.112). Social phobics showed a stronger increase over time (time × social phobia: $F_{(3.309,446.650)}$=10.344; p<.001; ε^2=.071) and higher avoidance over the entire experiment (social phobia: $F_{(1,135)}$=26.574; p<.001; ε^2=.164) (Figure 7-18).

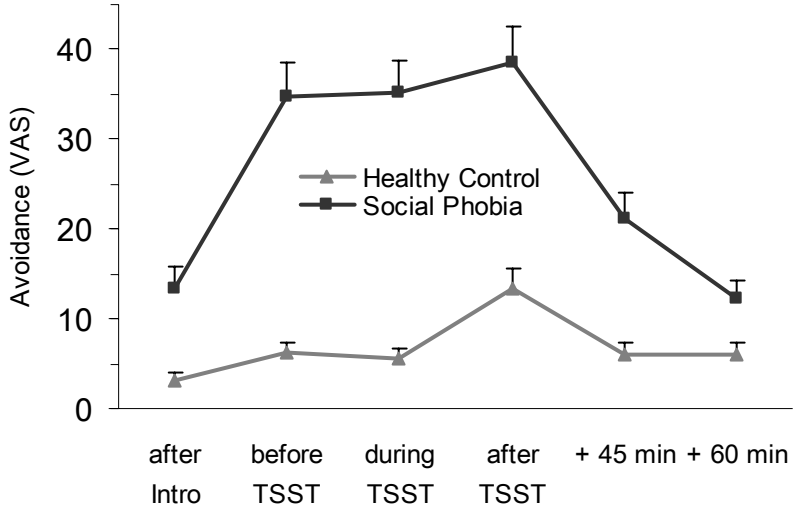

Figure 7-18: Mean (+SEM) avoidance in healthy controls and social phobia

There was a significant time by social support interaction (time × social support: $F_{(3.309,446.650)}$=2.555; p=.049; ε^2=.019), revealing a higher increase for participants without support. In addition, there was a time by social support by oxytocin interaction (time × social support × oxytocin: $F_{(3.309,446.650)}$=2.911; p=.030; ε^2=.021) underlining lower increases of avoidance for participants with social support and oxytocin. This effect was more pronounced in the social phobic group (time × social phobia × social support × oxytocin interaction: $F_{(3.309,446.650)}$=2.733; p=.038; ε^2=.020) (Figure 7-19).

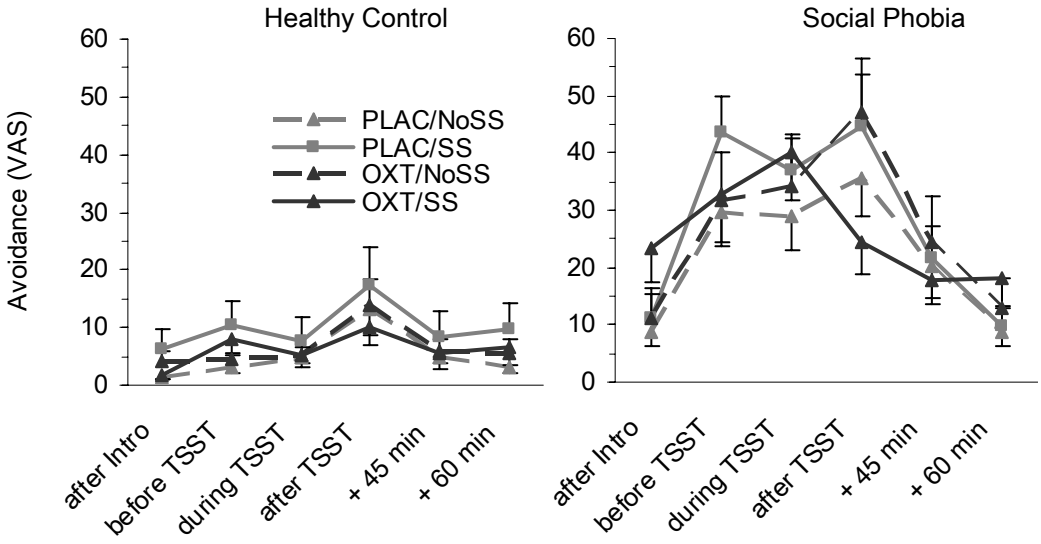

Figure 7-19: Mean (+/-SEM) Avoidance for healthy controls and social phobics without social support (NoSS) or with social support (SS) and placebo (PLAC) or oxytocin (OXT)

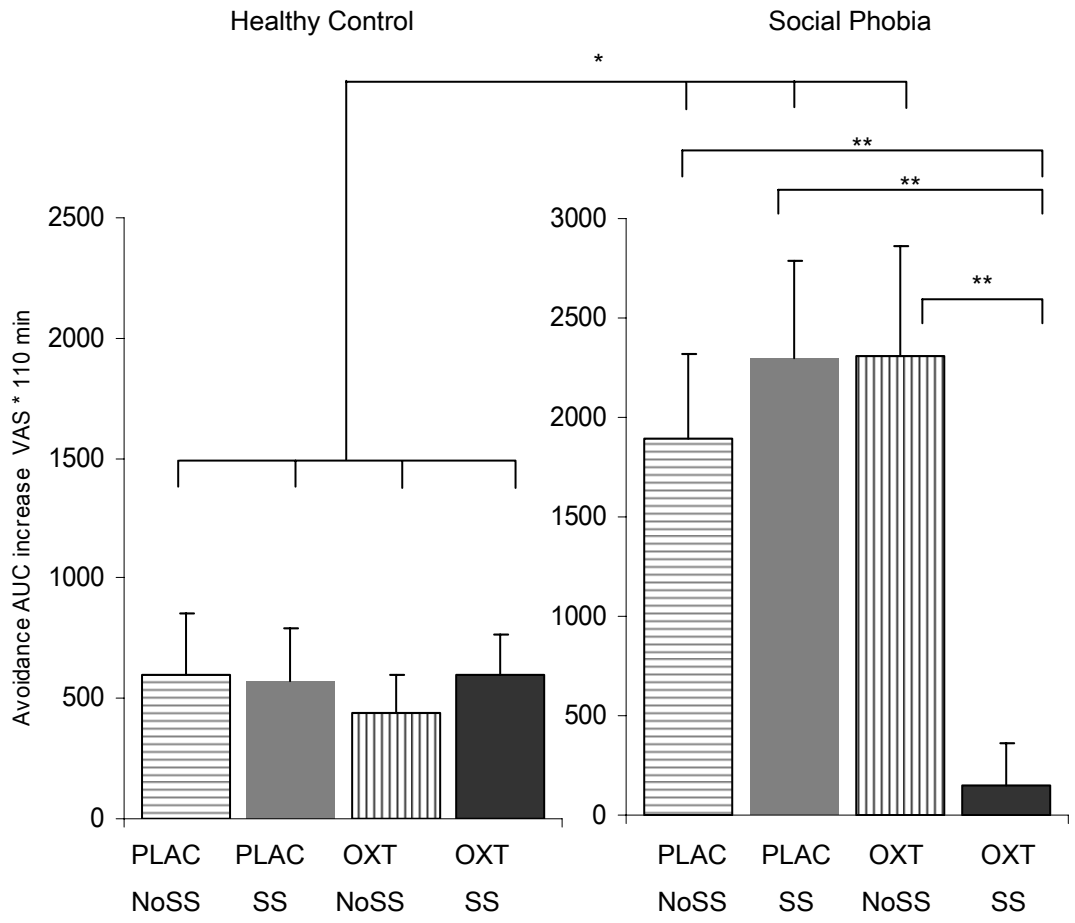

Figure 7-20: Mean (+SEM) AUC increase avoidance for healthy controls and social phobics without social support (NoSS) and with social support (SS) and placebo (PLAC) or oxytocin (OXT)
(**= p<.001; * = p<0.05; # = p<.10)

Moreover, there was a trend towards a time by oxytocin interaction (time × oxytocin: $F_{(3.309,446.650)}$=2.409; p=.060; ε^2=.018) indicating lower increases of avoidance over time for oxytocin. Three-way ANOVAS revealed that the $AUC_{G\ (avoidance)}$ (social phobia: $F_{(1,136)}$=46.251; p<.001; ε^2=.254) and the $AUC_{I\ (avoidance)}$ (social phobia: $F_{(1,136)}$=22.639; p<.001; ε^2=.143) were both higher in patients compared to controls. In addition, the $AUC_{I\ (avoidance)}$ was significantly lower in the oxytocin group (oxytocin: $F_{(1,136)}$=4.061; p=.046; ε^2=.029) and there was a significant social phobia by social support interaction for $AUC_{I\ (avoidance)}$ ($F_{(1,136)}$=4.104; p=.045; ε^2=.029), indicating stronger effectivess of social support in the patient group. An oxytocin by social support interaction ($F_{(1,136)}$=6.569; p=.011; ε^2=.046) and finally a social phobia by social support by oxytocin interaction (social phobia × social support × oxytocin: $F_{(1,136)}$=8.771; p=.004; ε^2=.061) for $AUC_{I\ (avoidance)}$ revealed the lowest increase in avoidance for social phobic patients who had received social support and oxytocin. Results of post-hoc comparisons are described in detail in

Figure 7-20.

Anxiety increased over time (time effect: $F_{(3.430,463.109)}$=16.028; p<.001; ε^2=.106). Social phobics showed a stronger increase over time (time × social phobia: $F_{(3.430,463.109)}$=16.028; p<.001; ε^2=.106) and higher anxiety over the entire experiment (social phobia: $F_{(1,135)}$=28.976; p<.001; ε^2=.177) (Figure 7-21).

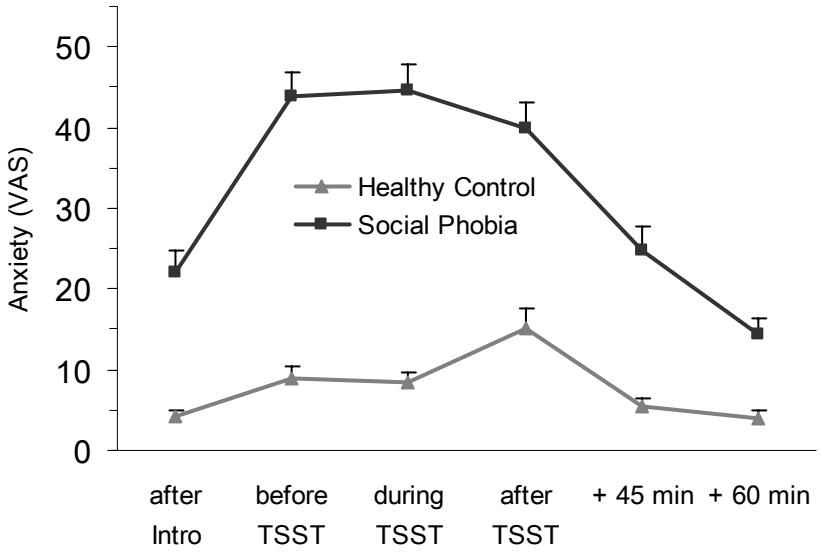

Figure 7-21: Mean (+SEM) anxiety in healthy controls (HC) and social phobia

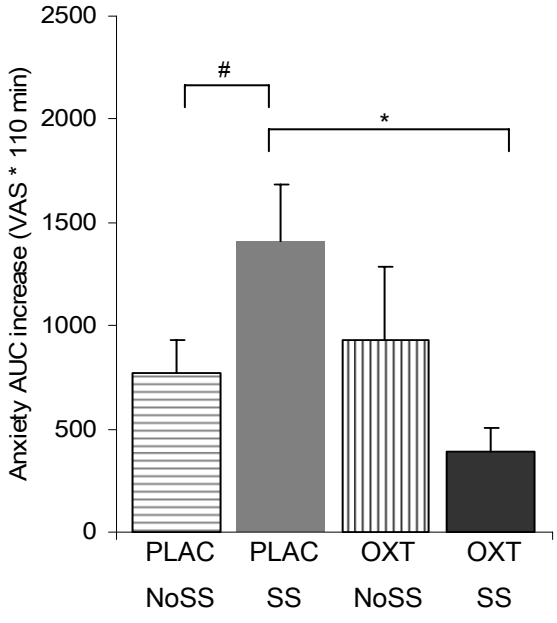

Figure 7-22: Mean (+SEM) AUC increase anxiety with placebo (PLAC) or oxytocin (OXT) and without social support (NoSS) or with social support (SS) (**= p<.001; * = p<0.05; # = p<.10)

There was a significant time by social support by oxytocin interaction (time × social support × oxytocin: $F_{(3.430,463.109)}$=3.569; p=.010; ε^2=.026) underlining lower increases in anxiety for participants with social support and oxytocin. In addition, there was a trend towards a time by oxytocin interaction ($F_{(3.430,463.109)}$=2.230; p=.075; ε^2=.016), indicating lower increases of anxiety over time for the oxytocin group. Again, three-way ANOVAS revealed that the $AUC_{G\ (anxiety)}$ (social phobia: $F_{(1,136)}$=74.560; p<.001; ε^2=.354) and the $AUC_{I\ (anxiety)}$ (social phobia: $F_{(1,136)}$=7.082; p=.009; ε^2=.049) were higher in patients compared to controls. In addition, there was a significant oxytocin by social support interaction for both the $AUC_{G\ (anxiety)}$ (oxytocin × social support: $F_{(1,136)}$=5.301; p=.023; ε^2=.038) and the $AUC_{I\ (anxiety)}$ (oxytocin × social support: $F_{(1,136)}$=5.308; p=.023; ε^2=.038) (Figure 7-22).

Physical reaction symptoms increased over time in response to stress (time effect: $F_{(3.499,472.363)}$=15.051; p<.001; ε^2=.100). Again, the social phobic patients showed a stronger physical reaction over time (time × social phobia: $F_{(3.499,472.363)}$=10.851; p<.001; ε^2=.074) and over the whole experiment (social phobia: $F_{(1,135)}$=25.956; p<.001; ε^2=.161).

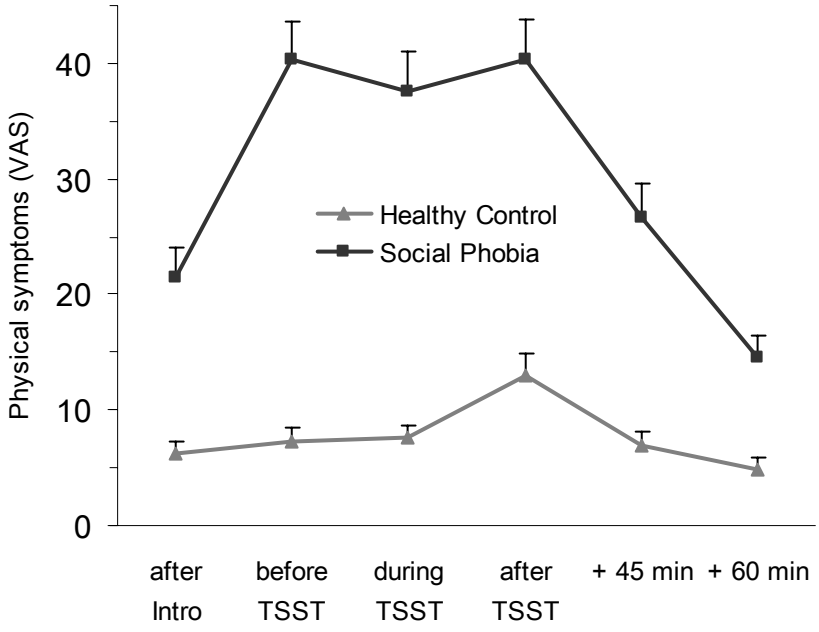

Figure 7-23: Mean (+SEM) physical symptoms in healthy controls (HC) and social phobia (SP)

In addition, the oxytocin group showed lower physical reaction over time (time × oxytocin: $F_{(3.499,472.363)}$=4.873; p=.001; ε^2=.035) and there was a significant main effect of oxytocin ($F_{(1,135)}$=5.502; p=.020; ε^2=.039) indicating lower physical symptoms in the oxytocin group throughout the whole experiment (Figure 7-24).

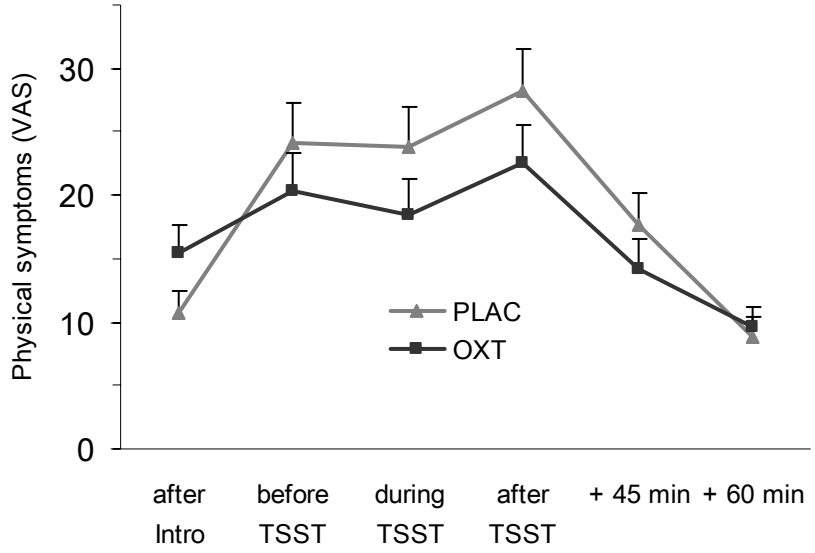

Figure 7-24: Mean (+SEM) physical symptoms in placebo (PLAC) and oxytocin (OXT)

Again, this effect occurred predominantly in the social phobic patients (time × social phobia × oxytocin: $F_{(3.499,472.363)}$=5.193; p=.001; ε^2=.037). These effects are once more supported by the results of two three-way ANOVAS with the area under curve.

The $AUC_{G\ (physical\ symptoms)}$ (social phobia: $F_{(1,136)}$=68.347; p<.001; ε^2=.334) and the $AUC_{I\ (physical\ symptoms)}$ (social phobia: $F_{(1,136)}$=15.950; p<.001; ε^2=.105) were higher in patients compared to controls.

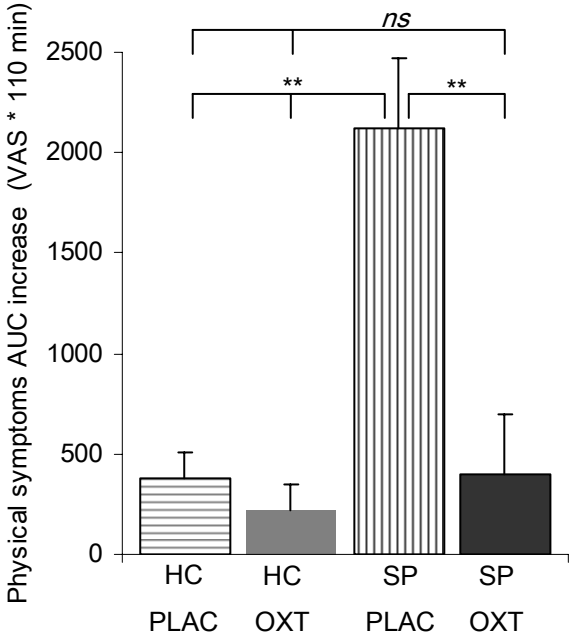

Figure 7-25: Mean (+SEM) AUC increase physical symptoms in healthy controls (HC) and social phobia (SP) with placebo (PLAC) or oxytocin (OXT) (**= p<.001; * = p<0.05; # = p<.10; ns=non significant)

In the oxytocin group, the $AUC_{I\ (physical\ symptoms)}$ was significantly lower (oxytocin: $F_{(1,136)}$=16.435; p<.001; ε^2=.108). Again, this effect was more pronounced in the social phobic participants (social phobia × oxytocin: $F_{(1,136)}$=11.365; p=.001; ε^2=.077) (Figure 7-25). Post-hoc comparisons revealed significant differences between social phobics with placebo and all three other groups. Finally, there was a trend towards a social support by oxytocin interaction (social support × oxytocin: $F_{(1,136)}$=2.780; p=.098; ε^2=.020), with lower levels of physical symptoms for participants with social support and oxytocin.

7.4 Discussion

Oxytocin and social support clearly reduced the psychobiological stress response in social phobic patients. This is the first study to investigate these effects in social phobia compared to healthy adults, providing an insight into the neurobiological and psychological underpinnings of the disorder.

The clear-cut difference between social phobic patients and controls in trait anxiety as well as social anxiety measures validates our diagnostic screening process and presents homogenous groups of controls and patients, which fortunately reduced further uncontrollable confounds.

Interestingly, the patients were less satisfied with their relationship, perceived less emotional and instrumental support (from their whole social network) and stated that they sought less social support compared to the healthy controls. These results are in line with studies investigating the quality of life in social phobia and again accentuate the deficit of these patients in protective social determinants (Wittchen, Fuetsch, Sonntag, Müller, & Liebowitz, 2000; Yonkers, Dyck, & Keller, 2001). Marital status and perceived social support represent important factors for emotional and physical well-being (Reblin & Uchino, 2008; Robles & Kiecolt-Glaser, 2003). Since all participants had been in a stable relationship for at least several years, we can nevertheless assume that these subjects were better off than the “average” social phobic patient, who mostly struggles greatly with dating (Hart, Turk, Heimberg, & Liebowitz, 1999; Robles & Kiecolt-Glaser, 2003). Our results therefore underline the importance of relationship satisfaction and social support in therapeutic approaches in social phobia.

In addition, social phobic patients showed higher baseline levels as well as stronger reactivity to stress in cortisol and higher baseline heart rate, indicating higher resting activity and stronger reactivity of HPA axis as well as higher baseline activation of SAM. Several reviews suspect both systems to be dysregulated in social phobia (Marcin & Nemeroff, 2003; Stein, 1998) but experimental studies reveal exaggerated HPA activity (Condren, O'Neill, Ryan, Barrett, & Thakore, 2002; Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001) and in other subjects blunted HPA function (Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001), while the experimental

evidence for the SAM indicates higher activity in social phobia. Social phobic patients showed higher heart rate during confrontation with an embarrassing task (Gerlach, Wilhelm, & Roth, 2003), and they showed higher cardiac reactivity in direct eye gaze (Wieser, Pauli, Alpers, & Mühlberger) and higher skin conductance even if the perception of social cues was unconscious (Tsunoda et al., 2008). Moreover, they already showed higher heart rate when anticipating a public speech (Davidson, Marshall, Tomarken, & Henriques, 2000). Taken together, the heightened levels of baseline cortisol and heart rate could, of course, reflect a very early anticipatory reactivity, but nevertheless represent, in line with the heightened HPA reactivity during the TSST, a potential health burden in social phobic patients.

Not surprisingly, social phobics showed significantly higher baseline levels in all anxiety and stress-related psychometric measures and always showed a very pronounced reactivity to the TSST. This is in line with the psychopathology of this disorder and underlines the capacity of the TSST as a strong and valid anxiety or stress stimulus for generalized social phobic patients. The previously reported physiological elevated stress response is again supported by this finding.

Moreover, there was a differential effect of social support treatment for social phobics compared to healthy controls. Whereas controls show a stronger decrease in calmness, the phobic patients showed a faster recovery and ultimately even higher levels of calmness than at baseline. Social phobic patients seem to profit more strongly from social support, which appears plausible since they have such a deficit in this domain (Wittchen, Fuetsch, Sonntag, Müller, & Liebowitz, 2000; Yonkers, Dyck, & Keller, 2001). On the other hand, they showed a much stronger stress response to the TSST. The baseline differences have already been accounted for in the ANCOVA and cannot be responsible for this effect.

There were protective effects of oxytocin and support for the whole group of participants. For all subjects, oxytocin reduced the initial increase in heart rate during the TSST and the combination of social support and oxytocin resulted in the lowest increase in anxiety on the visual analogue scale. To our knowledge, this is the first study to investigate the causal influences of oxytocin on autonomic reactivity. In animals, oxytocin was shown to produce negative inotropic and chronotropic effects

in rats (Costa-e-Sousa et al., 2005), effects on blood pressure maintenance, and baroreceptor reflex and to reduce sympathetic reserve (Jankowski et al., 2000; Michelini, Marcelo, Amico, & Morris, 2003; Petersson, 2002). Effects are different in the periphery (oxytocin receptors are abundant in the heart) (Gutkowska, Jankowski, Mukaddam-Daher, & McCann, 2000) and the central nervous system, respectively. Since the intranasal application of oxytocin should increase the availability of OXT in the brain, central nervous system mechanisms seem to be responsible for the lowering of heart rate in both control subjects and social phobic patients and are in line with animal research. Oxytocinergic fibers project, for instance, from the PVN to the locus coeruleus and the vagal nuclei, important regions for cardiovascular regulation (Petersson, 2002). It is proposed that central effects of oxytocin on heart rate are mediated via vagal efferent activity from the dorsal motor nucleus of the vagus (Porges, 2007). Heart rate is not an index of heart rate variability, but increasing heart rate reflects a shift in regulatory influence on the heart from parasympathetic (vagal) to sympathetic dominance and is in line with a parasympathetic withdrawal (Malik et al., 1996). Taken together, the lower increase in heart rate after oxytocin application suggests the peptide as a cardiovascular protective agent in stress reactivity in healthy controls as well as social phobics, indicating a reduced increase in sympathetic activity as well as assuming stronger vagal activity under oxytocin.

The combination of oxytocin and social support resulted in lower increase in anxiety (VAS) for all subjects. This result is in accordance with the findings of Heinrichs and colleagues (2003), who reported a trend towards an oxytocin by social support by time interaction for state anxiety before and after the TSST in their study on healthy subjects who were supported by their best friend.

Moreover, there was a differential effect of social support treatment for social phobics compared to healthy controls. Whereas controls show a stronger decrease in calmness, the phobic patients showed a faster recovery and ultimately even higher levels of calmness than at baseline. This finding might reflect the stronger need for social support in social phobia (Wittchen, Fuetsch, Sonntag, Müller, & Liebowitz, 2000)

Our results further indicate that social support and oxytocin are buffering treatments especially in social phobic stimulation. In social phobic patients, the increase in salivary cortisol was reduced by oxytocin. Moreover, these subjects showed the lowest increase in plasma cortisol. Social phobic patients who had received placebo showed the highest decrease in calmness, whereas patients with oxytocin did not differ from controls. Exactly the same was found with regard to state anxiety over the experiment. Patients who received oxytocin had the same increase in anxiety as the healthy controls but phobics with placebo showed a pronounced increase in state anxiety. And finally, patients with oxytocin experienced the same increase in physical symptoms as the healthy controls. Again, it is the patient group without any protective factor that shows the highest increase in perceived physical symptoms.

The combination of social support and oxytocin revealed buffering effects in heart rate in social phobia and brings to light an elevated response of subjects with only placebo treatment. Patients who received oxytocin and social support from their spouse had the overall lowest increase in heart rate. Patients with either support or oxytocin or the combination of both did not differ from healthy subjects in their heart rate increase. Social phobic patients already showed higher baseline heart rate. However, in the overall analysis they did not show higher reactivity to stress. It might be the case that there was simply not enough power to detect this effect since all three groups with either support, oxytocin or both showed normal increases. In animals, social isolation was recently shown to increase heart rate in female prairie voles (Grippo, Lamb, Carter, & Porges, 2007) and it has been demonstrated in numerous studies that social isolation in humans elevates the risk for several physical and mental disorders and even mortality after myocardial infarction (Ozbay et al., 2007; Reblin & Uchino, 2008). Moreover, anxiety disorders (including social anxiety) are correlated with coronary heart disease (Shen, Wachowiak, & Brooks, 2005). Both oxytocin and social support seem to buffer the increase in heart rate in social phobic patients. This finding further implies a role for the oxytocinergic system in the biological foundations of social support (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Heinrichs & Gaab, 2007; Ozbay et al., 2007; Uvnäs-Moberg, 1998).

The combination of oxytocin and support was also the most effective treatment for reducing avoidance in social phobics. This group differed significantly from all other phobic groups and showed even lower avoidance than all healthy controls. In avoidance, one factor alone was not enough to reduce avoidance in phobic patients. Only the combination of support and oxytocin was able to reduce avoidance. Social support in this case could have made the confrontation inescapable since the spouse was accompanying the patient to the lab and probably wanted to know about the experience of the patient later in the evening. However, only if the patient additionally had higher levels of oxytocin available did he experience lower subjective avoidance (and perhaps not only social pressure from the wife). But what might the effects of oxytocin have been in this situation?

It was found that oxytocin increases prosocial interaction, like trust in an interaction paradigm (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). In our study, this effect might have been resulted in a less negative encounter with the TSST. Moreover, oxytocin has previously been reported to reduce anxiety and subjective and objective stress response in healthy adults (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). In addition, oxytocin was able to reduce amygdala activation to several stimuli (Domes et al., 2007; Kirsch et al., 2005) and reduce the output from the amygdala to the brainstem (Kirsch et al., 2005), presumably by gabaergic inhibition of vasopressin neurons (Huber, Veinante, & Stoop, 2005). The latter mechanisms might be responsible for the dampening effect of oxytocin on the HPA and SAM as well as the subjective experience of anxiety, physical symptoms or avoidance.

Recently, oxytocin has been shown to shift gaze to the eye region in humans (Guastella, Mitchell, & Dadds, 2008) and improve the ability to infer others' mental states from eye regions (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). Usually, social phobic patients have persistent irrational beliefs about others' thoughts and evaluations when they undergo scrutiny by others. Since stress-induced cortisol has previously been shown to reduce memory for positive words (Domes, Heinrichs, Rimmele, Reichwald, & Hautzinger, 2004), one can imagine that the already very anxious attitude of the social phobic patient is raised dramatically under stress induced cortisol increase.

Oxytocin might have helped them to overcome their avoidance by dampening arousal and in addition making their perception of the TSST less catastrophic and more realistic. Of course, this does not leave them completely relaxed and without any agitation, but with an average stress response that makes it possible to deviate from their usual irrational beliefs and negative memories of previously encountered embarrassment. Adam Guastella and colleagues (2008) further found that with more oxytocin available in the brain, participants remembered more positive faces over negative or neutral faces. This means that the phobic patients might have retrieved fewer of their earlier negative memories regarding social situations during the TSST.
A very interesting finding by the group of Ray Dolan is in line with this finding (Petrovic, Kalisch, Singer, & Dolan, 2008). Participants were found to no longer evaluate previously aversively conditioned faces more negatively if they had received oxytocin. Oxytocin could have helped the patients to encounter the evaluating situation (TSST) without their strong burden of past catastrophic memories. Petrovic et al. (Petrovic, Kalisch, Singer, & Dolan, 2008) showed that attenuated activity of anterior medial temporal and anterior cingulate cortices was associated with oxytocin. This was also found by Baumgartner and colleagues in a social interaction paradigm (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008). After subjects received feedback on the betrayal by their counterparts, they continued to act prosocially and compared to the placebo patients showed lower activation in the anterior cingulate cortex, a brain area active in conflict monitoring as well as affective and anxiety processing. Precisely this area was shown to be more strongly activated in anxious individuals while performing an affective appraisal task (Simmons et al., 2008), and another study revealed higher glutamatergic signaling in the anterior cingulate cortex in social phobic patients (Phan et al., 2005). Oxytocin might reduce the activity of crucial brain structures such as the amygdala or ACC to an average level, elevating approach behavior and reducing avoidance behavior.

But why do social phobic patients benefit more strongly from oxytocin and social support? Again, it should be emphasized that the TSST resembles a genuine social stressor that acutely triggers psychopathological symptomatology in social phobia: the physiological system was kicked off, cortisol and heart rate increased even more strongly and much earlier than in healthy controls and subjectively, the social phobic patients experienced strong agitation, bad mood, weariness, high increase in anxiety

and physical symptoms (such as blushing, palpitation etc.). Finally - and also characteristic for the disorder - they had an increasing desire to escape the situation and avoid the confrontation in the TSST. Social anxiety seems to develop from 'behavioral inhibition' in early childhood and several studies suggest neurobiological dysregulation in social phobic patients (vigilance, hyperarousal and cognitive dysfunction).

The impact of environmental towards genetic factors resembles approximately two thirds to one third and many authors assume early adverse childhood experience in these patients (Kessler, Stang, Wittchen, Stein, & Walters, 1999; Marcin & Nemeroff, 2003). Moreover, a vast body of evidence from animal literature and growing evidence in human research assumes a dysregulation of the oxytocinergic system in the development and the psychopathology of several disorders including autism spectrum disorder, obsessive compulsive disorder, borderline personality disorder or early trauma (Bartz & Hollander, 2006b; Carter, 2007; Heinrichs & Domes, 2008). One could hypothesize that patients suffering from social phobia show an altered oxytocinergic system reflecting differing density distribution of receptors, altered receptor sensitivity and lower release of oxytocin. A combination of impaired social skills, neurobiological imbalance (including secretion and receptor sensitivity to oxytocin) as well as low social support (all factors impaired chronically) might make social phobic patients highly sensitive to socially relevant treatment like social support or oxytocin. One study has already shown altered sensitivity to intranasal oxytocin in participants with early parental separation resulting in lower cortisol increase after stress (MeinIschmidt & Heim, 2007). Further studies need to investigate the direct mechanism of the oxytocinergic action, disentangling the possible paths of action especially in psychiatric disorders of the social domain.

Taken together, oxytocin alone already attenuated the stress response in both groups (healthy controls and social phobia) and the combination of oxytocin with social support also did so. But most importantly, it was the group of social phobic patients that showed a strong beneficial effect from these two treatments, resulting in a stress reactivity that was not different from healthy controls, or was even lower, as it was shown in terms of the increase in avoidance. These results appear to be very promising in terms of behavioral therapy and exposure techniques. Reducing

psychobiological reactivity increases the chance of successful behavioral exposure, role-play and other social interactions in social phobic patients. This could increase the treatment efficacy for psychotherapy in this disorder and improve quality of life and health in these patients.
However, as the study sample investigated here comprised social phobics with low comorbidities who were in stable romantic relationships, generalizations should be made with caution.

Future studies should further investigate the quality of the social support as well as the mediating process of subjective relationship quality and satisfaction with social support on the effects of oxytocin and support in stress. In addition, experiments on long-term treatment effects as well as dose-response studies need to be conducted in healthy subjects and patients with social phobia. To disentangle the vagal and sympathetic output and the effects of oxytocin on either component, measures of heart rate variability should be analyzed. Finally, the effects of oxytocin as well as social support need to be evaluated in imaging studies that also take into account genetic variation.

8 General Discussion

Two studies on the neuropeptidergic foundations of human social behavior were presented. The first comprised the effects of OXT and AVP on altruistic punishment in healthy men. The second took a clinical approach and investigated the modulation of anxiety and stress response by OXT in social phobia and healthy controls. Both experiments were critically discussed regarding the underlying biological mechanisms.

8.1 Study I: Summary, methodological considerations and limitations

OXT and AVP have been repeatedly shown to modulate social behavior both in animals and in humans (Heinrichs & Domes, 2008; Landgraf & Neumann, 2004; Neumann, 2007). Whereas OXT increases trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) and improves positive social functioning, AVP was found to promote and regulate aggression in humans (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998; Thompson, Gupta, Miller, Mills, & Orr, 2004; Thompson, George, Walton, Orr, & Benson, 2006). What are the effects of OXT and AVP on prosocial aggressive behavior? It was expected that AVP increases punishment in humans while OXT reduces it.

In a randomized and double-blind placebo controlled study, a total of 288 healthy male subjects participated in a social decision making task. They received either OXT, AVP or placebo and were assigned to one of three roles. As ‘player A’ they first had to make a decision on whether they show trust and transfer their money. If they do so, they could subsequently punish the other participants who had betrayed them.

Punishing altruistically implies reducing the other`s endowment (this is costly!). Since the interactions where anonymous and one-shot, the sanctioning is regarded as altruistic. If the other person behaves better after the punishment, the ‘punisher’ will not profit, because he will never be paired with that person again. Altruistic punishment represents a pro-social gift towards the community and on the individual`s level an aggressive act.

We found that AVP increased the frequency of punishment compared to placebo and OXT. The mean number of punishment points applied as well as the frequency of maximum punishment was significantly higher for AVP compared to OXT. If the participants were coupled with persons who were not permitted to decide but were forced by a die to betray, there was no effect of AVP or OXT on punishment. The peptides had no influence on subjective ratings such as mood, anger or anxiety and also did not influence cortisol, testosterone, heart rate or blood pressure.

To our knowledge, this is the first study to investigate causal influences of AVP and OXT simultaneously in social behavior. As it was suggested in earlier studies from humans (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998; Thompson, Gupta, Miller, Mills, & Orr, 2004; Thompson, George, Walton, Orr, & Benson, 2006) and animals (Caldwell, Lee, Macbeth, & Young, 2008; Ferris, 2005), AVP enhances aggression. One possible route of modulation would be activation of the amygdala (Debiec, 2005) with an imbalance towards reduced prefrontal inhibition (Siever, 2008) or modulation of AVP in reward-related areas (Insel, Winslow, Wang, & Young, 1998). Other empirical studies revealed an AVP-driven negativity bias (Thompson, Gupta, Miller, Mills, & Orr, 2004; Thompson, George, Walton, Orr, & Benson, 2006) that might have added insult to injury if participants had been betrayed in our study. OXT might also have been unable to modulate punishment, since we found no increase in anxiety or stress in our study. Presumably, OXT might be more relevant in altruistic reward and does not impact on altruistic punishment.

Our design was not able to investigate trust and altruistic punishment at the same time. Due to a ceiling effect, we were not able to investigate the effects of OXT and AVP on trust. Future studies should investigate these effects to reveal the action of AVP on trust in humans.

In our clear-cut behavioral experiment, we revealed the effect of AVP on altruistic punishment. It is now of further interest whether this effect holds true for different aggressive behaviors and different contexts. Do the same results occur, for instance, in borderline personality-disordered patients and might their aggression be reduced by OXT?

In addition, functional imaging can investigate the effect of AVP in the brain. While a series of fMRI studies have already been conducted to study the effects of OXT in the brain, such studies are lacking for AVP. The AVP and OXT receptor distributions should also be further clarified in humans (radiolabeled ligands for OXT and AVP receptors are needed).

Dose-dependent studies would be important to further strengthen the link from AVP to pathological aggression. Is there a critical dose, a linear increase or any other relationship between AVP application and aggressive behavior in humans? These questions need to be combined with genotyping of the receptor gene polymorphisms since they have been shown to have an impact on brain activation (Meyer-Lindenberg et al., 2008) and might also modulate the effects of intranasally applied neuropeptides.

Further studies are needed to truly disentangle the neural mechanisms of AVP and OT in humans and to investigate the behavioral role of both peptides also in psychiatric disorders like borderline personality disorder, social anxiety or autism. Moreover, studies should try to disentangle the interplay of the two peptides. Their interplay in modulating behavior and psychopathology is of important interest. Whether a ‘ying yang action’ on brain circuits and behavior in humans holds true needs to be proven in the future.

8.2 Study II: Summary, methodological considerations and limitations

Social phobia ranks as the third most common mental disorder and is characterized by strong and persistent fear of social encounters and scrutiny by others. The disorder impairs social functioning and leads to poor quality of life and has a great many comorbidities (Wittchen & Fehm, 2003). Neurobiological changes have been discussed, and imaging studies have repeatedly demonstrated hyperactivation of the amygdala to be crucial in social phobia (Etkin & Wager, 2007). Common pharmacological and psychotherapeutic treatments show 30-65 % non-responders (Davidson, 2003), which implies a strong need for further improvement of therapeutic strategies. Effective treatment for social phobia needs to bring under control fear, avoidance and physiological symptoms, restore self-esteem and social functioning (improve quality of life) and treat the associated comorbidity.

OXT has been shown to reduce fear, biological and psychological stress response as well as amygdala activation and, moreover, elevates trust in healthy humans, and the effects on stress were even pronounced when combined with social support (Domes et al., 2007; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirsch et al., 2005; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). A connection between OXT and social phobia has been repeatedly assumed but not yet proven (Heinrichs & Domes, 2008; Heinrichs & Gaab, 2007).

The effects of OXT in social phobia and, further, the interaction of OXT and social support were assumed to dampen the psychobiological stress response.

In a randomized controlled double-blind study, 65 patients with social phobia and 79 healthy controls were assigned to four treatment conditions, resulting in a total of eight groups. Subjects were confronted with a psychosocial stress paradigm, the ‘Trier Social Stress Test’ (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirschbaum, Pirke, & Hellhammer, 1993). Fifty minutes before the stress, they received either OXT or placebo, and before the TSST, they were given social support by their spouse or not.

We found stress-dampening effects for OXT and for the combination of OXT and social support in the whole group. Of significance was the finding that the social

phobic patients showed the best treatment response. If treated with OXT, phobic patients showed lower saliva and plasma cortisol, a lower decrease in calmness by the stressor, less increase in state anxiety and fewer physical symptoms. The combination of OXT and social support dampened anxiety in all subjects and, moreover, the heart rate reactivity and avoidance of the social phobics. The social phobics who received OXT and social support had the overall lowest increase in avoidance compared to all other groups including the controls. The treatments OXT and support led to a stress and anxiety response that was comparable to healthy controls.

This is the first study to directly investigate cardiovascular effects of OXT. We found reduced activity both in healthy controls and social phobics. These results are in line with animal research (Costa-e-Sousa et al., 2005; Jankowski et al., 2000; Michelini, Marcelo, Amico, & Morris, 2003; Petersson, 2002) and might be mediated by direct action of OXT at the heart or via increased vagal efferent activity from the dorsal motor nucleus of the vagus by OXT (Porges, 2007).

Moreover, we discussed three possible routes for the effects of OXT on dampening HPA activity and subjective experience of avoidance, anxiety and physical symptoms. One route lies in actions at the amygdala, which have been discussed previously (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Domes et al., 2007; Huber, Veinante, & Stoop, 2005). Another possibility might be increased activation of reward-related areas, which might have led to different experiences of the stress situation (Insel, 2003). Impairment in mesocorticolimbic pathway and dopamine turnover was found in patients with social phobia. Social phobic patients do not perceive social encounters to be as rewarding as others do (Coupland, 2001; Sareen et al., 2007; Schneier et al., 2000; Schneier et al., 2008). In addition, Petrovic et al. (2008) show that attenuated activity of anterior medial temporal and anterior cingulate cortices was associated with oxytocin. This was also found by Baumgartner and colleagues in a social interaction paradigm (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008). After subjects received feedback on the betrayal by their counterparts, they continued to act prosocially and compared to the placebo participants showed lower activation in the anterior cingulate cortex, a brain area active in conflict monitoring as well as affective and anxiety processing.

Precisely this area was shown to be more strongly activated in anxious individuals while performing an affective appraisal task (Simmons et al., 2008), and another study revealed higher glutamatergic signaling in the anterior cingulate cortex in social phobic patients (Phan et al., 2005).

Earlier experimental findings additionally show a shift towards positive memories by OXT (Guastella, Mitchell, & Mathews, 2008), which would mean a decrease in negativity bias of social phobic patients. Moreover, OXT was shown to reduce affective response towards aversively conditioned faces (Petrovic, Kalisch, Singer, & Dolan, 2008). Since conditioning is assumed to be important in the etiopathology of social phobia, OXT might have helped to overcome the avoidance and fear by weakening the stimulus response interconnection. Participants no longer evaluated previously aversively conditioned faces more negatively if they had received oxytocin. Oxytocin could have helped the patients to encounter the evaluating situation (TSST) without their strong burden of past catastrophic memories.

In the present study, OXT might have reduced the activity of crucial brain structures such as the amygdala or ACC and increased activation in reward-related areas, which might have increased approach behavior and reduced avoidance behavior. This might have led to fewer anxiety and stress symptoms on both a psychological and physiological level.

After a single-dose application, OXT alone and in interaction with social support was able to reduce symptoms that are main therapeutic targets in social phobia: fear, avoidance and physiological symptoms. The participants could not tell whether they had verum or placebo and did not report side-effects. This is important for attribution and effectiveness of behavioral methods like confrontation, where strong anxiolytic drugs like benzodiazepines are a counter indication since they blur the psychological effectiveness of the behavioral technique and lead to use as-needed. This might lead to dependency in the long run and has strong side effects. One might expect that the restoration of self-esteem and social functioning (improvement of quality of life) might be second-line action of OXT but this needs to be investigated.

Studies on stress reactivity in social phobia have found hypo- as well as hyperreactivity (Coupland, 2001; Marcin & Nemeroff, 2003) of the HPA axis. Our results speak for overall higher baseline activation and stronger stress reactivity. One limitation lay in the relatively small group sizes, especially for the biological measures.

Moreover, our restriction to social phobia without comorbidity does not reflect a realistic sample since social phobia is highly comorbid (Wittchen & Fehm, 2003). The comorbidity might further account for different physiological changes. In addition, it would be valuable to include a second control group (e.g. generalized anxiety disorder). If support and OXT only dampen anxiety and stress response in social phobia, one could assume truly social effects. Otherwise, the effect could be anxiolytic (via amygdala reduction) irrespective of a social component of the situation or the disorder.

Our treatment showed significant effects, but in addition, the baseline levels of nearly all physiological and psychological measures were elevated. This might be due to general hyperactivity in social phobia but could on the other hand reflect very early and pronounced anticipation of stress. Further studies should evaluate psychobiological measures either on a separate baseline testing day or obtain measures via ambulatory measurement. This would rule out the spill-over of anticipation.

In addition, we found lower quality of social support and less relationship satisfaction in social phobia. This phenomenon has been found previously (Safren, Heimberg, Brown, & Holle, 1996; Wittchen, Fuetsch, Sonntag, Müller, & Liebowitz, 2000). It would be of interest to establish whether the quality of support modulates the stress response in social phobia and whether the experimental social support differs according to whether the relationship quality is good or bad. Without doubt, stable romantic relationships represent an important protective factor especially in social phobia (Hart, Turk, Heimberg, & Liebowitz, 1999), but if the quality of the relationship is low, it might turn into a chronic stressor.

Since we investigated a standardized social stress paradigm, it might be of interest whether this situation was more or less relevant to the patients. The group statistics reveal that it was relevant, but show a high variance among patients. It might be of special interest to either evaluate the stressor with regard to its relevance for the personal symptomatology or to test a series of different situations. Our study design could also be of high interest in the area of exposure therapy. This of course leads to lower internal validity and higher noise. The clinical implications would be highly important and might improve the individual therapy.

Moreover, there are several methodological issues with regard to OXT that should be taken into account. We demonstrated the single-dose effect of the peptide. But are there long-term effects of this single-dose application? What are the effects of long-term application? Studies investigating daily application of OXT need to be undertaken. In addition, dose-response studies are of special interest. We know nothing about behavioral effects of doses lower or higher than 24 international units. Animal studies have shown that different doses have distinct effects (Bales et al., 2007; Popik, Vetulani, & van Ree, 1992). Finally, it was shown that early developmental effects occur in the OXT system. Parental separation influenced the sensitivity towards the peptide (Meinlschmidt & Heim, 2007). Studies on OXT application need to report early adverse life events to at least have a rough proxy. In addition, genotyping of OXT receptor gene polymorphisms might account for important variance.

In addition, functional imaging studies as well as PET studies with radiolabeled ligands for OXT receptors binding would increase the knowledge about the functional role of OXT in the brain and, moreover, on the receptor distribution in different brain areas.

Studies on the long-term effects of OXT treatment in combination with cognitive behavioral therapy are required. A randomized controlled trial on the effects of OXT in cognitive behavioral group therapy in social phobia is currently being conducted by our group. If the associated comorbidities are also dampened by the combination of OXT and CBT, one could conclude that all important therapeutic areas are targeted

and the treatment represents a promising therapeutic approach towards social phobia.

Before this conclusion can be drawn, there is much work still to be done. Nevertheless, it should be noted that one common comorbidity is depression. Depression, in turn, has repeatedly been assumed to be modulated by AVP and OXT and it would be worth investigating the effects of the peptides in affective disorders (Berton & Nestler, 2006).

8.3 Neuropeptidergic modulation of social behavior, aggression, anxiety and stress

These are the first results to reveal an increase in aggression for AVP in healthy men, whereas OXT shows clear anxiolytic and stress-dampening effects in both healthy controls and patients with social phobia. These findings contribute important evidence for the modulation of social behavior by OXT and AVP and their importance in psychopathology. The results on enhancing aggression in humans lend important weight to AVP and its share in psychopathology. The positive treatment effects in social phobia appear promising and provide hope with regard to new treatment approaches in this disorder.

Central nervous system sites of action for both peptides might be the mesocorticolimbic pathway and interactions with dopamine (Insel, 2003), the anterior cingulate cortex (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Petrovic, Kalisch, Singer, & Dolan, 2008) and finally, the amygdala and brainstem regions including the autonomic nervous system, which are the best studied aspects in this regard (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Domes et al., 2007; Huber, Veinante, & Stoop, 2005; Meyer-Lindenberg et al., 2008; Petrovic, Kalisch, Singer, & Dolan, 2008). Except for the dopaminergic pathways, all of these structures seem to be influenced by both peptides and for some functions even in a converse fashion. As discussed, these pathway need to be evaluated in future research. However, in addition to the behavioral results, these neural mechanisms underline the strong interrelatedness of the two peptides and hint at a corporate modulation of social behavior for both peptides.

The results are perfectly in accordance with the previous research that was discussed earlier and is summarized in Heinrichs and Domes (2008). They present a model on the interactions between anxiety and stress, social approach behavior, and the oxytocinergic system and how this system might be approached in psychopathology (e.g. autism, social phobia) (Figure 5-1).

But can our results be embedded into a model of health and psychopathology and further explain the etiology and maintenance of disorders related to impaired social functioning? We discussed the social domain from highly prosocial towards highly asocial behaviors and hypothesized health to be located in the center. This does not mean 'zero' sociality but rather a balance of pro-social behavior and also aggressive behavioral components. According to circumstances, either one or the other tendency comes to the forefront and both occur in healthy functioning. We reported altruistic punishment as an aggressive act. This is a sanction towards free-riders that is important for maintaining cooperation in societies and is usually driven by non-selfish motives (Fehr & Fischbacher, 2004), although it was shown to activate the dorsal striatum (de Quervain et al., 2004). We called this kind of aggression 'pro-social', which includes defensive aggression rather than instrumental aggression (Siever, 2008). It implies that the individual or the community is threatened and one needs to 'fight for your right' (or the right of siblings, family, friends or your community). In healthy humans, these acts stay within the excepted behavioral norms but nevertheless can be seen as aggressive. As described earlier for the stress response, this defensive aggression is nothing 'evil' per se. Only if taken to extremes and leading to violent or reactive aggression can it become harmful for all involved persons.

Psychopathologies that include such elevated levels of aggression are subgroups of patients with borderline personality disorder, who show high reactive aggression or, on the other hand, patients with social phobia who are partly also high in aggression, but usually their 'shy' temperament dominates, resulting in very poor social functioning of not only positive but also aggressive social encounters. For example, they have strong impairments in negotiating directly with authorities and asserting their rights.

Figure 8-1 integrates the action of AVP and the behavior of prosocial aggression into the model of Heinrichs and Domes (2008) taking into account anger as well as early developmental and genetic influences and environmental demands and finally defensive aggression. In a state of health, the OXT and AVP system are delicately balanced. AVP enhances amygdala activation as well as anger, anxiety and stress and might directly or via the route of anger, anxiety and stress increase social aggression or, as reported, altruistic punishment.

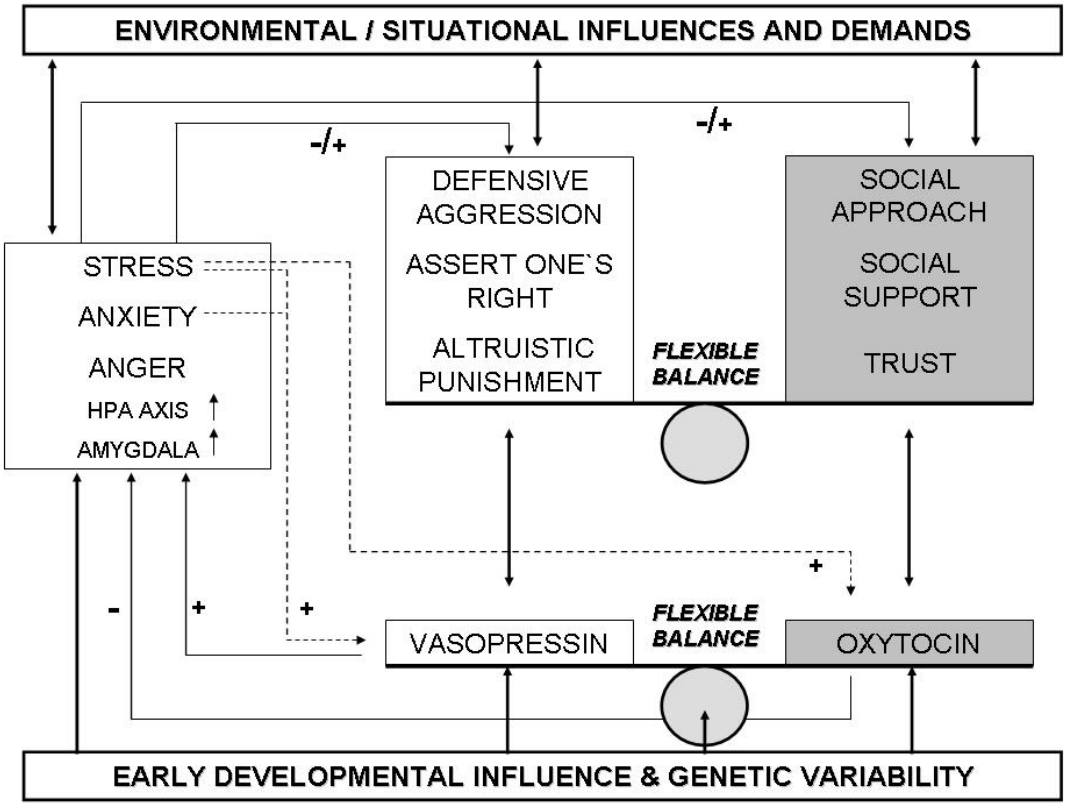

Figure 8-1: Fine-tuned modulation of prosocial behavior and social aggression in humans; effects of OXT, AVP, early developmental, genetic and environmental influences

On the other side of the balance is OXT. It can reduce amygdala activation, stress and anxiety and might directly or via the route of stress and anxiety reduction lead to prosocial behavior. Both peptides as well as both behavioral aspects are kept in flexible balance in healthy humans.

In psychopathology, an imbalance of the peptide systems might lead to imbalance in physiological as well as behavioral processes. In social phobia, the balance might tilt towards the OXT side, leading to increased anxiety, stress, HPA functioning and amygdala activation and resulting in strong social impairment. Our results argue that

suitable psychotherapy and OXT application might be a possibility to adjust the balance.

In borderline personality disorder, an imbalance of the neuropeptidergic system and increased AVP action might lead, via stress, anxiety and hyper-arousal, towards pathological increase in aggression and other dysfunctional patterns (self-harm) to reduce tension. Again, it might be hypothesized that dialectic behavioral therapy in combination with OXT application will be able to calm the system and rebalance it. Our results further strengthen the link from AVP towards aggression. Although in our study OXT was not able to reduce punishment significantly compared to placebo, it showed significantly less punishment than AVP. This dampening effect might be pronounced in psychopathology where aggression and AVP input is strongly increased. In his current review, Siever (2008) reports an inverse correlation between CSF OXT and aggression (unpublished data by Coccaro et al., 2006, cited after Siever, 2008).

These results further strengthen the important interplay of the peptides in aggression and imply a role for OXT in dampening social aggression. The effects of OXT in our study were also most pronounced in the impaired social phobic group.

As in the original model by Heinrichs and Domes (2008), therapeutic targets are behavioral where psychotherapeutic techniques would act on (CBT in social anxiety or DBT in borderline personality disorder). Behavioral changes should then lead to better balance of the neuropeptide system. To further improve therapy and provide a biological basis to start from, OXT agonist and possibly in future also AVP antagonist application might act as a ‘catalyzer’ that better prepares or enables patients for psychotherapeutic interventions .

Finally, the modulatory effects of early developmental influences and genetic variability as well as environmental demands need to be taken into account, which makes the interactions even more complicated. In addition, different receptor sensitivity, distribution as well as differences in peptide synthesis and secretion and, moreover, multiple neurotransmitter interactions are important to gain a full understanding of the behavior. Last but not the least, possible gender effects need to

be considered and investigated. Against this background, the proposed model reflects only a very simplified schematic outline.

To understand the multimodal interactions of the social neuropeptide system, a multi-method, multi-disciplinary approach is needed that unifies basic animal and human research with translational and clinical approaches. Although research in the field of neuropeptides and their importance in behavior and psychopathology is growing tremendously, many questions still remain to be answered.

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