On oxytocin and social behavior

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Cover illustration: *Hector taking leave of Andromache: the Fright of Astyanax* by Benjamin West

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To Jess

second star to the right
and straight on till morning

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ABSTRACT

Complex social cognitive processes underlie social behavior. Oxytocin has long been recognized as crucial in social behavior in animals, but its role in regulating human social cognition and behavior is less clear, particularly with regard to endogenous oxytocin. The aims of this thesis were to investigate (i) how endogenous oxytocin affects face and emotion recognition in humans, (ii) how it may modulate social impairments in autism spectrum disorder and antisocial behavior, (iii) how exogenous (intranasal) oxytocin may influence the salience of human faces, and finally (iv) the role of endogenous oxytocin in zebrafish social behavior.

We investigated endogenous oxytocin by studying genetic variation in oxytocin-related genes, and found that oxytocin influences social cognition in humans, specifically via modulation of face recognition (Paper I) and via modulation of emotion recognition in women (Paper II). In addition, we found tentative associations between variation in oxytocin-related genes and autistic-like traits in the general population (Paper III), and showed that variation in the oxytocin receptor gene is associated with antisocial behavior in men (Paper IV). We also showed that exogenous (intranasal) oxytocin acts to increase the salience of human faces (Paper V), a mechanism that may underlie its behavioral effects. Finally, we demonstrated that an oxytocin receptor antagonist decreases social preference in adult and larval zebrafish (Paper VI).

In conclusion, this thesis confirms the importance of endogenous oxytocin for social cognition in humans, and demonstrates one mechanism by which exogenous oxytocin may act. Furthermore, we established an animal model for future research on the oxytocin system.

Keywords: oxytocin, social cognition, autism, antisocial behavior, zebrafish

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SAMMANFATTNING PÅ SVENSKA

Socialt beteende underbyggs av komplexa kognitiva mekanismer (social kognition), som gör det möjligt för oss att till exempel känna igen personer vi tidigare träffat, och att korrekt identifiera de känslor de uttrycker. Detta gör det möjligt för oss att fungera i sociala situationer, där vi behöver ge korrekta gensvar.

Oxytocin har en väl etablerad betydelse för socialt beteende hos djur, men dess betydelse för socialt beteende och social kognition hos människa är mer oklar. Studier på oxytocin administrerat via nässpray har gett ett flertal intressanta resultat, men vilken roll kroppseget oxytocin spelar har varit svårt att studera. Genom att titta på variation i oxytocin-relaterade gener kan man dock etablera en länk mellan kroppseget oxytocin och socialt beteende.

Många psykiatriska sjukdomar karaktäriseras av svårigheter med sociala interaktioner – ett exempel på detta är autismspektrumstörning, där svårigheter med sociala interaktioner är ett kärnsymptom. Det är därmed av yttersta vikt att finna specifik och effektiv farmakologisk behandling for sociala svårigheter, vilket idag saknas. Oxytocin har föreslagits som behandling, men den underliggande mekanismen bakom dess effekter är dock inte klarlagd.

I denna avhandling kunde vi visa att kroppseget oxytocin påverkar hur väl man känner igen ansikten, och att detta är kopplat till aktiveringsgrad i hjärnregionen amygdala. Vi kunde även koppla kroppseget oxytocin till känsloigenkänning hos kvinnor. Vidare undersökte vi hur endogent oxytocin påverkar svårigheter med sociala interaktioner, och kunde visa att det kan influera autismliknande drag i normalpopulationen såväl som aggressivitet hos män. Experimentellt påvisades också hur oxytocin givet i form av nässpray påverkar visuell perception, där oxytocin ökar hur framträdande ett mänskligt ansikte är i medvetandet. Slutligen visas att kroppseget oxytocin spelar roll för socialt beteende hos zebrafiskar.

Sammanfattningsvis understryker denna avhandling oxytocinets betydelse för mänsklig social kognition, och undersöker en mekanism genom vilken det kan verka. Vi etablerar även en djurmodell för att ytterligare studera hur oxytocin påverkar hjärnan vid socialt beteende.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Westberg, L., Henningsson, S., Zettergren, A., Svärd, J., **Hovey, D.**, Lin, T., Ebner, N., Fischer, H. (2016). Variation in the oxytocin receptor gene is associated with face recognition and its neural correlates. *Frontiers in Behavioral Neuroscience 10*, 178.

II. **Hovey, D.**, Henningsson, S., Cortes, D. S., Bänziger, T., Zettergren, A., Melke, J., Fischer, H., Laukka, P., Westberg, L. (2018). Emotion recognition associated with polymorphism in oxytocinergic pathway gene *ARNT2*. *Social Cognitive and Affective Neuroscience 13*, 173.

III. **Hovey, D.**, Zettergren, A., Jonsson, L., Melke, J., Anckarsäter, H., Lichtenstein, P., Westberg, L. (2014). Associations between oxytocin-related genes and autistic-like traits. *Social Neuroscience 9*, 378.

IV. **Hovey, D.**, Lindstedt, M., Zettergren, A., Jonsson, L., Johansson, A., Melke, J., Kerekes, N., Anckarsäter, H., Lichtenstein, P., Lundström, S., Westberg, L. (2016). Antisocial behavior and polymorphisms in the oxytocin receptor gene: findings in two independent samples. *Molecular Psychiatry 21*, 983.

V. **Hovey, D.**, Martens, L., Laeng, B., Leknes, S., Westberg, L. The effect of intranasal oxytocin on visual processing and salience of human faces. *Submitted manuscript*.

VI. Landin, J., **Hovey, D.**, Xu, B., Lagman, D., Zettergren, A., Larhammar, D., Kettunen, P., Westberg, L. Endogenous oxytocin regulates social preference in zebrafish. *Submitted manuscript*.

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ABBREVIATIONS

ALT	Autistic-like trait
ARNT2	Aryl hydrocarbon receptor nuclear translocator 2
ASD	Autism spectrum disorder
A-TAC	Autism-Tics, ADHD and other Comorbidities inventory
AVP	Arginine vasopressin
AVPR	Arginine vasopressin receptor
CATSS	Child and Adolescent Twin Study in Sweden
CD38	Cluster of differentiation 38
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
ERAM	Emotion Recognition Assessment in Multiple modalities
fMRI	Functional magnetic resonance imaging
LHA	Life History of Aggression questionnaire
OXT	Oxytocin (mammals)
OXTR	Oxytocin receptor (mammals)
Oxtr	Oxytocin receptor (zebrafish)
Oxtrl	Oxytocin receptor like (zebrafish)
SBN	Social behavior network
SDM	Social decision-making network
SIM1	Single-minded 1
SNP	Single nucleotide polymorphism
SRD	Self-Reported Delinquency scale
TCHAD	Twin Study of Child and Adolescent Development

PREFACE

Social interactions characterize human life from the moment we are born to the moment we die. The ability to function adequately, in the multitude of daily social transactions we participate in, is crucial to our well-being. The sophistication of social behavior requires a set of highly specialized cognitive skills. This social cognition encompasses several different phenomena, such as the ability to recognize and remember other individuals; to ascertain some notion of their state of mind by recognizing their emotional expressions; to imagine and understand their idiosyncratic emotional and cognitive perspectives, needs, and aspirations; and to respond appropriately to these socially-induced internal states and the external social environments.

The importance of the neuropeptide oxytocin (OXT) for social behavior and its associated social cognition in animals is well-established [1-5]. While there is support for involvement of this neuropeptide in human social behavior and cognition, the precise role of endogenous OXT in humans remains somewhat unclear, in part due to the difficulties of measuring OXT levels in a satisfactory way [6]. However, studying genetic variation in OXT-related genes provides an opportunity to establish a link between endogenous OXT and social cognition and behavior in humans.

Several psychiatric disorders are characterized by difficulty in social functioning [7], including autism spectrum disorder (ASD), where social impairments are a core feature [8]. It is of great importance to find targeted and effective treatment for social impairments. While OXT is an appealing treatment candidate, the mechanism and the neural underpinnings of the effects of exogenous (and endogenous) OXT on social cognition are still unclear.

The aims of this thesis were to investigate (i) how endogenous oxytocin affects face and emotion recognition in humans, (ii) how it may modulate social impairments in autism spectrum disorder and antisocial behavior, (iii) how exogenous (intranasal) oxytocin may influence the salience of human faces, and finally (iv) the role of endogenous oxytocin in zebrafish social behavior.

This text aims to provide a background, summarizing relevant research on OXT as it pertains to the included papers. Chapter 1 briefly discusses social behavior, including the importance of social impairments in

psychiatric disorders, using ASD as an example. Chapter 2 introduces OXT as a molecule – its structure, receptor, evolution, and current literature about its location and function in the brain. Chapter 3 examines the role of OXT in social behavior and social cognition. Chapter 4 summarizes the findings of the studies included in this thesis, and finally, a concluding discussion is found in Chapter 5. The Appendix briefly discusses methodology used in the various papers.

1 SOCIAL BEHAVIOR

In Song VI of The Iliad [9], Trojan prince Hector meets his wife Andromache and their son Astyanax at one of the gates of Troy, sharing a moment with them prior to returning to battle with the Greeks. The scene encompasses the interactions between husband and wife, and between parents and child. Hector reaches for his son, but his plumed helmet obscures his face and scares the child. Removal of the helmet facilitates face recognition, and his son is no longer frightened. Hector is also able to perceive the grief of his wife and attempts to comfort her, before he ultimately returns to the battle and is killed by Achilles.

This scene describes characteristics of social interactions: the ability to convey emotion [10], and *social behavior*, here defined as behavioral responses to socially relevant stimuli. The passage highlights the body language of Hector, Andromache, and the young Astyanax: Hector smiles, Andromache sighs and weeps, and the child cries with fear. More importantly, when the child displays fear, Hector can interpret that, understands that his visage is altered by the plumed helmet on his head, and removes it, whereupon Astyanax happily lets his father hold him.

Social behavior is present in virtually all species of animals, from insects [11] to humans. Honey bees display brood care, defensiveness, aggression, and an intricate dance language [12]. Zebrafish form cohesive shoals, and display coordinated motion, territorial aggression, and kin preference [13]. Monk parakeets form monogamous pairs, share foraging information, and establish dominance hierarchies [14]. Non-human primates share many of the features of human social culture, such as symbolic elements in communication, and a rich emotional range which can be clearly displayed – indeed, the term "social culture" has been applied to non-human primate interactions [15]. Humans also exhibit "theory of mind" – i.e. the ability to take another individual's perspective, knowing that other people know, want, and feel things, and the ability to perceive their mental state [16, 17].

Social behavior is thus an incredibly diverse phenomenon, and terms that were previously used to describe particular behaviors, such as "sociality" and "prosocial behavior", have gradually become more broadly applied to encompass a wide variety of behaviors [18]. The term social behavior includes (but is not limited to) pair-bonding, grouping behavior, parental behavior, and aggression [18]. It is also important to

bear in mind that the presence and prominence of these behaviors vary by species [18] – for example not all species form monogamous pairs or parental behavior. While it is convenient to use an umbrella term, it is important to not conflate these social behaviors, but rather study them as distinct phenomena.

Nonetheless, these behaviors have been evolutionarily selected for because they ultimately and consistently serve to increase the likelihood of survival and reproduction. Affiliative behavior (sometimes called prosocial behavior) can be exemplified by pair-bonding (the dyadic constellation of individuals displaying marked partner preference for each other) and grouping behavior (the aggregation of conspecifics in cooperative formations – in animals exemplified by flocks, herds, and shoals). Pair-bonding in animals provides benefits such as increased offspring survival [19], and has been linked to physical and mental health in humans [20]. Grouping behavior in animals similarly provides survival benefits, such as protection, access to sexual partners, collective foraging, shelter, etc. [21]. In humans, collective behavior allows for the sharing of information and thus has been argued to shape much of our cultural development and adaptation to novel environments [22]. Aggression, in turn, is prevalent throughout much of the animal kingdom [23], and can be defined as behaviors with the intention of doing harm [24]. It is necessary for survival and fitness, including competition for resources and mates [25]. However, aggression can also be abnormal, so that it is excessive in the context where it is displayed. While excessive aggression can be elicited in animals, it has also been argued that it is something exclusive to humans living in an organized society [26]. The term *antisocial behavior* in the following chapters serves as an umbrella term comprising both aggressive and non-aggressive behavior in humans, broadly characterized by the violation of social and legal norms.

1.1 SOCIAL COGNITION

Social behavior is an outwardly visible and quantifiable phenomenon. For instance, one can assess how much one rat sniffs another [27], or observe humans interacting in a controlled setting [28], and thus quantify behavior according to a set of specific parameters. However, the observed behavior must necessarily be the product of some form of neural processing [29]. Thus, while social behavior can be regarded as the *output* (or the response, appropriate or not, to any given social interaction), the *input* (social cues, context, factors outside of the

individual) is necessarily *processed* in cortical and subcortical circuits which serve to determine manifest behavior.

Social interaction involves a number of possible sensory communication avenues (such as vision, hearing, and body language), receiving input in the form of sensory cues specific to social behaviors and based on dynamic information from a conspecific that is also making its own decisions [29]. *Social cognition*, i.e. the mechanisms through which animals acquire and process social information in order to respond to social situations, thus includes the ability to assess, evaluate, and respond to social signals and cues [30]. For instance, a prerequisite for interaction with conspecifics is social recognition, as in recognizing a face, which in humans conveys a wealth of social information, including identity, ethnicity, and gender [31]. In addition, processing of emotional expressions – emotion recognition – conveyed by faces, voices, or body language, is equally crucial to determine the correct response to any given social situation [32].

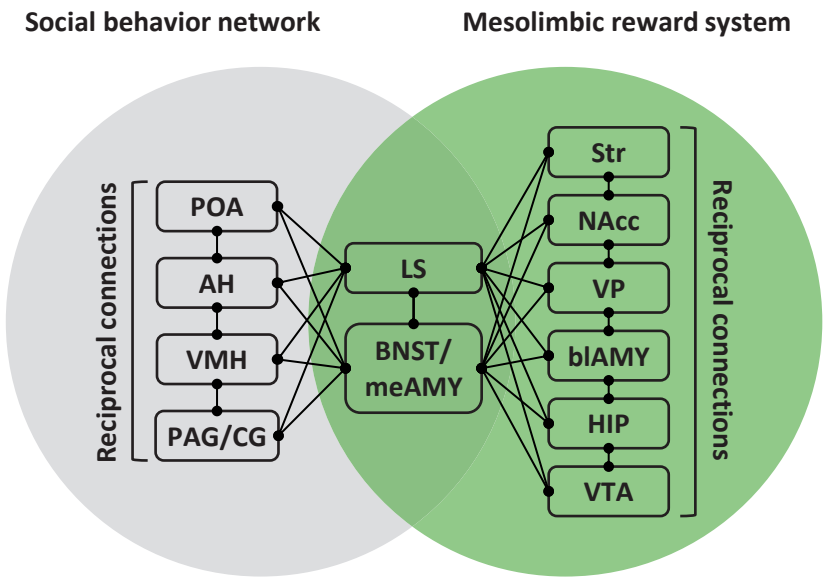

Figure 1. The social decision-making network. POA: preoptic area. AH: anterior hypothalamus. VMH: ventromedial hypothalamus. PAG: periaqueductal gray. CG: central gray. LS: lateral septum. BNST: bed nucleus of the strial terminalis. meAMY: medial amygdala. Str: striatum. NAcc: nucleus accumbens. VP: ventral pallidum. blAMY: basolateral amygdala. HIP: hippocampus. VTA: ventral tegmental area. Adapted from O'Connell 2011 [33].

Social cognition requires engagement of a multitude of brain areas, and it is beyond the scope of this thesis to review this in full. However, from animal literature it has been suggested that social cognition, with its evaluative and decision-making process, depends on a social decision-making network (SDM; see Figure 1) [33], consisting of a synthesis of the social behavior network (SBN) [34, 35], and the mesolimbic reward system [33, 36]. This SDM seems to be remarkably conserved throughout vertebrate evolution, from teleost fish to mammals [33].

The SBN, as posited by Newman, contains six nodes: the preoptic area, anterior hypothalamus, ventromedial hypothalamus, parts of the midbrain (periaqueductal and central gray), lateral septum, and the bed nucleus of the stria terminalis/medial amygdala [34]. Each of the nodes responds to various stimuli – behavioral contexts elicit distinct activation patterns across the nodes, and these nodes serve as the "core" of the social brain, integrating input from other areas involved in social decision-making [35]. Due to its associative function for sensory processing areas, the SBN plays an important part in complex social cognition [37].

Crucially, the mesolimbic reward system serves to evaluate stimuli for salience, and underlies appetitive behavior [36]. Treated as a part of the SDM, it contains eight nodes, where dopaminergic projections from the ventral tegmental area to the nucleus accumbens are central. Additional nodes are the basolateral amygdala, ventral pallidum, striatum, hippocampus, lateral septum, and the bed nucleus of the stria terminalis [33]. Two nodes of the SBN are shared with the mesolimbic reward system: the lateral septum and the bed nucleus of the stria terminalis, and the various nodes of both systems are heavily interconnected [33]. This coupling of the SBN to the mesolimbic reward system allows social behavior to be rewarding and reinforcing, and thus adaptive – allowing for not only the evaluation of social stimuli, but also for social learning, where bonds and behaviors may be reinforced.

Many of the relevant structures for social cognition in humans have been deduced using functional magnetic resonance imaging (fMRI), showing for instance that the fusiform gyrus is necessary for face processing [38, 39]. Several of the areas activated in the evaluation of a social situation in humans also recapitulate the hypothesized SDM. The ventral striatum plays a part in evaluating relationships [40], and the result of a social decision is evaluated by engaging the dopaminergic midbrain and the striatum [41, 42].

1.2 SOCIAL IMPAIRMENTS IN PSYCHIATRIC DISORDERS

Many psychiatric disorders present with impairments in social cognition, and some argue that almost all of these disorders imply some level of social impairment [7]. For example, schizophrenia patients show impairments in theory of mind, i.e. trouble inferring other people's intentions and mental states [43, 44], and psychopathy is associated with difficulties in reading certain facial expressions, such as fear [45]. Social anxiety patients show a negative bias toward interpreting ambiguous social cues [46], and attend more to negative facial expressions such as anger [47].

One example of a disorder characterized by social impairments is ASD, which – according to the most recent diagnostic criteria – encompasses two core symptom domains: (a) impairments in social communication and social interaction, and (b) restricted and repetitive behavior [8]. First described by Leo Kanner in 1943 [48], ASD is pervasive and typically life-long. Historically and commonly referred to simply as autism, this disorder was originally considered quite rare, but later epidemiological studies have placed the prevalence at approximately 1% of the population [49-51], with some estimates exceeding that [52]. There is some debate concerning what the cause of this increased prevalence is, and while it is difficult to definitely rule out an increase in prevalence, recent studies indicate that the increase in diagnosed cases does not correlate with a corresponding increase of symptomatology in the general population [53], and that it can be at least partly explained by changes in clinical practice [54].

Autistic-like traits (ALTs) are problems with social interaction or repetitive behavior that do not meet formal criteria for a diagnosis of ASD. Population-based studies suggest that an ASD diagnosis represents the lower end of a normally distributed spectrum of social interaction abilities [55, 56]. Thus, while the diagnosis is based on a clinical cut-off point of impairments, this continuous spectrum of social ability exists within the normal population, and many individuals exhibit ALTs [55].

The etiology of ASD remains unknown, but epidemiological studies indicate a strong genetic influence, with higher concordance rates for monozygotic twins (60% to 90%) than dizygotic twins (0% to 30%) [57]. Heritability estimates vary somewhat, but ASD has been characterized as a highly heritable disorder, with heritability estimates

mostly between 70 and 90% [58-60]. Higher ALTs in parents also to some extent predict the emergence of ASD in their children [61, 62], further supporting a genetic background.

Molecular genetic studies of ASD have identified a large number of risk genes with rare causative mutations in 10-25% of ASD patients, and common genetic variants could additionally explain a significant proportion of the heritability of ASD [63]. This suggests significant heterogeneity in the genetic etiology of ASD [57]. The influence of common variants seems substantial, but causality is difficult to prove since there are a high number of variants, each of which is only associated with a very modest risk [64]. However, the core symptom domains have been suggested to have partly different genetic influences [65], which means that the clinical heterogeneity displayed by individuals with ASD could partly be explained by their underlying genetic idiosyncrasies. Furthermore, ALTs and ASD have through twin studies been shown to share common genetic and environmental influences [66, 67], showing that they are etiologically linked – thus studying the molecular genetics of ALTs in the general population may be informative for ASD as well.

2 OXYTOCIN

Sir Henry Hallett Dale received the Noble Prize in 1936 (with Otto Loewi) for his demonstrations of how acetylcholine acts in neurotransmission, a fundamental and paradigmatic discovery. Given his other groundbreaking discoveries, Dale's involvement in discovering the contractile properties of OXT seems rather incidental. In the days of Dale, the specific hormones of the pituitary had not yet been isolated and defined, and "pituitary extract" would instead be applied in various preparations to elicit physiological effects. Thus, in 1906, while studying the effects of ergot on the physiology of several organ systems, he noted almost in passing: "…dried ox-pituitary was given intravenously, producing the rise of blood-pressure and contraction of the uterus…" [68], marking the first recorded observation of what would later form an integral part of obstetrics (which was initiated not much later, when such pituitary extracts were used clinically to induce uterine contractions in cases of post-partum hemorrhage [69]).

Less than a decade after Dale described the uterine contractions caused by pituitary extracts, their involvement in lactation was discovered [70]. In 1928, the two highly homologous neuropeptides OXT and arginine vasopressin (AVP) were distinguished from each other [71]. In the 1950s, OXT was successfully synthesized [72]. The genetic sequence of OXT was characterized in the 1980s [73], and the OXT receptor (OXTR) was sequenced in 1992 [74].

For close to 60 years after the discovery of its peripheral roles, OXT was mainly seen as the facilitator of childbirth and breastfeeding. This role, constrained to female reproduction, is apparent in its name, taken from the Greek words ὀξύς (oxys) and τόκος (tokos): "quick birth".[1] However, some early observations of behavioral effects of neuropeptides were noted. In 1955, vasotocin – the homologue of AVP in bony fish – was found to induce a spawning reflex in killifish [75], and in the 1960s OXT and AVP were demonstrated to alter the rate of extinction of conditioned avoidance behavior [76]. However, the seminal breakthrough for the study of OXT as a mediator and regulator of social behavior was the experiments carried out in the 1970s by Pedersen and Prange,

[1] Having experienced the births of his two daughters, one of them by induction of contractions using exogenous OXT, the author wishes to remark that this may be somewhat of a misnomer.

illustrating that intracerebroventricular (icv) injections of OXT in virgin female rats induced maternal behavior [77]. Following this, the interest in OXT as a behavioral modulator has steadily increased, as evidenced by the great body of research that has been generated over the past four decades, specifically investigating the role of the neuropeptide in social behavior in a variety of species (for reviews illustrating this, see [1, 3, 78]).

2.1 THE OXYTOCIN MOLECULE AND ITS RECEPTOR

Mammalian OXT is a small molecule composed of nine amino acid residues (nonapeptide), where a disulphide bridge joins the cysteine residues at position 1 and 6 [1]. This general nonapeptide structure of OXT is shared with AVP, and indeed with all neurohypophyseal hormones of all species where they have been observed [79]. It is worth noting that OXT (and AVP) homologues exist outside of vertebrate taxa, for instance in insects and nematodes [3], illustrating that these molecules are strongly conserved, with only slight variation between species [80, 81]. However, to allow better focus, the brief overview of the evolution of nonapeptides presented next is limited to the vertebrata taxa (see Table 1 for a comparison of structure between selected vertebrates).

Table 1. Comparison of nonapeptides in vertebrate taxa.

	1	2	3	4	5	6	7	8	9	Taxa
Oxytocin	Cys	Tyr	Ile	Gln	Asn	Cys	Pro	Leu	Gly	Placentals
Mesotocin	*	*	*	*	*	*	*	Ile	*	Marsupials, avian
Isotocin	*	*	*	Ser	*	*	*	Ile	*	Osteichthyes
Vasotocin	*	*	*	*	*	*	*	Arg	*	Nonmammalian
Vasopressin	*	*	Phe	*	*	*	*	Arg	*	Mammals

Adapted from Jurek 2018 [3].

The mammalian OXT and AVP genes (*OXT* and *AVP*) are highly homologous and located on the same chromosome (chromosome 20 in humans), separated by a short intergenic region of about 11 kilobases (kb) in humans (the length of this intergenic region is variable between

species). Both contain three exons and two introns, but have opposite transcriptional directions (see Figure 2) [1]. The ancestor gene of all nonapeptides is *vasotocin*, which still exists in its original form as the AVP homologue in certain species, for instance birds and teleost fish [3]. Vasotocin underwent gene duplication before the divergence of vertebrates, and the vast majority of vertebrates possess two nonapeptides: an OXT-like form and an AVP-like form, where the different forms of each constitute two families of nonapeptides. The distinction between the OXT family and AVP family is based on the amino acid at position 8, where the AVP family contains either lysine or arginine (both basic amino acids), whereas the OXT family contains a neutral amino acid – leucine in humans, and isoleucine in birds and teleost fish [79]. In addition, secondary gene duplications have led to marsupials possessing three AVP-like nonapeptides and two OXT-like peptides [3].

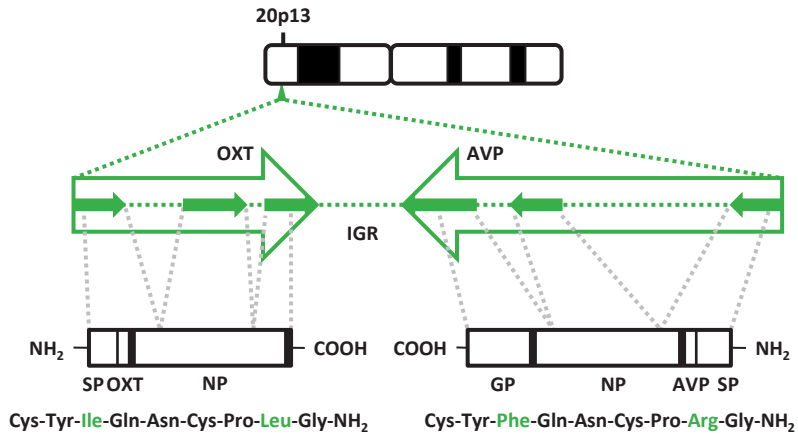

Figure 2. *OXT* and *AVP* (large arrows) on human chromosome 20, with exons (small arrows). The preprohormones (boxes) contain a signal peptide (SP), a neuropeptide (OXT or AVP), neurophysin (NP), and in the case of AVP, a glycopeptide (GP). Two amino acids vary between the neuropeptides (green). Adapted from Lee 2009 [1].

In parallel with the evolution of the nonapeptide molecules, their receptors have followed a similar trajectory, displaying the same highly conserved biochemical structure [82, 83]. An ancestral vasotocin receptor gene gave rise to both the AVP and the OXT families of receptors [84]. All these receptors belong to the G protein-coupled

receptor superfamily, and contain seven transmembrane α-helix domains [85].

For practical purposes, this section describes only the receptors in humans (mammals) and zebrafish (teleost fish), as these are most relevant to the papers included in this thesis. Mammals have only one recognized OXT receptor (OXTR), while there are three AVP receptors [79]. In teleost fish, the OXT homologue isotocin differs from OXT on position 4 (in addition to position 8), where isotocin contains serine in place of glutamine. Isotocin binds to two receptors, which have resulted from a secondary gene duplication in the teleost lineage (the same is true for the teleost AVP receptors) [86]. The isotocin receptors are termed the oxytocin receptor (Oxtr) and oxytocin receptor like (Oxtrl).

Having evolved from the same ancient precursor, OXT and AVP have partly similar functionality [87]. Mammalian AVP has three receptor subtypes: vasopressin receptor 1A (AVPR1A), 1B (AVPR1B), and 2 (AVPR2), of which the 1A receptor mediates most of the effects of AVP on social behavior [88]. AVP receptors are found throughout the primate brain, with AVPR1A being most widespread [89]. There is significant cross-talk between these peptides and their receptors. Peripherally administered OXT can act through AVPR1A to induce physiological effects, and AVP can similarly act through OXTR [85]. The same holds true for OXT administered in the brain, where icv administration of OXT can act via AVPR1A to rescue social behavior deficits in *OXTR* knockout mice [90]. Conversely, administration of AVP into the septum of a strain of rats which lack AVP altogether improves social recognition by acting through OXTR [91]. It has been suggested that OXT may be more directed towards "altruistic" behavior (i.e. maintenance of the social group or species through sexual behavior, birth, and bonding), and AVP towards "selfish" functions and behavior (i.e. aggression, maintenance of homeostasis, arousal, memory) [92]. However, given the complexity of the OXT and AVP systems, and the cross-talk between them, this may be an oversimplification. More research is needed to clarify how these two systems complement each other, and how they differ.

2.2 OXYTOCIN NEURONS

OXT is primarily produced in magnocellular neurons of the paraventricular and supraoptic nuclei of the mammalian hypothalamus, but some synthesis also takes place in parvocellular neurons of the paraventricular nucleus [93-96]. Magnocellular neurons project to the

neurohypophysis, while the parvocellular neurons do not, but both have extrahypothalamic projections [97-99]. While the number of OXT axons is rather low and varies between brain regions [93], magnocellular neurons in rodents have been found to terminate in widespread areas of the brain, including the prefrontal cortex, anterior olfactory nucleus, nucleus accumbens, lateral septum, hippocampus, and medial and central amygdala [93, 96, 98, 100, 101].

In addition to axonal release of OXT, there is also evidence for dendritic release of the neuropeptide, whereby it is hypothesized that OXT subsequently diffuses through extracellular space to exert its effects [102]. However, given that there are axonal projections of OXT neurons to OXTR-containing regions of the brain, and additionally the rapid onset of effects of OXT neurotransmission as well as the estimated necessary concentrations for sufficient receptor binding, it seems unlikely that dendritic release would be a primary mechanism [103].

Differentiation of OXT neurons is influenced by the co-expressed and heterodimerizing transcription factors aryl hydrocarbon receptor nuclear translocator 2 (ARNT2) and Single-minded 1 (SIM1) [104, 105], and mice haploinsufficient for SIM1 display a near 80% reduction in OXT expression in the paraventricular nucleus [106]. Furthermore, cluster of differentiation 38 (CD38), a transmembrane protein, plays an important role in OXT release in the hypothalamus of mice [107].

2.3 OXYTOCIN RECEPTOR DISTRIBUTION

In addition to identification of origin and projection of OXT neurons, studying the location of OXTR can also help toward understanding the role of OXT in the neurophysiology underlying social behavior. The distribution of OXTR in mammalian brains has been extensively studied in rodents, where a relatively large and diverse number of areas have been identified as containing OXTR to various degrees [3]. It should be noted that, as illustrated in prairie and montane voles, expression levels of OXTR seem highly species-specific [108]. That being said, the text here briefly describes the areas where OXTR has been reported to be expressed in mammals.

While there is widespread expression of OXTR in many parts of the mammalian brain [3], the most well-established expression in rodents is found in the hypothalamus, the prefrontal cortex, the hippocampus, and the amygdala. In the hypothalamus of mice, there is relatively sparse

expression in the paraventricular nucleus [109-111], but the expression is more pronounced in the ventromedial hypothalamus of rodents, non-human primates, and humans [112, 113]. In the hippocampus and medial prefrontal cortex of rodents, OXTR is expressed on inhibitory interneurons [114, 115], and finally, OXTR expression has been confirmed in the central and medial amygdala of several species, including rodents and humans [116].

One of the issues with locating OXTR in primate brains has been ligand promiscuity. While ligands that selectively bind only to OXTR are available in rodents, those same ligands are promiscuous for OXTR and AVPR1A in primates [117]. It is therefore only very recently that receptor locations have been determined in primates with some certainty. Early attempts at localizing OXTR in human brain, unaware of the promiscuity of the ligands used, gave a brief and early indication of receptor localizations [109, 118]. A later attempt using more specific methods found OXTR in the central and basolateral regions of the amygdala, medial preoptic area, anterior and ventral hypothalamus, olfactory nucleus, and lateral septum, but not in the hippocampus [119] – however, this was performed using only a single brain sample from a female human. More recently, a specific autoradiographic protocol was developed, and used to establish location of OXTR in several brain areas of the rhesus macaque important for gaze control, visual attention, and auditory processing, as well as the ventromedial hypothalamus [117]. In the coppery titi monkey, OXTR has been found in similar areas, and also in the hippocampus, and primary visual cortex [89]. Applying the same protocol to human brain stem and spinal cord, OXTR was found in the nucleus prepositus, which is important for eye gaze stabilization [120]. Thus, while there has been progress in establishing receptor locales in primates including humans, the relative certainty possible for rodent receptor distributions is lacking in primates. Given the previously mentioned specificity of expression, mapping receptors and their expression levels in humans would be highly informative.

It should be noted that OXTR displays not only species-specific, but also sex-specific differences. While there are intriguing species comparisons, such as the case of the prairie and montane voles [108], analyses of sexual dimorphism in several species commonly used in research are lacking, and the literature so far covers AVP receptors to a larger extent than OXTR [121]. While this is too broad a subject to cover in any great detail here, some examples can be mentioned. For instance, OXTR expression was higher in male than in female Wistar rats in the nucleus

accumbens, putamen, lateral septum, bed nucleus of the stria terminalis, hippocampus, and the medial amygdala [122]. Similarly brain-region-specific sex differences have been found in species of voles [123, 124], and in mice [125]. As stated above, there is still a paucity of studies on OXTR distribution in humans and non-human primates, and those carried out either had few subjects of either sex or did not perform analysis on sex differences [89]. Furthermore, OXTR expression is regulated by gonadal hormones through estrogen receptor alpha, which can bind to a response element in the promotor region of *OXTR* [126]. Treatment with gonadal hormones, as well as gonadectomy, and estrus status in females, lead to changing in OXTR binding densities in male and female rats [122, 127, 128]. In conclusion, there is significant evidence that the OXT system displays sexual dimorphism, which is also supported by sex-specific behavioral effects of exogenous administration of OXT [121, 129]. While there are still unanswered questions, particularly regarding this sexual dimorphism in humans, it is something that should be considered when studying OXT.

On a final note, there is significant overlap between the SDM and the OXT system, at least confirmed in rodent species. OXT neurons have been found to project to the lateral septum [100], the amygdala [93], nucleus accumbens [101], and the striatum [130]. In addition, OXTR has been found to be expressed to varying degrees in large parts of the SDM (see [3] for details on relative expression levels). This underlines the importance of OXT in social decision-making in rodents and implies a significant role of OXT in human social interactions. Indeed, it has been proposed that the function of OXT (and AVP), may in part be to enhance functional connectivity between nodes in the SDM, as well as between other brain areas important in the processing of social information [5, 131].

3 THE ROLE OF OXYTOCIN IN SOCIAL BEHAVIOR AND SOCIAL COGNITION

The role of OXT in regulating social behavior is most clearly established in animal models. Therefore, the following sections first focus on the importance of OXT for animal behavior, and then summarize what has been shown for humans.

It should be mentioned that OXT has been reported to have many and varied behavioral effects that are not restricted to social behavior. It has been shown to reduce avoidance behavior during shock training in rats [132], induce depression-like forced swimming behavior in rats [133], and reduce anxiety in the open field test in mice [134, 135] and the elevated plus maze in rats [136]. OXT has also been demonstrated to induce non-social place preference in rats [137]. OXT is also established in regulating food intake and energy balance, with potent anorexigenic effects [138], and in some species it may be involved in sodium excretion [139]. Thus, while this thesis pertains mainly to the social behavior functions of this neuropeptide, it is important to remember that its regulatory effects reach beyond the social dimension.

With regard to social behavior, this text is restricted to more in-depth summaries of the more relevant behaviors for the papers assembled herein. However, it is worth mentioning that OXT has been associated with more social behaviors than the ones listed below. For example, OXT affects various aspects of sexual behavior [140], which is not addressed here.

3.1 ANIMAL MODELS

Initial focus on behavioral OXT research was directed on maternal behavior, such as the previously mentioned induction of maternal behavior in virgin rat females by use of icv administration of OXT [77]. OXT is crucial for the establishment of maternal behavior and the bond between mother and offspring in several mammalian species, including rats [77, 141], mice [142, 143], and sheep [144]. Of note here, OXT elicits maternal behavior in virgin female rats, by modulating the balance between excitation and inhibition in the left auditory cortex. Once retrieval behavior has been established, it is not abolished by infusion of

OXT antagonist, suggesting that OXT acts a facilitator of the establishment of behavior [143].

Apart from the bond formation between mother and offspring, pair-bonding has also been studied in some detail. Approximately 3-5% of mammals develop persistent monogamous pair bonds between partners [2, 3, 145]. One of the most established animal models used to discern the role of OXT in affiliative behavior – specifically pair-bonding – is the monogamous North American prairie vole, which in addition to dyadic bonding exhibits biparental care for its offspring. The prairie vole is often contrasted with the polygamous montane vole, and it has been demonstrated that the prairie vole has higher OXTR densities in nucleus accumbens compared to the montane vole [108, 146], highlighting a possible mechanism for species-specific affiliative behavior. Infusion (icv) of OXT also triggers partner preference in female prairie voles [147], while icv administration of an OXT antagonist abolishes it in both sexes [148, 149]. In addition, altering the densities of OXTR in nucleus accumbens of female prairie voles changes partner preference behavior [150, 151].

There are comparative studies of OXTR distributions in other animals, for instance between the monogamous California mouse and the polygamous deer mouse [152]. This comparison also demonstrated differing receptor expression between key brain regions, but the pattern between the two species of mice was not consistent with the pattern between the above two species of voles. While this underscores the idea that social organization may in part be underpinned by OXTR distributions in the brain, it remains to be clarified how these differences relate to specific behavior in specific species.

Although the great detail with which prairie and montane voles have been scrutinized is not available in non-human primates, there are still some indications that OXT plays a part in social bonds in chimpanzees, where urinary OXT concentrations are higher after grooming with bonded individuals than non-bonded individuals [153]. Preference for novel faces of infant rhesus macaques correlates with cerebrospinal fluid concentrations of OXT [154], and the same species show altered OXTR expression levels in the hippocampus of reared by another individual than their mother [155].

The above pair-bond formation of prairie voles has been suggested to be underpinned by the influence of OXT on social recognition [156], a social

cognitive trait. Social cognition in animals is often studied through behavioral proxies, such as relying on the tendency of rodents to investigate an unfamiliar individual more than a familiar one – this then is utilized as a measure of social recognition [157]. There is ample evidence to suggest that OXT plays an important part in social cognition in rodents. For example, icv administration of an OXT antagonist decreases investigatory social behavior in both rats and mice [158]. OXT in the medial amygdala has been shown to be crucial for social recognition in mice [37, 159, 160]. Furthermore, Global as well as forebrain-specific *OXTR* knockout has been shown to decrease social recognition in mice [134, 161]. Finally, considering emotion recognition, this is naturally difficult to study in animals, but one may consider consolation behavior in prairie voles, which requires the ability to recognize distress or grief, and which is blocked by infusion of an OXT antagonist [162].

Thus, from the various models mentioned, it can be concluded that in mammals, endogenous OXT or treatment with exogenous OXT facilitates social behavior, while antagonism of OXT results in social deficits. Similar regulatory functions have been demonstrated in avian species for the avian OXT homologue mesotocin [131], which influences flocking behavior [163]. The matter is somewhat less clear in zebrafish [164]. Exogenous OXT has been demonstrated to increase zebrafish social preference and decrease fear response in a dose-dependent manner [165], and embryonal ablation of OXT neurons in the posterior tuberculum of zebrafish results in decreased social preference [166]. Furthermore, OXT and the OXT agonist carbetocin rescue social deficits in zebrafish caused by treatment with a glutamate antagonist [167].

While there are indications that OXT functions as a regulator of social behavior in zebrafish, this remains to be established. In Paper VI, we used a selective OXT antagonist to block the zebrafish Oxtr and Oxtrl. This decreased social preference in both adults and larvae, and decreased grouping behavior in adults.

In terms of aggressive behavior, there are indications that OXT is involved in maternal aggression and pup defense – an adaptive form of aggression serving to protect the offspring [168]. However, extant findings seem highly species- and brain region-specific, and the effect of OXT is modulated by factors such as the anxiety level of the individual, and the sex and age of the intruder being defended against [3, 168].

While maternal aggression is adaptive and defensive, OXT has also been implicated in offensive aggression, which is proactive and/or rewarding rather than reactive or protective. Animal studies of offensive aggression are usually conducted on males – thus, the following section refers to studies on males.

Most studies seem to indicate that OXT decreases offensive aggression in rodents (however, see [169] and [170]). In genetic models, aggression increases in knockout mice lacking either *OXT* or *OXTR* [90, 134, 171, 172]. Initial studies on exogenous administration of OXT showed that it decreases offensive behavior in male prairie voles and rhesus macaques [173, 174]. Additionally, as with the effect on pair-bonding, the effect of exogenous OXT administration seems species-specific – as opposed to prairie voles, no effect was found on aggressive behavior for OXT treatment in montane voles [174].

More recent studies on exogenous OXT administration show that icv OXT in male rats reduces aggressive behavior, with a stronger modulation in highly aggressive rats [175], suggesting a differential effect of oxytocin dependent on baseline aggressive levels. The same anti-aggressive (and pro-affiliative) effect in rats was achieved with intranasal administration of OXT [176]. Excessively aggressive rats display a lower amount of OXT expression in the paraventricular nucleus and elevated OXTR binding in the central amygdala compared to rats that are not excessively aggressive at baseline [177]. Thus, the neurobiological architecture of the OXT system could play a part in response, not only between species and strains, but also between individuals. Furthermore, chronically altered OXT levels in the rat brain causes enduring effects, where OXT infusion over several days decreases aggressive behavior, while similar infusion of an OXT antagonist only slightly increases it [178]. This suggests that chronically heightened OXT levels contribute to the establishment of social behavior. Also, microinjection of OXT into the central amygdala produces marked anti-aggressive effects in male rats, which can then be reversed by injection of OXT antagonist in the same area – an OXT antagonist by itself does however not affect aggression when injected in the central amygdala [179]. Taken together, the results from animal studies generally point to a moderating effect of exogenous OXT on offensive aggression in male rodents. The role of endogenous OXT is less clear – a complete and life-long loss of OXT function does increase aggression, but treatment with an antagonist does not seem to produce the same effect.

In conclusion, animal studies show that (1) OXT is crucial for social behavior in several species, (2) its exact function is species-specific, and finally that (3) its effects are dependent on the context and the individual. In addition, OXT is important for social recognition, a social cognitive aspect. The role of OXT in human social cognition and associated behavior is however less clear.

3.2 HUMANS

Much of the wealth of experimental methods available in animal experiments is not feasible when investigating the effects of OXT in humans. Thus, human studies generally utilize methods such as measuring peptide levels, investigating genetic variation, or intranasal delivery of OXT [180]. There has been a large number of these studies conducted in humans (see [3, 181] for extensive reviews), and while this text cannot summarize them all, it describes selected findings from genetic and pharmacological studies.

GENETIC ASSOCIATION STUDIES. Social behavior is heritable, with genetic influences ranging between approximately 20% and 60% for various behaviors [78]. While there are a multitude of genetic association studies on social behavior or social cognition in relation to the OXT system, many of them utilize small sample sizes, investigate phenotypes that are relatively disparate, and their findings are often constrained to subgroups, e.g. specific patient groups. This section is limited to summarizing the most pertinent findings thus far, and which relate to the papers included in this thesis.

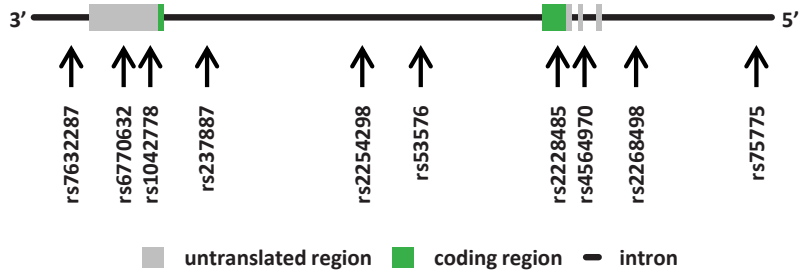

Figure 3. *OXTR* with selected SNPs.

The most studied OXT-related gene with regards to social functioning is *OXTR*. This gene contains several single nucleotide polymorphisms

(SNPs; see Figure 3 for *OXTR* polymorphisms discussed below) that have been shown to influence various social abilities [181]. Two of these SNPs have prominently featured in genetic association studies of social behavior, namely rs53576 and rs2254298, both localized in intron 3. A meta-analysis of studies carried out on these two polymorphisms showed no combined effect on human sociability of either SNP [182]. However, a later meta-analysis maintained that the earlier analysis may have conflated general sociability with sociability in close relationships, and found an overall effect of rs53576 on general sociability [183].

For analysis of closer relationships, the *OXTR* rs7632287 polymorphism in the 3' downstream region has been associated with pair-bonding in women, and with childhood social problems in girls – and childhood social problems was also demonstrated to predict pair-bonding later in life [184]. This provides a human parallel to the previously mentioned studies on voles [108], indicating that OXT may be crucial for pair-bond formation in humans as well.

With regard to the social cognitive aspect of face recognition, congenital prosopagnosia (i.e. face blindness) has been associated with polymorphisms rs53576 and rs2254298 [185]. The rs237887 polymorphism, also localized in intron 3, has been shown to affect face recognition [186] – however, see [187]. While studies directly testing the role of *OXTR* variation in face recognition are limited to those mentioned above, there have been several investigating how variation in *OXTR* influences the anatomy or activation of the amygdala, which is involved in processing social stimuli, including faces [188]. Larger amygdala volumes have been demonstrated in rs2254298 A allele carriers [189-191], and A allele carriers also show heightened amygdala response when viewing facial stimuli [191]. Functional resting-state connectivity between various amygdala sub-regions and face processing areas (e.g. the fusiform gyrus) are modulated by rs2268498, located in the promoter region [192]. Variants in the genes encoding CD38 and catecholamine-O-methyltransferase (metabolizes dopamine) show an epistasis effect, where the effect of intranasal OXT on amygdala activity while viewing social stimuli is modulated by both genes [193]. Levels of *OXTR* methylation has also been linked to amygdala activity when viewing fearful and angry faces [194]. There is thus evidence that variation in *OXTR* modulates amygdala activity while processing social stimuli, and this may influence performance on social cognitive tasks.

There are few studies linking *OXTR* variation to both amygdala activity and face recognition performance. In Paper I, we found that the rs7632287 polymorphism in *OXTR* affects face recognition in adult humans. This was accompanied by a neural correlate, i.e. altered amygdala activity during encoding of faces.

The argument for the role of the amygdala in face processing can be made for emotion recognition as well. Genetic studies on *OXTR* and this social cognitive aspect show more consistent results than those for face recognition. Carriers of the rs2268498 T allele performed significantly better at an interpersonal perception task [195], and displayed more accurate recognition of facial emotion [196]. The exonic polymorphism rs2228485 has been associated with better performance on the Reading the Mind in the Eyes test [197]. In addition, rs53576 affects processing of emotional social cues as measured by electroencephalography [198].

While variation in *OXTR* has previously been investigated in relation to emotion recognition, other OXT-related genes have not. In Paper II, we demonstrated that the rs4778599 polymorphism in *ARNT2* affects emotion recognition in adult women.

As for antisocial behavior, many of the genetic studies on OXT and this behavior have focused on psychopathy. Psychopathic traits in adolescence predict antisocial behavior in adulthood [199]. *OXTR* SNPs rs6770632 and rs1042778 in the 3' untranslated region have been tentatively linked to callous-unemotional traits in extreme childhood-onset aggression [200-202], and the potentially functional rs1042778 [201] has also been associated with callous-unemotional traits in children with conduct problems [202]. A recent, large-scale fMRI study in men also showed that rs1042778 was also linked to higher right amygdala reactivity to angry faces, which in turn was correlated with antisocial behavior [203]. Furthermore, greater methylation of *OXTR* has been associated with both higher callous-unemotional traits and lower circulating oxytocin [204]. Two other SNPs in *OXTR* were shown to interact with alcohol for trait anger in a population sample [205], and of these, rs4564970 in intron 1, showed a similar interaction with alcohol on aggressive behavior in an experimental setup [206]. A later meta-analysis found a significant main effect of total variation in *OXTR* on aggressive behavior under the influence of alcohol in experimental setups [207]. Furthermore, the above mentioned rs53576 was found to interact with social stress, such that one allele produces higher levels of

antisocial behavior after experiencing high social stress [208]. Lastly, an interaction between childhood abuse and *OXTR* methylation in predicting psychopathology has also been demonstrated [209]. Taken together, these studies offer support for the notion that endogenous OXT modulates antisocial behavior in humans.

Most of the cited studies above were carried out using relatively small samples, or focused on groups with extreme phenotypes. In Paper IV, we showed that the rs7632287 polymorphism in *OXTR* is associated with an increase in interpersonal aggression in a large sample of young men from the general population.

INTRANASAL OXYTOCIN. In the past decade and a half, there has been a great wealth of studies published on the effects of exogenously applied OXT, mostly administered through intranasal spray, on social cognition and social behavior. Initially, intriguing results showed an effect of intranasal OXT on trust in humans [210, 211]. However, these studies on OXT and trust have since been the subject of some criticism, and indeed a recent meta-analysis of studies on the link between OXT and trust failed to find collective evidence that OXT influences trust in humans [212] – however, see [213] for potential effects on trust depending on in-group and out-group relationships.

Among the great many other studies on intranasal OXT, effects have been indicated on social memory and processing of emotional faces [214-216], recognition of facial emotional expressions [217] and body language [218], socio-emotional responses [219], perception of trustworthiness and attractiveness [220], and reduced cortisol response during social conflict [221]. However, while all the above stated effects are positive and significant, their effect sizes are small, and there is a number of studies showing opposite effects or no effect at all (see for example [222] and [223]), forming a relatively disparate picture [224].

Two meta-analyses of the effect of intranasal OXT on emotion recognition found positive effects on recognition of basic emotions, particularly happy and fearful faces [225, 226], but there was no effect on interpretation of emotions in neuropsychiatric clinical populations [225]. The potential clinical effect on social cognition in neuropsychiatric disorders was also found to be modest in a recent meta-analysis, which found only a small effect on theory of mind [227]. Thus, meta-analyses provide some indication that intranasal OXT may improve social cognition in healthy and clinical populations, but the picture remains

incomplete. However, there may be factors that are not considered in the studies included in the meta-analyses, such as the fact that the effect of OXT may be contingent on personality and context [224].

The studies directly assessing the effect of exogenously administered OXT on aggression in humans are relatively few. In the Point Subtraction Aggression Paradigm – a monetary game that allows for self-interested, punitive, or collaborative action – OXT has been shown to interact with anxiety in women such that women with higher anxiety were more aggressive under placebo, with a significant reduction of their aggressive behavior under OXT [228]. A study on healthy males found no main effect of intranasal OXT in this paradigm, but did find a positive correlation between aggressive responding under OXT and antisocial personality traits [229]. A recent study, also utilizing a version of the same paradigm, found pro-aggressive effects of OXT, but only when the participants receiving OXT were unfamiliar with the paradigm [230]. Individuals with a selfish value orientation who received intranasal OXT showed increased cooperative behavior in a prisoner's dilemma paradigm if playing against a partner they were familiar with, but increased self-interested behavior when playing against a stranger – this effect was however not apparent in individuals with a prosocial value orientation [231]. In a similar vein, intranasal OXT increased propensity for intimate partner violence, but only in participants who were already inclined toward physical aggression [232]. Thus, these pharmacological studies on OXT and aggression collectively indicate that exogenous OXT may modulate aggressive behavior, but display conditional effects, where the study context and the characteristics of individual participants seem to create differential effects – in some cases even increasing the propensity for aggressive behavior. Considering the modest power of the studies conducted so far, the results should however be interpreted carefully.

THE SOCIAL SALIENCE HYPOTHESIS. The disparate results in studies on intranasal OXT, on both prosocial and antisocial outcomes, and the potentially modulating effect of context and personality, have engendered efforts to formulate hypotheses regarding what the *primary* function of OXT might be – one that may possibly encompass and explain all the extant results of these studies. Bartz and colleagues proposed that the social effects of OXT may be influenced by the context in which the neuropeptide is administered, along with individual factors [223]. They further proposed that a hypothesis of social salience would be most suited to explain the varied findings, something later expanded on by

others to include a dopaminergic mechanism by which OXT makes social cues salient [222, 234]. According to this *social salience hypothesis*, OXT would work to facilitate salience of social cues in the environment, and it has been further suggested that OXT may regulate approach and avoidance to personally relevant and emotionally evocative stimuli, whether they are social or not [235]. Strictly considering social stimuli, the social salience hypothesis may indeed explain many studies on intranasally applied OXT, in particular those that show a reinforcing of cooperative in-group and antagonistic out-group behavior [236-238]. It seems probable that OXT exerts its effects on behavior through subtle modulation of social cognition, which is also moderated by background factors such as personality and learned patterns (e.g. expectations, coping strategies).

In Paper V, we showed that intranasally administered OXT in humans increases the salience of human faces, regardless of the emotions those faces display. This provides further support for the social salience hypothesis.

3.3 OXYTOCIN IN AUTISM SPECTRUM DISORDER

Impaired social cognition in ASD is supported by several studies, particularly with regard to emotion recognition [239-243] and face recognition [244-247]. Given that OXT has been demonstrated to play a part in social cognition, it has been hypothesized that a dysfunctional OXT system might underlie or influence ASD symptomatology [248]. This is further supported by animal models of ASD, where administration of OXT rescues social deficits [249], including those where the OXT system has been disturbed, such as *OXTR* or *CD38* knockout rodents [250].

Some human studies indicate slightly lower plasma levels of OXT in individuals with ASD compared with controls, but few ASD patients in these studies fall outside the range of the plasma levels of the controls [251-253]. Furthermore, sex differences and methodology further influence these results [254]. One study found that the relationship between plasma levels of OXT and social cognition was stronger than the relationship between plasma levels and ASD diagnosis, and in addition that the association between the *OXTR* rs53576 SNP and social cognition was independent of ASD diagnosis [255], which suggests that the functionality of the OXT system may modulate social impairment in ASD, rather than be linked to the diagnosis per se.

While there is at least one case of an ASD patient with a deleterious heterozygous mutation of *OXTR* [256], such examples of major genetic aberrations in the OXT system are rare and hard to draw conclusions from. However, several SNPs in *OXTR* have been associated with ASD, including rs22554298, rs237887, rs1042778, rs7632287, and rs75775 [257-266]. A recent meta-analysis including 16 polymorphisms, 11 studies, and a total of 3941 subjects, found an association between ASD diagnosis and four *OXTR* polymorphisms, as well as the gene as a whole in a gene-based test [267].

While *OXTR* is the most studied gene in the OXT pathway pertaining to ASD, a handful of other OXT-related genes have also been investigated. SNPs in the *OXT* have been tentatively associated with ASD or ASD symptoms [262, 268]. Polymorphisms in the *CD38* gene have been linked to ASD [269], and *ARNT2* [104] also contains polymorphisms linked to ASD [268].

Few studies have looked at ASD in relation to variation in OXT-related genes outside of *OXTR*. In Paper III, we showed an association between the rs3434354 polymorphism in *SIM1* and ALTs in nine-year-old boys.

The etiology of ASD remains unknown. However, among the many genetic studies on ASD, a growing number implicate genes with a role in synaptic plasticity [57, 270, 271], such as those coding for neuroligins [272], the three SH3 and multiple ankyrin repeat domains (SHANK1, SHANK2, and SHANK3) [273], and contactin associated protein-like 2 (CNTNAP2) [274]. All of the above genes code for proteins important for synaptic function, and it has therefore been hypothesized that ASD is characterized by aberrant synaptic connectivity, or a failure of synaptic homeostasis [57].

It is interesting to note that OXT in rodents plays a role in the modulation of synaptic plasticity, by modifying synaptic properties and neural activity, in the hippocampus [275], and in social neurocircuits such as the medial amygdala [276, 277]. In reference to the above-mentioned genes, rats lacking SHANK3, a rodent model of ASD, display reduced synaptic plasticity in cortical pathways, and social recognition deficits – these deficits were attenuated with OXT treatment [278]. In addition, CNTNAP2-deficient mice present with social deficits, and these deficits were rescued by both exogenous and evoked OXT [279]. A neurobiological *in vitro* model, using a neuroblastoma cell line, was used to demonstrate that OXT increased expression of SHANK1 and SHANK3,

and in addition increase neurite outgrowth – demonstrating that OXT may be involved in synaptic scaffolding [280]. Taken together, these findings suggest that OXT may well play an important part in synaptic homeostasis.

It has also been suggested that there is an excitatory to inhibitory imbalance in ASD [281], which is supported by animal experiments [282, 283]. Furthermore, ASD is often comorbid with epilepsy, and an increased excitatory to inhibitory ratio could explain increased excitability and propensity for epileptic seizures [284]. This has led to promising trials using bumetanide, a diuretic that reduces intracellular chloride levels, so that the excitatory to inhibitory ratio is lowered [285-287].

OXT has been implicated in the so-called γ-aminobutyric acid (GABA) switch. In immature neurons, GABA-A receptors are excitatory, and there are two GABA switches during early development, where the receptors go from being excitatory to inhibitory: one which is transient and takes place during parturition [282], and one which is postnatal and permanent [288]. Maternal OXT seems to play an important part during parturition in rats, by triggering the initial transient switch [282]. Pre-delivery treatment with OXT in two rodent models of ASD (valproate-exposed rats and Fragile X mice) rescued social behavioral deficits [283]. Moreover, OXT also seems important for the permanent switch [288], and these switches are dependent on chloride transporters, of which OXT directly influences expression levels [288]. *OXTR* knockout mice also display increased seizure susceptibility, as well as an altered excitatory to inhibitory balance [90]. Thus, OXT seems important in establishing the correct excitatory to inhibitory balance in early development.

Taken together, human and animal studies show that while it may be difficult to say that ASD would be primarily underpinned by aberrations in the OXT system, OXT may play a significant part in modulating the symptomatology of the disorder. Furthermore, recent animal literature [278-280] suggests that OXT deserves further research as a candidate for treatment of ASD.

3.3.1 OXYTOCIN AS TREATMENT FOR AUTISM SPECTRUM DISORDER

Several researchers have investigated the usability of exogenously administered OXT as treatment in ASD, with the hope that this may improve social functioning, even if it is unlikely to target core pathophysiology. This thought is appealing, since in the hitherto conducted studies of repeated administration of OXT to ASD patients, OXT has been well tolerated during and after treatment [289]. Furthermore, intranasal OXT is relatively easy to administer, with minimal training required.

There are a number of pharmacological single dose studies where exogenous OXT has been administered to ASD patients. Single intravenous administration of OXT resulted in improved ability to remember social information [290], and in reduction of the frequency and severity of repetitive behaviors [291]. Intranasally administered OXT in a single dose to ASD patients has additionally been shown to improve empathic accuracy [292], strengthen inference and recognition of emotions [293, 294], improve interactions with a cooperative partner [253], and mitigate sociocommunicative deficits [295]. A recent study employed a real-time, naturalistic interaction setting to demonstrate that single dose OXT increases the level of eye contact in ASD patients [296]. Thus, the effects of single-dose administration are promising. It should however be noted that in one study, a single dose of OXT restored attentional preference to faces in ASD individuals with high social anxiety [297], and genetic variation in *OXTR* seems to predict the response to intranasal OXT in single dose administration [298]. This suggests again that the effects of OXT are modulated by background factors.

While single dose studies can give insights into the potential of a drug to alleviate symptoms, and repeated administration studies have confirmed safety, randomized controlled trials with a longitudinal design are crucial in order to establish efficacy and optimization of a treatment. Clinical trials to date have used intranasal spray as the medium of administration. The earliest clinical trial where ASD was treated with OXT included primarily male adult patients, and reported no changes after six weeks of treatment in social functioning or repetitive behavior, but an improvement in secondary outcomes, including the Reading the Mind in the Eyes test [299]. A later study on male adults treated over six weeks, reported significant improvement on their primary outcome of

social responsiveness [300]. A recent study on young adults with high-functioning autism showed that the effect of intranasal OXT over 24 weeks of treatment was modulated by dosage, where the high but not low dose would yield a positive effect, and as with single dose administration that variation in *OXTR* would predict outcomes for individuals in the low dose group [301].

Studies on children and adolescents have yielded mixed results. One study, treating primarily male children aged 3-8 years over five weeks in a cross-over design, did report significant improvement in social responsiveness [302]. However, male adolescents aged 12-18 years treated over an eight- week period, did not show any improvement in social responsiveness [303], and likewise male children aged 7-16 years treated for four days showed no improvement in behavioral outcomes compared to placebo [304]. Finally, a study including both adolescents and adults, where male ASD individuals aged 15-40 years were treated over eight weeks, reported no significant improvement of symptoms [305].

Thus, while there is some indication that exogenous OXT may be fruitful when given to ASD patients, the studies to date show mixed results, potentially due to mixed designs. Between studies, there is poor standardization and inconsistent reporting of adverse events, and no data regarding adherence to the treatment regimen, and a lack of consistent outcome measures [306]. Furthermore, looking at the studies above, various doses are used, the participants are of varying ages, and mostly male. Larger and more standardized studies are therefore needed in order to evaluate the efficacy of OXT treatment for ASD. In addition, given the potentially context- and personality-dependent nature of the effect of OXT [224] and the single- and multidose studies that indicate differential effects based on genotype and phenotype [297, 298, 301], future studies should take this into consideration.

4 SUMMARY OF RESULTS

4.1 PAPER I – OXYTOCIN AND FACE RECOGNITION

The ability to recognize previously encountered individuals is crucial for successful social interactions. OXT is essential for social recognition in rodents [37, 157, 307], and specifically involves the amygdala [159]. Intranasal OXT has been shown to enhance face recognition in humans [215, 292, 308-310]. The role of endogenous OXT for face recognition in humans is however less clear.

Face recognition has been shown to be substantially heritable (61%) [311], and to correlate negatively with ALTs [312]. There are two genetic association studies on face recognition [186, 187]. SNPs in *OXTR* have previously been associated with activity in the amygdala when viewing faces [191, 313], but there is a paucity of studies looking simultaneously at variation in OXT-related genes and brain activation in relation to remembering faces. The aim of this study was therefore to investigate associations between variation in *OXTR* and ability to recognize neutral faces, as well as amygdala activity during encoding of those faces. A sample of 54 male and female participants was included in the analyses, genotyped for 12 SNPs in *OXTR*, and exposed to a face encoding and recognition paradigm while in an fMRI scanner, looking specifically at amygdala activation during encoding and recognition.

The rs7632287 polymorphism in *OXTR* (see Figure 3 for location in *OXTR*) showed an association with face recognition, such that GA genotype carriers displayed higher accuracy than GG carriers. This effect was not modulated by sex or age. Additionally, there was a correlation between face-elicited right amygdala activity and face recognition accuracy, and GA carriers displayed a higher face-elicited right amygdala activity than GG carriers. Our findings thus indicate that variation in *OXTR* affects social cognition through an amygdala-dependent mechanism, which is in line with animal studies on social recognition [37, 159].

4.2 PAPER II – OXYTOCIN AND EMOTION RECOGNITION

Being able to accurately perceive facial emotional expressions is important to respond appropriately in social situations. Heritability studies of emotion recognition in humans are few, but there is some evidence for moderate heritability in processing expressions of affect [314], and emotion recognition deficits shared between first-degree relatives further support this [315, 316]. Previous studies investigating genetic variation in emotion recognition have focused mainly on *OXTR*. This study aimed to expand on this by scrutinizing *OXT*, *AVP*, *OXTR*, *AVPR1A* and *AVPR1B*, the transcription factor genes *ARNT2* and *SIM1*, and *CD38*. Expanding the scope to other genes in the OXT pathway is further motivated by results from animal literature, where for instance *CD38* knockout mice display impaired social recognition [317]. In addition, rodent knockouts of *OXTR* and *OXT* do not necessarily display the same outcome in behavior [134, 171, 172]. In light of the fact that emotion recognition is a social cognitive aspect previously linked to ALTs, alexithymia, emotional expressivity, and perspective taking [318-321], we also included assessments of these traits to investigate if they modulated the genetic influence. Participants of both sexes (n=492) from the general population were included, and their emotion recognition ability was assessed using the Emotion Recognition Assessment in Multiple modalities (ERAM) test. ERAM presents emotions of varying difficulty, contains 12 different expression (both positive and negative emotions), and presents these emotions in three different modalities – video only, audio only, and combined audio and video. Thus, the study in Paper II is unique, in that it has a substantial number of participants, along with a test designed to be highly sensitive, with a large number of emotions, different modalities, and live emotional displays rather than images.

The main finding, surviving correction for multiple testing, was an association between rs4778599 in *ARNT2* and audio-visual emotion recognition in women, such that the A allele carriers displayed a lower ability to discern emotions in this audio-visual condition. ARNT2 is a transcription factor important for the migration and development of OXT (and AVP) neurons [104]. We hypothesize that this finding may reflect a role for OXT (or AVP) in integrating multimodal stimuli, as it has been shown that OXT influences different sensory modalities and promotes cross-modal cortical integration during development [322]. In line with

previous studies of rs2268498 in *OXTR* [196, 323], we were able to find a nominal association between the T allele of this SNP and superior visual emotion recognition. This SNP has previously been linked to altered expression levels of OXTR in the hippocampus [324].

The rs4778599 finding was not moderated by ALTs, nor were ALTs associated with any *ARNT2* SNPs. In fact, none of the other traits investigated – alexithymia, expressivity, or perspective taking – modified our main finding. One reason for the lack of moderation by ALTs may be that while emotion recognition has previously been associated with ASD, this holds true only for certain subgroups of individuals with ASD [325], such as those with comorbid alexithymia [326], and these subgroups were likely not present in our sample. Indeed, our sample contained no individuals with a clinical ASD diagnosis.

4.3 PAPER III – OXYTOCIN AND AUTISTIC-LIKE TRAITS

ALTs are highly heritable, with estimates ranging from 60% to 77% [327]. While previous studies had looked at genetic variation in *OXTR* in relation to ASD or ALTs [184, 259, 328], few [268] had looked at other genes in the OXT pathway, such as *SIM1* and *ARNT2* (coding for transcription factors involved in the development of OXT neurons [104]), and *CD38* (involved in OXT release [329]), or the *OXT* gene itself. In addition, many studies used small sample sizes, and often relied on dichotomous case/control outcomes, when in fact looking at ALTs in the general population may yield greater variability and thus increased power to detect effects. The purpose of this study was therefore to investigate how normal variation in *OXT*, *CD38*, *ARNT2*, and *SIM1* relates to ALTs in a large sample of nine-year-old children from the general population. In total, nine SNPs in these four genes were investigated, based on either that they had previously been associated with ASD or ALTs, or that they are potentially functional with regard to transcriptional activity. The study was carried out by leveraging a large population sample of twins available in Sweden through the Child and Adolescent Twin Study in Sweden (CATSS) [330], resulting in one of the largest samples at the time of publication to investigate ALTs in relation to these genes, comprised of 1771 nine-year-old children. ALTs were investigated using the Autism-Tics, ADHD, and other Co-morbidities inventory (A-TAC) [331], describing the overall level of ALTs in each individual as a single score. This total score was a summation of three

scores each describing one of the three core symptom domains of ASD as defined in the DSM-IV: language impairment, social interaction impairment, and restrictive and repetitive behavior [332].

The only finding that survived correction for multiple testing was the rs3734354 polymorphism in *SIM1*, where male carriers of the TT genotype scored significantly higher on language impairment. While this result is tentative and restricted to a small group of individuals, it is interesting since the minor T allele has been shown to be potentially functional, by lowering transcriptional activity of *SIM1* in humans [333].

We also found SNPs nominally associated with ALTs. The *CD38* rs6449182 minor G allele was in our sample linked to lower language impairment scores in both sexes. The G allele has previously been shown to increase CD38 transcript levels [334], and *CD38* transcript levels have further been linked to social communication abilities [335]. Furthermore, we found a nominal association between the *ARNT2* rs3901896 polymorphism and ALTs.

4.4 PAPER IV – OXYTOCIN AND ANTISOCIAL BEHAVIOR

As with ALTs, antisocial behavior has been shown to be heritable (67%) [336]. When Paper IV was published, several animal studies had indicated the importance of OXT in rodent aggression (see [175-179]), but in humans, there had been relatively few and small studies on antisocial behavior, including a handful of studies on OXT levels in antisocial personality disorder [337], and genetic studies on psychopathy [202, 204, 208].

Antisocial behavior, like most disorders and aberrant behaviors [338], is arguably a quantitative trait. The aim of this study was to investigate the phenomenon of antisocial behavior, in relation to genetic variation in *OXTR*, in two large independent samples from the general population.

The discovery sample was drawn from the CATSS study, where genotype and phenotype data were available for 2372 18-year-olds. The phenotype data consisted of two scales commonly used to measure antisocial behavior: the Life History of Aggression questionnaire (LHA) [339], and the Self-Reported Delinquency Questionnaire scale (SRD) [340]. The SRD was divided into two subscales: covert aggression (i.e. not targeting another individual directly) and overt aggression (i.e.

targeting another individual directly). The replication sample consisted of 1232 twins aged 16-20 years old from the Twin Study of Child and Adolescent Development (TCHAD) [341]. This sample contained another version of the SRD, which did not include enough overt aggression items to justify the subdivision carried out in the discovery sample – please see Paper IV for details.

In the discovery sample, two SNPs were associated with antisocial behavior in males after correction for multiple testing, namely rs7632287 and rs4564970 (see Figure 3 for locations in *OXTR*). Particularly, rs7632287 was associated with overt aggression, i.e. targeting other individuals. We were also able to replicate the results for rs7632287 in the replication sample. The rs4564970 SNP has previously been linked to aggressive behavior [205, 206]. Additionally, we found a nominal association between antisocial behavior in males and rs53576.

The rs7632287 polymorphism has not been directly linked to antisocial behavior in previous studies (but it has been associated with ASD [267] and lower relationship quality and higher social impairments [184]) – however, it is in strong linkage disequilibrium with rs6770632 (which has been associated with childhood-onset aggression [201]) and a previous *in silico* analysis has indicated that it may influence transcription factor binding [181], which was further supported by our *in silico* analyses in Paper IV.

4.5 PAPER V – OXYTOCIN AND SALIENCE OF FACES

The social salience hypothesis of OXT suggests that the primary function of this neuropeptide may be to increase the salience of social cues, and thus the subsequent behavioral results of this increase in salience is dependent on the cues the individual is exposed to and their idiosyncratic background [234]. The purpose of this study was to investigate if exogenous OXT increases the salience of social cues using the psychophysiological phenomenon of binocular rivalry. In brief, this visual phenomenon appears when each eye is presented with a different picture, and results in the alternating dominance of either one of these pictures in what the subject actually perceives as seeing, or a mix of the two [342]. This phenomenon has previously been used as a means to investigate questions relating to visual consciousness, and what

information becomes salient and takes precedence in our conscious minds [342].

The study employed a randomized, double-blind, cross-over design, and included a final sample of 45 adult male participants. During each of two sessions, and following administration of either intranasal OXT or placebo, participants were presented with visual stimuli, where each eye would be exposed to either a face or a house, or vertical or horizontal lines (Gabor patch). The faces displayed one of six emotions, or were neutral.

The results showed a robust effect that OXT increases the salience of human faces, i.e. social stimuli, such that the average dominance duration of a face was increased compared to placebo. Moreover, this effect was not modulated by the emotional expression of the face. In addition, we were able to tentatively show that OXT may increase the dominance durations of non-social stimuli as well.

4.6 PAPER VI – OXYTOCIN AND ZEBRAFISH SOCIAL BEHAVIOR

The zebrafish is an emerging model which has shown great potential for elucidating neural mechanisms of behavior. The influence of OXT (more specifically the teleost homologue isotocin) on social behavior in zebrafish has not been extensively researched, albeit there are indications that it plays a part in agonostic interactions [343], social preference [165, 166] and predator avoidance [165].

The aim of this paper was to further elucidate the importance of endogenous OXT for zebrafish social behavior, utilizing the specific and nonpeptidergic OXTR antagonist L-368,899 [344]. Firstly, we conducted *in vitro* studies to ascertain ligand potencies for isotocin, vasotocin, and mammalian OXT, along with the affinity of L-368,899, on zebrafish OXT and AVP receptors. For details on the endogenous ligands, please see Paper VI. L-368,899 showed affinity for the two zebrafish OXT receptors Oxtr and Oxtrl, but no affinity for any of the AVP receptors. This confirmed that L-368,899 is highly specific for OXT receptors in zebrafish as well.

We then proceeded to test how antagonism of endogenous OXT affected anxiety and social behavior in zebrafish. In brief, L-368,899 treatment

decreased social preference in adult and larval zebrafish, and decreased grouping behavior in adults, compared to vehicle treatment. This effect appeared independent of anxiety.

5 DISCUSSION

The neuropeptide OXT is important for social behavior in many animal species [3, 4], but hard evidence is lacking with regard to its role and function in human social behavior [345, 346]. Experimental studies of exogenous OXT have shown promising results, but endogenous OXT is somewhat more difficult to study in humans, since much of the experimental methods used in animals are not feasible. OXT as a candidate for targeted drug treatment of social impairments is appealing, given (a) its well-established role in social behavior in animals, (b) its ease of administration, and (c) its apparent lack of major side effects. However, several issues remain to be clarified. For instance, how does endogenous OXT influence social cognition in humans, and how does it modulate social impairments? What is the mechanism of and neural underpinnings of the effects of exogenous and endogenous OXT? This thesis attempted to shed some light on these questions.

5.1 ENDOGENOUS OXYTOCIN IN SOCIAL COGNITION

Genetic association studies allow us to study the function of endogenous OXT in humans and to clearly establish a link between the genetic code and behavior, even if we cannot draw firm conclusions about the mechanisms underlying that link. We thus investigated the role of endogenous OXT in social cognition, by looking at face recognition and emotion recognition.

In Paper I, we showed an association between rs7632287 in *OXTR* and superior face recognition, in line with previous results on variation in *OXTR* and face recognition [186]. A later study, which did not include rs7632287, intriguingly found only one SNP nominally associated with face recognition, and that SNP is in perfect linkage disequilibrium with rs7632287 [187]. Additionally, we found that rs7632287 predicted higher amygdala activation during encoding of faces. This is comparable to studies showing that variation in *OXTR* is linked to amygdala connectivity [192], and heightened amygdala activity when viewing facial stimuli and performing a face-matching task [191]. Taken together these results indicate the importance of the OXT system in face recognition in humans. In addition, our research group has previously found an association between rs7632287 and pair-bonding [184]. In

animals, social recognition has been suggested to underlie pair-bonding [156], and our findings indicate that this may be the case in humans as well. In animals, OXT seems to have subtle sex-specific effects on social recognition [121], but we did not find any sex difference in the effects of this polymorphism on face recognition.

In contrast to Paper I, our findings from Paper II highlight the sex-specificity of the OXT system. Firstly, along with previous studies showing that exogenous OXT improves recognition of emotions [347, 348], our finding in Paper II that variation in *ARNT2* affects emotion recognition in women provides further indication that the OXT system is important for social cognition. Secondly, we found sex-specific effects, which are in agreement with prior studies that show that intranasal OXT dampens amygdala response to affective stimuli in men [349-352], but increases it in women [353, 354]. As the neurobiological details of this sexual dimorphism are not well defined in humans, more research is needed to shed further light on this issue.

5.2 ENDOGENOUS OXYTOCIN IN SOCIAL IMPAIRMENTS

The social cognitive traits of face and emotion recognition have been suggested as potential endophenotypes of ASD and antisocial behavior [239-247, 355]. Since both exogenous and endogenous OXT seems to influence social cognition in humans, it is of interest to establish whether it can modulate social impairments seen in ASD and antisocial behavior. In addition, elucidating the role of OXT in these impairments may help clarify its importance for human social behavior in general.

ALTs are prevalent in the population and provide a continuous distribution of traits which share genetic influences with ASD, a disorder at the extreme end of this distribution. Our conclusion in Paper III that a potentially functional SNP in *SIM1* may influence language impairments in ASD is an indirect link between OXT and social impairments, but it is nevertheless interesting, given that language acquisition is highly dependent on social interactions between children and their parents [356]. OXT has previously been linked to speech learning and processing in humans, such that intranasal OXT facilitates speech comprehension [357], and both variation in *OXTR* and OXT plasma concentrations have been associated with impairments of verbal communication in ASD patients [358, 359]. In addition, the avian OXT homologue mesotocin has

been shown to play a part in the vocal learning and behavior of songbirds [360-362]. OXT has also been theorized to be linked to language development, as it affects traits that are crucial for this process, such as eye contact and social responsiveness [363]. Furthermore, a role for OXT in language development is supported by its interactions with dopamine (see more on this in Section 5.3), where OXT stimulates dopaminergic neurons in the ventral tegmental area, which has many projections to vocal learning systems in songbirds and humans [362].

The findings of Paper III replicated some findings from earlier studies. Our nominal finding that rs3901896 in *ARNT2* is associated with ALTs was also subsequently supported in another study [364]. However, we note that our own preliminary analyses of a subsequent larger sample, also drawn from the CATSS population, show unclear results for the same *SIM1* SNP (unpublished data). The sample in Paper III was somewhat enriched in individuals reaching the validated ALT threshold for potential ASD diagnosis (due to recruitment procedures at different times in data collection), which suggests that as with other phenotypes – such as emotion recognition [325] – the effects of endogenous OXT on language development or social impairments may be contingent on subgroups in the general or clinical population. Additionally, we are currently analyzing data from a genome-wide association study on the same large sample of twins, where we included all normal variation in OXT pathway genes. Preliminary analyses suggest that even with a relatively liberal correction for multiple testing, we are unable to find any stable association with ALTs (unpublished data).

These results taken together highlight the need for more in-depth studies of the importance of OXT in ALTs and ASD. It may be that the A-TAC is not sensitive enough to reflect how OXT plays a part in ASD, or perhaps there are subgroups which distort the effect across the whole population. *OXTR* polymorphisms rs53576 and rs2254298 differentially affect social abilities across neuro-developmental disorders, increasing social deficits in ASD, but decreasing them in attention deficit hyperactivity disorder (ADHD) [365]. Since ADHD is commonly comorbid with ASD [366] this may have confounded the results, as our sample included individuals with ADHD traits. Previous studies have indicated that OXT may not directly affect ASD, but may exert independent and additive effects on social functioning, and modulate the symptoms and their severity [255]. While there are intriguing results from animal studies showing links between OXT and ASD risk genes [278-280], the differential effects of endogenous OXT in

neurodevelopmental disorders [365] highlight the importance of considering subgroups within the clinical population [248].

We also investigated antisocial behavior (Paper IV) as a continuous trait found in the general population. In contrast to ALTs, our results in Paper IV indicate that variation in *OXTR* seems to clearly affect antisocial behavior, which we could replicate in a second independent sample. Parallel with the idea that OXT may modulate ASD symptomatology, a recent study found that variation in *OXTR* may underlie aggressive behavior in ASD [367].

Impaired processing of faces has been suggested to partly underlie disorders characterized by antisocial behavior, and intranasal OXT has been shown to improve emotion recognition in antisocial personality disorder [355]. Interestingly, the rs7632287 AA genotype in *OXTR* was associated with antisocial behavior in Paper IV, and the A allele was associated with higher amygdala activity when viewing faces in Paper I. Due to the small sample size in Paper I, the AA genotype (associated with higher antisocial behavior in Paper II) could not be properly assessed for face recognition or amygdala activity, and future work needs to include a larger sample in order to clarify the effect on face processing of this genotype. However, this further provides an intriguing and potential link between processing of faces and antisocial behavior.

Two large meta-analyses of genome-wide association studies on antisocial behavior have been carried out since the publication of Paper IV. One of these investigated a broad spectrum of (aggressive and non-aggressive) antisocial behavior across age groups ranging from seven-year-old children to adults in their 50s, and found that in a gene-based analysis of candidate genes, the only gene which attained nominal significance was *OXTR* [368]. The other meta-analysis focused on children aged 3-7 and 12-15, and included mainly maternal assessments of childhood aggressive behavior [369]. They also performed gene-based analyses of a select number of candidate genes (not including *OXTR*), and found that *AVPR1A* significantly associated with antisocial behavior. The suggestive results for *OXTR* and *AVPR1A* are highly intriguing. Taken together, we would conclude that our study and previous studies provide intriguing support for the notion that endogenous OXT modulates antisocial behavior.

5.3 EXOGENOUS OXYTOCIN AND SOCIAL SALIENCE

The effects of OXT on social cognitive aspects such as face and emotion recognition have been suggested to depend on the ability of OXT to increase the salience of social stimuli [234, 310]. Building on our genetic association studies, we carried out a human experimental study (Paper V), specifically to investigate the effect of exogenous OXT on the salience of human faces displaying different emotions, compared to non-social stimuli. Here, we demonstrated that conscious visual perception of a face, when competing for conscious awareness of a non-social stimulus, increased following OXT administration, which is in line with the social salience hypothesis. This increase was true regardless of the emotion conveyed, which implies that all social cues, regardless of valence, become more salient following exogenous OXT administration. Indeed, the social salience hypothesis was proposed in order to attempt to explain extant results from intranasal OXT studies, where both prosocial and antisocial effects have been noticed [222, 224]. It is reasonable that an increase in salience might lead to an increase in emotion recognition, or in the ability to remember a face [310]. Future studies should incorporate measures of face or emotion recognition abilities – this could provide a clearer link between salience and social recognition. Moreover, given the aforementioned sex-specific effects of OXT, future studies should examine women in their samples, to ascertain whether this effect is sex-specific or not. In addition, attempts have previously been made to establish neural correlates of reward effects on binocular rivalry using fMRI [370], and a similar approach of combining OXT treatment and brain imaging may well be highly informative in exploring the effects of the neuropeptide on social salience.

Our binocular rivalry experiment also invites speculation on possible mechanisms underlying the effects of OXT on subsequent ability to recognize faces or emotion, and ultimately on behavior. While top-down influences play a part in determining the dominance patterns in binocular rivalry [342, 371], it has been described as a reciprocal and fluctuating lateral inhibition of the visual cortices [372]. This is interesting in light of several animal studies showing that OXT is involved in regulating the balance between excitation and inhibition [90, 143, 282, 283, 288, 373], and the fact that OXTR has been documented in the primary visual cortex of rodents [374] and primates [375], where such a regulation might take place.

Regarding potential top-down mechanisms, serotonin has been shown to influence dominance durations in binocular rivalry [376, 377]. The connection between OXT and serotonin is well-established in rodents [135, 378-380]. In humans, administration of ecstasy – a releasing agent and reuptake inhibitor of serotonin – causes an elevation in plasma OXT levels [381]. Furthermore, the link between OXT and serotonin has been demonstrated using positron emission tomography scans showing an inhibitory role for OXT in the regulation of serotonin signaling [382]. Taken together, this suggests that an alternative way for OXT to influence binocular rivalry may be through serotonin signaling.

It should be noted that social reward mediated through the nucleus accumbens requires simultaneous activation of both OXTR and serotonin receptors in mice [101], highlighting a potential mechanistic interaction between OXT and another monoamine neurotransmitter, dopamine. The nucleus accumbens is a crucial part of the mesolimbic reward system, and dopamine neurons in the ventral tegmental area project to the nucleus accumbens and the amygdala, two structures involved in assessing the value and valence of stimuli [383]. Dopamine also plays a role in attention [384], which has been shown to influence binocular rivalry [385]. In rodents, there are well-documented interactions between dopamine and OXT in social behavior [386-390], along with expression of OXTR in both the nucleus accumbens, the amygdala, and the ventral tegmental area [3]. Specifically, OXTR is expressed on dopaminergic neurons projecting from the ventral tegmental area to the nucleus accumbens of mice [391], and pharmacological manipulation of OXTR in the ventral tegmental area of rodents affects social behavior [392, 393], indicating that social reward is also driven by OXTR receptors in the ventral tegmental area. This interaction between OXT and dopamine in the ventral tegmental area and nucleus accumbens is the central mechanism of the social salience hypothesis of OXT [234], where attention to social stimuli is held to be driven by the interplay of OXT and dopamine.

5.4 ENDOGENOUS OXYTOCIN AND SOCIAL BEHAVIOR IN ZEBRAFISH

Elucidating the neural mechanisms of the OXT system is crucial to understanding its role in social cognition and behavior, and will aid in developing treatment options based on this neuropeptide. While the architecture and function of the OXT system frequently display species-

specificity, there is homology between species – in part supported by the findings of our group that face recognition (Paper I) and pair-bonding [184] are both influenced by endogenous OXT, analogous to the case in voles [156]. Therefore, we wanted to investigate the role of OXT in social behavior in zebrafish, an animal model with great potential to help clarify the neurobiology of social behavior.

In Paper VI, we showed that endogenous OXT is important for social preference in both adult and larval zebrafish, and for grouping behavior in adult zebrafish. These results align with the relatively few studies on exogenous OXT in zebrafish, which showed that manipulation of OXT (via administration of OXT or its agonist) could rescue social deficits in zebrafish. Social interaction deficits induced by the glutamate antagonist MK-801 were reversed following treatment with the OXT agonist carbetocin [167]. In a dose-response study, OXT had a bell-shaped effect on zebrafish social preference such that increasing dose at first increased social preference, and then further increases in OXT dose decreased social preference [165].

Our finding that an OXT antagonist decreases grouping behavior are in line with previous work on birds, where the homologue mesotocin increases flock formation, while a mesotocin antagonist reduces it [163]. Previous work in zebrafish on the effects of intraperitoneal injections of isotocin and its antagonist on shoaling behavior had been inconclusive [164], and highlights a need for zebrafish studies that explore behavior following manipulation of centrally available or endogenous OXT.

While our results clearly showed that endogenous OXT is an important modulator of social preference in zebrafish throughout the lifespan, the details of this modulation are still unclear. This animal model provides excellent opportunities for genetic and pharmacological manipulation [394], and future studies could utilize this model to further explore the neural mechanisms of the OXT system in social behavior. For instance, our antagonist blocked both Oxtr and Oxtrl – these receptors have arisen due to a gene duplication event in the zebrafish lineage, which is proposed to serve as an evolutionary mechanism for adapting genes to new functions [395]. Future studies can help determine if these two receptor types serve different functions. Moreover, looking at neural activation patterns may delineate patterns across the SDM in response to specific social stimuli. Given the sophistication of genetic manipulation available in zebrafish, manipulation of genes upstream or downstream of OXT, or targeting potential interactions between OXT and the

aforementioned monoamines (dopamine and serotonin), could provide further clarity about OXT mechanisms underlying vertebrate social behaviors. In addition, use of larval zebrafish may facilitate high-throughput screening of compounds that could be used to alleviate social impairments.

5.5 CONCLUDING REMARKS

While the popular notion of OXT is often limited to its proposed prosocial benefits, the effects of the neuropeptide on social behavior is characterized by a great degree of nuance and complexity. The nature of its involvement in human social behavior is by all appearances far more intricate than the popular press and even some scientists hold to be the case. While this neuropeptide has been linked to social behavior and social neurocircuits in humans, much remains to be clarified.

This thesis provides support for the role of endogenous OXT in human social cognition, specifically by showing that it influences face recognition and amygdala activation in both sexes, and that it may modulate emotion recognition in women. We were also able to show that exogenous OXT increases the salience of human faces, regardless of what emotional signals those faces convey. This increase in salience may serve as a mechanism for affecting aspects of social cognition such as face and emotion recognition. The ultimate behavioral effects of such an increase in salience by exogenous OXT may however depend on several factors, such as dosage regimen [396], genetic variation in OXT-related genes [298, 301], sex [397], personality, previous experiences, and expectations [224].

We also demonstrated that endogenous OXT may influence antisocial behavior, specifically interpersonal aggression in men, and potentially also ALTs in young children. It is likely that there are subgroups in the population, demarcated by various phenotypes, for instance ADHD and anxiety, which may show differential patterns in social functioning in relation to endogenous OXT [365]. While we did not look more closely into subgroups of the population, our sex-specific results support this idea, again highlighting the importance of looking at the individual differences and context when evaluating the function of OXT.

Given that social impairments are likely underpinned by dysfunction of social cognition, as posited for both ASD and antisocial behavior [355, 398], and given that OXT seems to work by modulating social cognition,

this naturally breeds the thought of using exogenous OXT as treatment for social impairments. The trials of OXT as treatment for ASD to date show mixed results [399], and many questions remain to be answered [400]. As stated above, defining the characteristics of the individual (his or her genotype, co-morbidities, and personality) more precisely should be fundamental for future studies to delineate the role of OXT in humans. In addition, further elucidation of specific neural circuits relevant to OXT is crucial. We here provide support for the role of the OXT system in social behavior in zebrafish. This animal model provides opportunities to clarify the specific neural mechanisms of social behavior, and offers the opportunity of screening for drug candidates in high-throughput settings.

APPENDIX: METHODOLOGICAL OVERVIEW

This section presents brief discussions on the methods used. Please see the Methods of each paper for details relevant to each study.

GENETIC ASSOCIATION STUDIES

In 1953, James Watson and Francis Crick described the double helix structure of deoxyribonucleic acid (DNA), and noted, presumably with some excitement, that "[i]t has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material" [401]. The clarification of the structure of DNA and the makeup of the genetic code laid the foundation for investigations into how simple and complex traits are inherited, and into how genetically underpinned disorders arise.

DNA consists of the nucleotides adenine (A), cytosine (C), guanine (G), and thymine (T), which bind in specific base pairs (A to T, and C to G) to form the DNA double helix. A gene typically consists of a variable number of exons, which are the coding parts specifying which amino acids will be integrated in the protein product, and introns, which are segments between exons that serve no coding function, but may have regulatory roles. Between genes there are intergenic regions, which also have no coding function, but of which parts contain regulatory elements, such as transcription factor binding sites.

Genetic variation between humans is limited to approximately 0.1% of the genetic code, where mutations have given rise to changes in the DNA sequence – this variation, in addition to environmental factors, is what makes individuals different [402]. Each locus of DNA has two copies – one on the maternal chromosome and one on the paternal. These complementary copies are termed *alleles*, and the combination of alleles is a *genotype*, which can be *homozygous* (identical alleles) or *heterozygous* (different alleles). A locus which has alleles with a frequency of >1% in the population is called a *polymorphism*.

There are several different kinds of variation in DNA, ranging in size from chromosomal (more or less than the standard two paired chromosomes – trisomy or monosomy), through copy number variation (duplications or deletions of large segments of DNA), to single base-pair variation (single nucleotide polymorphism, or SNP). Papers I-IV of this

thesis are all studies on common SNPs, i.e. occurring with a frequency of >1% in the population.

DNA was initially sequenced using rather time-intensive and costly Sanger sequencing [403], and the first whole genome was sequenced using a method based on this [404]. However, over the course of the last decades, significant progress has been made in decreasing the cost of DNA sequencing, where genotyping a single SNP incurs a fraction of the previous cost. Likewise, the cost of genome-wide association studies, whereby a large number of SNPs (often in the neighborhood of 500,000) is genotyped quickly and efficiently using chips. Similar advances have been made for whole genome sequencing, where so called next generation sequencing has substantially lowered the cost and increased efficiency.

The appeal of candidate gene studies is that they allow for the hypothesis-driven investigation of endogenous molecules in humans, which is otherwise somewhat difficult – especially given the difficulties of measuring endogenous OXT [6]. While in such studies it is difficult to draw any precise mechanistic conclusions about what exactly a particular molecule such as OXT does or how its receptor is affected to produce a particular phenotype, the advantage is that a genetic association can be established between the genetic code and that phenotype.

As all the genetic studies included herein investigate SNPs, it should be noted that many SNPs that associate with a particular phenotype fall outside the coding regions of genes and are therefore of unknown biological significance, but they may for example influence transcription levels, or be in linkage disequilibrium with a SNP that is functional. While there is a paucity of functional studies on SNPs in OXT-related genes, there are some – for instance, rs2268498 has been shown to affect transcription of *OXTR* in hippocampal tissue [324]. There is a need for functional characterization of polymorphisms, to inform conclusions drawn from genetic association studies.

INTRANASAL OXYTOCIN STUDIES

Intranasal OXT was first used in the 1960s to facilitate lactation in cases of unsuccessful milk-letdown [405], an application still used today. Intranasally applied OXT thus reaches the periphery, where it causes substantial spikes in plasma concentration [406]. The interest in

applying intranasal OXT to humans in order to try to affect behavioral outcomes, however, took longer to develop, but has increased drastically over the past decade [407]. One reason for why intranasal administration of OXT has become so prevalent is because this has been considered an alternative route across the blood-brain-barrier [408], which as a peptide OXT is effectively barred from crossing [409].

However, this has raised the fundamental methodological question of whether intranasal OXT does indeed reach the brain in sufficient quantity. Despite the vastly supraphysiological amounts (usually 24 IU, corresponding to 48 μg) of OXT regularly applied intranasally [3], only an estimated 0.002-0.005% has been proposed to actually reach the brain, and there is some inconsistency in extant findings [408, 410-413].

The studies investigating whether any quantity of OXT reaches the brain have been criticized, citing methodological issues with measuring CSF levels of OXT or microdialysis, as well as the failure to establish a plausible path for OXT to reach the brain after intranasal application [180]. Proposed routes from the nose to the brain include uptake through the olfactory and trigeminal nerve, followed by axonal transport to central targets – this has been questioned due to the time it would take for the neuropeptide to reach the brain [408]. Another mechanism might be passage into the subarachnoid space, but transport across the arachnoid membrane seems to be a relatively unimportant route for access to the brain [414]. The question of exactly how intranasal OXT reaches the brain thus remains unsolved.

However, effects of intranasal OXT on behavior in placebo-controlled studies support the argument that while the route is as yet unknown, central effects are achieved. Furthermore, recent studies on whether the peptide actually reaches the brain provide further support that such is the case. A mass spectrometry study, using labelled OXT applied intranasally and intravenously in rhesus macaques, demonstrated central uptake into the CSF of labelled OXT for both routes equally, without causing an increase in endogenous OXT [415]. Furthermore, a radiolabeled OXTR tracer was applied intranasally to rats, and subsequently demonstrated significant uptake in the olfactory bulb, at least indicating that this pathway is possible [416].

THE ZEBRAFISH AS A MODEL ORGANISM

The zebrafish (*Danio rerio*) is a small teleost fish of tropical origin, and has emerged as a model species for biomedical research, particularly in developmental studies and drug discovery [417, 418]. The species is relatively simple and cheap to breed and maintain, with a high rate of fecundity and short generation time; the offspring is independent and develop without parental support; and modern techniques for genetic manipulation and visualization of neural pathways make zebrafish a useful and convenient species for generating animal models of disease and behavior [394] – indeed, it has been used to elucidate neural circuitry for several behaviors, for example prey capture [419] and locomotor control [420].

In terms of social neurobiology, the zebrafish has also proven promising as a model for psychiatric disorders, including ASD [421] and the effects of social isolation [422]. Social behavior is well-established in zebrafish – they display preference for conspecifics [423], kin recognition [424, 425], as well as social interaction and group behavior in the form of shoaling [426-429]. These behaviors are quantifiable in zebrafish, and betray an impressively complex social behavioral repertoire. In addition, available neuroanatomical literature demonstrates that teleosts possess an SDM homologous to that in mammals [33, 35], making it further suitable as an animal model for investigating social behavioral circuits. In addition, a recent study identified a specific subset of OXT neurons in the zebrafish posterior tuberculum, and showed that embryonal ablation of these specific neurons decreased social preference [166], demonstrating the facility with which detailed neurobiological studies can be carried out in the species.

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