The modulatory effects of oxytocin on affective and social cognition

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Aalborg University

Author:
Nanna Hansen, study number: 20115103

Supervisor:
Thomas Alrik Sørensen

External supervisor:
Dea Siggaard Stenbæk

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AALBORG UNIVERSITY
DENMARK

Abstract

This master's thesis investigates the modulatory effects of oxytocin (OT) on measures of affective and social cognition. In order to appreciate these effects, the thesis employs a tripartite structure through three research questions. First, it aims to reply to how a cognitive neuroscientific perspective contributes to the understanding of affective and social cognition. It is argued that neuroscience provides a broader understanding including a biological anchoring of domains of affective and social cognition. Here, research on the affective and social cognitive domains of emotion, emotion recognition trust and affective memory are described.

Second, the thesis aims to investigate what the scientific literature can inform us about the effects of OT on affective and social cognition. This part comprises a systematized review, which includes 21 studies that assess the modulatory effects of intranasal OT on the mentioned types of cognition. The review concludes that a wide consensus of the effects of intranasal OT is not established. However, there is an overweight of studies reporting increased emotion recognition abilities after administration of intranasal OT. Furthermore, studies suggest that intranasal OT increases trust as well as empathic accuracy.

Third, the thesis aims to empirically elucidate how OT modulates performance of tests assessing trust, memory and recognition of emotional faces in healthy participants. The empirical study employs tests from the EMOTICOM test battery as well as an affective memory test to assess OT effects. Results showed that OT might modulate affective memory, however the result was borderline significant when correction for multiple comparisons. No OT effects were found on emotion recognition or trust. The discussion section provides a critical discussion of the effects of OT stressing the lack of knowledge concerning the pharmacokinetic properties of oxytocin, which entails methodological issues in the study designs. Here, the interpretation of the test results from the empirical study is also outlined. Furthermore, this section also encompasses a critical discussion of the employed tests from the EMOTICOM test battery. The thesis concludes that the modulatory effects of OT are prosocial, however the results from the studies are equivocal and more research is warranted. For future directions, the prospects of OT as a pharmacological treatment for individuals with autism spectrum disorder are outlined.

Table of contents

Abbreviations

Abbreviation	Meaning
AI:	Anterior Insula
ANOVA:	Analysis of Variance
ASD:	Autism Spectrum Disorder
BBB:	Blood-brain barrier
BOLD:	Blood-oxygen-level dependent
CFI:	Compassion Focused Imagery
CSF:	Cerebrospinal fluid
EEG:	Electroencephalography
EIM:	Emotional Intensity Morphing
ERP:	Event Related Potential
FEER:	Face and Eyes Emotional Recognition
fMRI:	Functional Magnetic Resonance Imaging
HPA:	Hypothalamic-pituitary-adrenal
ICC:	Intraclass Correlation Coefficient
OT:	Oxytocin
IU:	International Unit
IQ:	Intelligence Quotient
mPFC:	Medial Prefrontal Cortex
ms:	Milliseconds
NRU:	Neurobiology Research Unit
PET:	Positron Emission Tomography
STS:	Superior Temporal Sulcus
ToM	Theory of Mind
TPJ:	Temporo-Parietal Junction

Note: The table lists the abbreviations employed in the thesis

Introduction to the Thesis

Motivation for writing the thesis

The relation between brain and behavior has always fascinated me and inspired me to specialize in cognitive neuroscience for my master's degree in psychology. Particularly, I wanted to learn and understand more about the neural mechanisms underlying human emotion and cognition. As part of my specialization in cognitive neuroscience, I was interested in obtaining practical research experience in working with the interface between biology, pharmacology, and psychology. I therefore applied for an internship at NRU at Rigshospitalet, Copenhagen. NRU is an integrated research unit comprising researchers from a variety of professions conducting research with respect to neuroscience and neuropharmacology.

The primary aim of the cognitive psychology group at NRU is providing a cognitive, psychological approach to the study of the connection between brain and behavior. The study of this connection is conducted in relation to both healthy individuals and individuals with psychiatric and neurodegenerative disorders e.g. depression and Alzheimer's disease. Another major aim is to study predicative aspects of drug effects on cognitive outcomes in healthy and psychiatric populations, e.g. the effect of antidepressant medication on cognition in depressed patients. In line with these aims, this master's thesis assesses the effects of OT on the particular cognitive subdomains of affective and social cognition in healthy volunteers.

Why study drug effects on affective and social cognition?

Affective and social cognitive processes are vital in interactions between individuals. They are also essential for mental health and disturbances in affective and social cognitive processes are core symptoms and debilitating aspects of a range of psychiatric and neurological disorders, e.g. in major depression disorder (Hirschfeld et al., 2000), autism spectrum disorder

(Frith, 2003, pp. 9-10), schizophrenia (Lee, Farrow, Spence, & Woodruff, 2004), dementia (Shany-Ur & Rankin, 2011) and Alzheimer's disease (Nelis et al., 2011). Improving the understanding of affective and social cognitive functioning includes gaining knowledge about the implicated biological mechanisms in relation to emotional operating systems (Panksepp, 2005). At the same time, an understanding of the brain basis of affective and social cognitive functioning requires clear concepts and assessment methods such as those provided by the field of cognitive psychology (Matlin, 2005). With new technological opportunities available for assessing cognitive domains, the field of cognitive neuroscience has developed. The merging of cognition and neuroscience raises the question of how cognitive neuroscience can contribute to the understanding of affective and social functioning including the advantages and limitations this approach adds to the science of psychology.

One of the contributions that cognitive neuroscience conveys to affective and social functioning is a broader understanding of "how brain function gives rise to mental activity" (Kosslyn & Shin, 1992 in; Sarter, Berntson, & Cacioppo, 1996, p. 13). This knowledge is provided by employing neuroscientific methods such as brain imaging and pharmacological interventions. These methods respectively allow assessment and modification of brain functioning in relation to affective and social cognition. Here neuroimaging techniques elucidate relations between social situations and brain activity (Todorov, Fiske, & Prentice, 2011, p. 4). Pharmacological interventions produces modifications of certain bio-molecular expressions in the brain and hereby assessing drug effects on cognitive psychological domains. In connection with this, the modulation of brain systems has been pharmacologically investigated with the hormone OT (Ochsner & Lieberman, 2001). Converging evidence suggest that OT is a key regulator of emotional and social behaviors and that is has potential to alleviate symptoms of autism spectrum disorders as well as anxiety- and depression-related symptoms and in other psychiatric diseases where abnormal social behavior is present (Neumann, 2008). In this context, it is important to understand how OT as a hormone specifically modulates

behavioral changes in both individuals with psychiatric disorders as well as healthy individuals, and to address the progressing OT research in this area. By broadening the knowledge of the complex role of OT on social behavior in both healthy and psychiatric population, this may also provide novel therapeutic modalities to aid psychiatric illnesses by alleviating symptoms (Cochran, Fallon, Hill, & Frazier, 2013).

Statement of the problem

The overall aim of this thesis in reflecting on and answering the following question:

What are the modulatory effects of oxytocin on affective and social cognition?

In order to reply to this question, it is first relevant to elaborate on the frame of psychology in which the field of cognitive psychology is constituted. In relation to this, the cognitive psychological subdomains of affective and social cognition are defined. Secondly, it is also relevant to address the existing scientific literature in the area. The thesis will comprise a review of the research conducted in this area in order to elaborate on the known effects of intranasal OT on affective and social cognition. Thirdly, to elucidate on the role of OT on affective and social cognition, the thesis comprises a description, analysis and discussion of the results from a pilot study on effect of OT on test performance on tests assessing affective and social cognitive functioning. The tripartite structure emerging here will be employed throughout this thesis in order to aid the answering of the above-mentioned statement of the problem. In answering the statement of the problem with the tripartite structure, the following three research questions will be applied.

1) ***How does a cognitive neuroscientific perspective contribute to the understanding of affective and social cognition?***

2) ***What does the scientific literature inform us about the effects of oxytocin on affective and social cognition?***

3) ***How does oxytocin modulate performance on tests assessing trust, memory and recognition of emotional faces in healthy participants?***

Outline of the Thesis

This section will describe the structure employed in the thesis and provide an overview of the contents of each of the three parts of thesis.

Part One: In the first part of thesis, the development of cognitive psychology is described. This is conducted in order to elucidate how a neuroscientific perspective aids the understanding of affective and social phenomena in cognitive psychology. To obtain a perspective to the current understanding of emotion, a historical overview of the thoughts of emotions and their function in the development of cognitive psychology is provided. Subsequently, the fields of cognitive neuroscience and affective and social neuroscience are defined.

Part Two: The second part of the thesis comprises an outline of the effects of OT including a review of previous research conducted with OT as a pharmacological tool.

Part Three: The third part of the thesis contains an empirical study of OT's effect on affective and social cognition. This study is a pilot study conducted in collaboration with NRU and will be presented according to the standard disposition of an article with introduction, methods, data analysis, results and discussion sections.

The three parts of the thesis provide various ways of elucidating the modulatory effects of intranasal OT on affective and social cognitive functioning. Subsequently to the three parts, the thesis comprises a discussion where the modulatory effects of intranasal OT on affective and social cognition will be discussed. This discussion will critically evaluate the

methodological difficulties concerning the administration of OT and neuropsychological testing of its modulatory effects. Here findings from the pilot study will also be discussed. Successively, suggestions will be provided to how future studies assessing the modulatory effects of intranasal OT on affective and social cognition are able to do this in a more beneficial manner.

Delimitation of the Thesis

This thesis is a demarcated project, which centers around the modulatory effects of OT on the psychological subdomain of affective and social cognitive functioning. In the thesis both central and peripheral effects of OT are described. However, the main focus is the central effects that can be modulated by nasal administration of OT. The possible modulatory effects of OT on other types of cognitive functioning will not be outlined or investigated in this thesis. When elucidating the emergence of the field of psychology, not all contributions to the establishment of this field is included due to space constraints. For instance Alan Turing's (Turing, 1950), Marvin Minsky's (Minsky, 1961) and Ulric Neisser's (Schultz & Schultz, 2004, pp. 486-488) contributions to the understanding of cognitive processes are not outlined in this thesis. In the outlining of theories of emotions and recognition of emotions, cultural differences in recognition of facial emotional expressions will not be outlined (for a meta-analysis see Elfenbein & Ambady, 2002).

With respect to the second part of the thesis, the presented review limits its scope to the research conducted on the effects on OT on affective and social cognition in healthy volunteers. Therefore, it does not incorporate the research conducted on the effects of intranasal OT in patient groups, nor does it include the modulatory effects of other hormones on affective and social cognitive functioning such as vasopressin (Heinrichs, von Dawans, & Domes, 2009). Other types of social cognitive functioning can be assessed in relation to OT effects such as self-other integration (Ruissen & de Bruijn, 2015) or social stress (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). These types of social cognition are included in the review conducted in relation to the thesis, but are not outlined and discussed in the thesis itself. The studies from the systematized literature review that are

discussed in the thesis are limited to the research that assesses emotion recognition, trust and empathy.

Part one

The aim of part one

In order to reply to the first research question, this initial part of the thesis comprises a description of how a cognitive neuroscientific perspective contributes to the understanding of affective and social functioning. To elucidate this contribution, this part emphasizes the field of cognitive psychology, since the cognitive framework constitute the fundamental aspects in affective and social cognition. Thus, the field of cognitive psychology as well as its foundation and basic concepts are outlined. Subsequently, the field of cognitive neuroscience is outlined including the subordinate fields of affective and social neuroscience. Since affective functioning encompasses inferring emotional states of others (Ong, Zaki, & Goodman, 2015), this part will encompasses the current understanding of emotions. To further elucidate the contribution of cognitive neuroscience to the understanding of affective and social functioning, this part will present how neuroscientific techniques have advanced the theoretical anchoring of affective and social phenomena.

Cognitive psychology

A new field emerging

The history of psychology comprises various movements resulting in new schools of thought as well as directions of focus within the field of psychology. Here, cognitive psychology can be seen as a counter reaction to the behavioristic and reductionist that existed from 1913 until the 1960's. Behaviorism have been argued to compromise the field of psychology to a study of behavioral factors dismissing concepts such as mind and

consciousness (Schultz & Schultz, 2004). It was not the first time that these cognitive processes had been mentioned in relation to psychology. The German physiologist and psychologist Wilhelm Wundt had already described consciousness as well as explained different degrees of consciousness. Furthermore, unlike behaviorists, he was engaged in cognitive processes such as introspection and argued that it is a valid source of knowledge (Wundt, 1918). Wundt's notions on cognitive processes and conscious experience have subsequently been significant processes of investigation in the field of cognitive psychology. Furthermore, it is argued that the field of experimental psychology can be ascribed to being part of Wundt's legacy (Schultz & Schultz, 2004, p. 102). Wundt strongly argued that psychology should be considered an experimental science investigating elements of thought and mental processes (Hergenhahn & Henley, 2013, p. 252). The research he conducted on reaction time is similar to the studies within the field of cognitive psychology today. In fact, some argue that Wundt contributed with the first example of a research program that exclusively assessing psychological issues (Hergenhahn & Henley, 2013, p. 253). Hereby, Wundt contributed to cognitive psychology by attempting to anchor it as a science as well focusing on cognitive processes and psychological research.

Establishing the field of cognitive psychology

Various other psychologist have played an influential role in establishing and shaping the field of cognitive psychology. For instance, the psychologist George Miller found that behaviorism was inadequate for providing a complete theory of the aspects relevant to human functioning (Schultz & Schultz, 2004, pp. 484-485). In 1956, he published an article, which would later be considered as one of distinct importance of contributions to cognitive psychology. The article "The Magical Number Seven, Plus or Minus Two; Some Limits on our Capacity for Processing Information" suggests the span of the immediate/working memory can hold of to seven bits plus or minus two. Miller hereby considered these mnemonic processes of the mind to be juxtaposed with perceptual processes with respects to its importance in describing the mind (Miller, 1956). Hereby, Miller contributed to psychology

with knowledge concerning cognitive capability of information processing and inspired other psychologists to conduct research on mnemonic processes (Schultz & Schultz, 2004, pp. 484-486). Like many others, Miller was inspired by the technological developments at the time. Here, the invention of the computer encouraged novel concepts of the functioning of the brain and resulted in employing of the computer metaphor when describing the human brain. From a cognitive psychological point of view, a computer have certain capabilities that are similar to processes in the human brain e.g. information processing, memory and problem solving. Now these terms function as basic concepts in describing processes of the human mind in cognitive psychology. These terms stand in opposition to the behaviorist view that an understanding of human beings can be derived from a stimulus response theory. Rather than excluding its focus to stimulus response, cognitive psychology is interested in the process of knowing. Furthermore, this field is interested in how the mind organizes and structures the experienced stimuli (Schultz & Schultz, 2004, pp. 488-489). Cognitive psychology has expanded as a field and has now employed neuroscientific methods to assess its fundamental concepts. The field of neuroscience and its contribution to cognitive psychology will be described in the following sections. In relation to this thesis, it is especially relevant how neuroscience provides knowledge to the psychological fields of affective and social cognition (Matlin, 2005).

Neuroscience expanding

Neuroscience is argued to have emerged in the year of 1650 as a result of the discoveries, methods and work of Thomas Willis. He was the first to associate brain damage with certain behavioral deficits. Willis was able to do this due to autopsies conducted on his patients, which he had treated for their entire lives and thus been aware of their medical history. He would then hold the results from the autopsy against the person's medical record and study this to gain knowledge of the relation between brain and behavior. The framework and knowledge acquired by Thomas Willis provided the groundwork for neuroscience to evolve further into the scientific field known today

(Gazzaniga, Ivry, & Mangun, 2009). Evidently, neuroscience has evolved greatly since 1650 where its focus was limited to neurology, and now neuroscience is an interdisciplinary field where its methods are employed to gain further knowledge about neurological foundation and functioning. Neuroscience today is implicated in scientific fields such as biology, neuropharmacology, clinical psychopharmacology (Ayd, 2000, p. 688) and psychology (Todorov et al., 2011).

The most prominent application of neuroscience in psychology is possibly in the field of cognitive psychology, which has since developed into the branch of cognitive neuroscience. When employing a cognitive neuroscientific perspective to the study of affective and social functioning, it is relevant to clarify the concepts and the framework in which the cognitive psychological field operates. Therefore, in order to elaborate further on how cognitive neuroscience has contributed to the understanding of affective and social processes, the embeddedness of cognitive neuroscience must first be established. Thus, the following will entail a description of the emergence of cognitive psychology as well as defining its framework and central concepts.

Cognitive neuroscience

Neuroscience is defined as the study of the nervous system and cognition is defined as "the process of knowing", where information is obtained from perception, awareness and reasoning (Gazzaniga et al., 2009). Thus, cognitive neuroscience assesses the neural basis and functioning of the brain in relation to cognitive processes such as perception, awareness and reasoning. The term 'cognitive neuroscience' was coined in the late 1970s by George A. Miller and Michael S. Gazzaniga (Gazzaniga et al., 2009). Only thirty years later did cognitive neuroscience employ its methods to gain additional understanding of the subordinate fields of cognitive psychology; social and affective cognition (Ochsner & Lieberman, 2001).

Affective neuroscience and social neuroscience are currently among some of the most expanding fields attempting to connect biology with the social sciences, the social science in this case being psychology (Cozolino, 2014). However, the literature in the field of affective and social

cognition employ the terms "affective cognition" and "social cognition" in an inconsistent manner and they often appear undefined. This is evident since some research in this area is referred to as affective neuroscience (Elliott, Zahn, Deakin, & Anderson, 2011) while others refer to it as social neuroscience or social cognitive neuroscience (Todorov et al., 2011). This of course causes inconsistency as well as confusion as to what the focus of the research is as well as the relationship between affective cognition and social cognition. A clear definition of these terms will clarify the limitations in relation to the terms and ease the process of designing experiments investigating affective and social cognitive processes.

Affective neuroscience

Affective cognition encompasses how individuals process and reason about other's emotions (Ong et al., 2015). Affective neuroscience is said to be the science of emotions and has its roots in physiological psychology and behavioral biology (Panksepp, 2004) and of course cognitive psychology. Since affective neuroscience has its roots in physiological psychology and behavioral biology, this science is also interested in the processing of emotional stimuli and mapping the neural correlates of emotional responses (Kruglanski & Higgins, 2007). The psychological definition of affect comprises aspects of valence, arousal as well as "power of surgency" defined as how much mental space the emotion occupies. Valence, in relation to emotions, refers to the intrinsic character of an emotion (Panksepp, 2005). For instance, fear has an intrinsic negative character hence a negative valence and happy has a positive valence (Colombetti, 2005). Arousal refers to the levels of psychological arousal that can be elicited by an emotion (Panksepp, 2005). This is seen in line with the fact that affect is intrinsically related to readiness of action e.g. emotional experiences of rage or anger (Panksepp, 2005). Being able to read affective cues from others such as emotions is a central aspect of social interactions and hereby affective functioning plays a vital role in inferring other's emotions and understanding social interactions (Ong et al., 2015).

Social cognitive neuroscience

Social cognitive neuroscience is defined as an interdisciplinary approach questioning and investigating social phenomena within a cognitive neuroscientific framework (Kruglanski & Higgins, 2007, p. 42). This definition clarifies that this field employs scientific methods to investigate and elucidate the connection between social phenomena and neuronal activity as well as underlying information processing. The social phenomena investigated are those encompassed in theories of social psychology (Kruglanski & Higgins, 2007, p. 42). Social psychology is defined as a scientific field seeking to investigate and understand both the foundations of individual behavior in social situations (Baron, Byrne, & Suls, 1989). For this reason cognitive psychology and social psychology appear as inseparable aspects in the field of social neuroscience (Todorov et al., 2011). In this thesis, a broad perspective is applied, so that when the subject of social interactions is referred to, it is comprehended as being within the field of social psychology. Furthermore, this thesis does not differ between the fields of "social neuroscience" and "social cognitive neuroscience".

The relationship between affective and social cognition

Since affective cognition concerns inferring affective cues in relation to emotional states of others and social cognition comprise investigation of social phenomena, there is a considerable overlap between these two types of cognition. A distinction between affective cognition and social cognition can be made since social cognition comprises the processing of social interactions e.g. understanding the social situation as a whole in relation to behavior, reactions and relations in social groups. However, affective neuroscience is interested in the specific part of social interactions relating to affect such as emotion processing and emotion recognition. This therefore warrants for the evident division that affective neuroscience can be seen as a subdivision of social neuroscience. The congregation of these sciences is comprised in the term affective and social cognition refer to cognitive processing of emotional information (Ong et al., 2015) as well as information that is elicited by, directed to and concerning other people (Kennedy & Adolphs, 2012).

Generally affective and social cognition can be understood as the numerous psychological processes that encompass social behavior including affective memory, motivation and decision-making (Kennedy & Adolphs, 2012).

The neuroscience of social cognition

The neuroscientific techniques have not merely been employed to assess classical mental processes described by cognitive psychological theory. Inspired by social psychology, cognitive psychology have combined its theory with neuroscientific measure to investigate neural substrates of social cognition. The field of social cognitive neuroscience emerged around the year of 2000 and has gained increasing interest since (Todorov et al., 2011). During this time, the field has emerged into that of social neuroscience embedded in revolutionary findings in neuroscientific research. The findings in this area warrants for the distinction of social cognition from non-social cognition warranting for the field of social cognitive neuroscience. This division is substantiated through recent neuro-imaging studies that support this psychological theory. Through tasks assessing social-cognitive processes, distinctive neuronal activity has been identified. The identified neuronal activity elicited when social elements are present differs from the elicited neuronal activity when the participant conducts tasks that does not include social elements. Specifically, studies investigating neuronal activity elicited in relation to social-cognitive tasks contributes convincing evidence that social cognition consistently recruits a specific set of neural regions above those recruited by non-social cognition. The neural regions recruited by social cognition comprise medial prefrontal cortex (mPFC), medial parietal cortex (precuneus), the superior temporal sulcus (STS), as well as the lateral parietal cortex, including the temporo-parietal junction (TPJ) (Todorov et al., 2011).

This cognitive neuroscientific research has been a major contribution to social psychology warranting for social neuroscience as a distinct approach. In their book, Todorov et al., (2011) elucidate the neuroscientific contributions to social psychology (the book uses the terms "social psychological theory" and "social theory", which in this thesis is

understood as the same as social psychology). Cognitive neuroscience has not only contributed to social psychology with respect to identifying the distinct neuronal activity related to social cognition. It has also further advanced social psychology since the mentioned has provided new techniques of assessing social cognitive processes. The definition of neuronal activity related to social cognitive function enables targeting and clarification of the neuronal activity attributed to the various social-cognitive processes. For instance, scientists have employed neuroscientific techniques in investigating the social cognitive process of mentalizing. Hereby, cognitive neuroscience contribute a framework and assessment methods aiding a greater understanding of emotions and social phenomena. The next section will outline how certain aspects of cognitive neuroscience has elaborated the understanding of certain domains of affective and social cognition. The affective and cognitive domains elaborated in the following section are those relevant to the empirical study in the thesis. Therefore, research on emotion including emotion recognition as well as emotional recognition for different emotional intensities will be described. Subsequently, research on affective memory and social cognition in relation to an Ultimatum Game will be elucidated.

Emotion research and social cognition

Current view of emotions

Today a wide consensus exists that both physiological responses and cognitive functions are fundamental parts of an emotional state and that this emotional state can elicit certain types of behavior such as facial expressions. These components are also reflected in the definition of an emotion, since it is characterized as "a subjective mental state that is usually accompanied by distinctive behaviors and involuntary physiological changes" (Breedlove & Watson, 2013).

The physiological responses to emotions in the autonomic nervous system is comprehended as a significant component in emotion responses (Kreibig, 2010). The activation in the nervous systems is elicited

by an emotional state such as fear, joy or anger. This activation can occur either in the sympathetic nervous system or the parasympathetic nervous system. The sympathetic nervous system has the function of preparing the body for action such as fight or flight. For instance, the sympathetic nervous system is activated when feeling fear, where it produces the bodily sensation of a racing heart. Conversely, the parasympathetic nervous system is activated to relax the body and reestablish homeostasis (Breedlove & Watson, 2013).

Cognitive components such as memory or social context are also known to play a role in the experience of an emotion. For instance, a memory or a social context can influence which emotion is experienced or intensify an emotion (Breedlove & Watson, 2013). The expression of an emotion also serves a purpose in a social context. When comprehending emotions from an evolutionary perspective, they have an important function of giving social information and affective cues. According to this view, emotions serve a purpose of informing others e.g. of a potential threat by showing fear or a probable next move by showing anger. From a social cognitive perspective, emotional facial expressions also have a vital function with respect to formation and regulations of interpersonal relationships from infancy and in life throughout. Therefore, emotional facial expressions are important in relation to the affective and social cognitive functioning of the individual. Being able to understand the emotions expressed by others and to infer their emotional state is crucial in understanding social contexts and interaction with conspecifics (Ekman, 1992).

There are eight basic emotional expressions, which have shown to be consistent across literate and illiterate cultures with high level of agreement with respect to what these basic emotions signal (Ekman, 1992). These emotions are happiness, fear, anger, sadness, disgust, surprise, contempt and embarrassment (Keltner & Ekman, 2000). The difference between an emotion and a feeling is that a feeling is defined as "the subjective representations of emotions" (Davidson, Scherer, & Goldsmith, 2003). Thus, one can experience the emotion fear and as a consequence feel fearful.

Emotional facial expressions are relevant to the thesis at hand since the tests in the third part of the thesis specifically assess emotional

cognitive functioning especially in relation to emotion recognition. Research of emotion recognition in relation to facial expressions is among the most assessed types of functioning in the area of affective and social cognition. Furthermore, classical cognitive processes such as memory, judgment, decision-making, inference and problem solving in relation to emotion have been vastly investigated (Davidson et al., 2003).

Emotion Recognition

Perception of emotions does not require awareness or reflection enabling the possibility of subliminal emotion processing. Studies with neuroimaging indicate show converging evidence that amygdala has greater activation when the participant is shown a picture of a face expressing fear as opposed to a face expressing anger or a neutral facial expression (Whalen et al., 2001). Other neural regions activated in emotion processing include mPFC, ACC, anterior insula (AI) and mirror neuron regions. Mirror neurons are defined as neurons that discharge both when an action is executed by an individual himself and when he observes an action executed by another individual (Acharya & Shukla, 2012). However, it is argued that some neurons in the mirror neuron system are inhibited to avoid the individual of conducting the same action they are observing. This has been documented by employing single cell recording techniques, where a subset of neurons showed excitation during action-execution and inhibition during action-observation (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010). Some argue that mirror neurons hereby enables us to infer the mental states of others and therefore are activated in all tests encompassing mentalizing or understanding emotions (Rizzolatti & Craighero, 2005).

Emotional recognition for different emotional intensities

The tests assessing emotion recognition have been further developed to encompass emotional facial expressions that have been morphed by a computer to express varying emotional intensities. Hereby the test is not

merely about discriminating emotions from each other, but this test also allows testing of the participant's ability to identify subtle emotional cues. A test such as Emotional Intensity Morphing Task assesses the point of recognizing an facial emotion (Buchheim et al., 2009). The test employs the same pictures of facial emotion in the ten different degrees. However, the Emotional Intensity Morphing Task differs in that the face expressing the emotion gradually changes in emotional intensity.

Affective memory

Throughout the lifetime of every individual, a vast majority of significant events occur. Some of these events are more memorable than others, e.g. holidays, weddings, funerals or the birth of a baby (Davidson et al., 2003, p. 93). From these examples, it is evident that events that are accompanied by high emotional arousal are easier to remember. This suggests that emotional arousal is significantly implicated in memory as well as the strength of the memory. A strong emotional arousal hereby produces a deeper imprint in our memory (McGaugh, 1992, pp. 248-251). In relation to this, neuropsychologist frequently assess the relation between emotional valences and memory. Typically, these valences are positive, negative and neutral. Several types of memory have been assessed in this regard including recall, implicit and explicit memory. Research in this area have elucidated the role of affective memory in relation to healthy cognition as well as in psychiatric disorders (Elliott et al., 2011). In some psychiatric disorders, a memory bias is present. This is for instance evident in seasonal affective disorder, where individuals with this disorder tend to have a negative bias in their depressive period (Jensen et al., 2015). Hereby, the importance of affect in relation to memory is established both in relation to healthy and non-healthy cognitive functioning.

Assessing Theory of Mind

The ability to understand and interpret the emotional and mental states of others are referred to as mentalizing or as having the ability of theory of mind, which was coined by Premack and Woodruff (1978). It is argued, that Theory

of Mind (Tachibana et al.) is very important in social interactions since it is crucial for the understanding of social emotions and eliciting appropriate responses in social situations. Social emotions are here understood as emotion originating from a social situation. For instance, lying to a friend could elicit social emotions of guilt and embarrassment. If a person can experience social emotions he is able to interpret the emotions of the people surrounding him, which again can only be derived if the person has the capacity of ToM. The ability of ToM requires that the person can infer the mental states of others enabling him to empathize, cooperate, understand actions and deceive others. In several psychiatric disorders (e.g. autism spectrum disorders), ToM is greatly compromised, making the testing of this ability a valuable diagnostic tool (Todorov et al., 2011).

The first implementation of a test, which assesses ToM, was in a study of children with autism conducted by Baron-Cohen, Leslie & Frith in 1985 (Baron-Cohen, Leslie, & Frith, 1985). The ToM test is known as the Sally-Anne test. In the test there are two dolls, one is called Sally and the other called Anne. The doll Sally places a marble in a basket and exits the room. Anne then transfers the marble from the basket to a box and only after this Sally comes back into the room. The participant now has to decide where he thinks Sally will look for the marble. If the participant thinks that Sally will look for it in the basket, it means that the participant is able to infer the mental state of Sally, since this doll does not know that Anne has moved the marble. If the participant thinks that Sally will look for the marble in the box, he is unable to infer the mental state of Sally, since he thinks she knows that it has been moved despite the fact that Sally did not attend the transition of the marble (Baron-Cohen et al., 1985).

With respect to adults, the ToM ability can be assessed with a test more appropriate to this age group. Here the participant is presented with a picture of a face and he then has to infer the mental state of the person in the picture by determining which emotional expression it elicits. This ability can be assessed by employing either pictures of faces or eyes (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997). Furthermore, the ability to infer mental states of others can be assessed by employing first-order or second-

order ToM tests. The two examples provided above are examples of first-order ToM tests. Second-order ToM test assesses whether a participant is able to infer what one person is thinking about another person's thoughts (Baron-Cohen et al., 1997).

Tasks assessing ToM have been investigated vastly with neuroscientific techniques. Neuro-imaging studies have shown that the neural network involved ToM is very similar to the neural network activated when the individual is engaged in self-relevant information, since both processes particularly activate the mPFC. The overlap of these cognitive processes seems to overlap the most when the person in asked to infer a mental state of someone similar to them. This suggests that ToM is related to asking the question of how you would feel or do if you were the person you are mentally simulating to be. ToM also activates neural regions such as STS and TPJ and in certain situations amygdala, however mPFC seems to be related mostly to the ToM process (Todorov et al., 2011).

Social cognition of moral judgment

As well as the ToM task, moral judgment is a cognitive process that includes the ability of mentalizing. The moral judgment task is like the ToM task also part of the social cognition category. Moral judgment is related to social situations where a moral dilemma occurs and the person has to choose between different ways of acting in this situation. Neuro-imaging research conducted concerning this test found that brain regions related to social cognition and emotion are particularly activated such as mPFC, STS and posterior cingulate cortex when the participant is engaged in a moral dilemma (Todorov et al., 2011).

Ultimatum Game

The Ultimatum Game is similarly under the category of social cognition. It is similar to the ToM test and the Moral Judgment test in that it also comprises the ability of mentalizing (Todorov et al., 2011). It differs from the other cognitive tests since it assesses economic decision-making. The Ultimatum Game is designed with two players, where one is a participant and the other

is usually a computer with a series of predefined choices. These two players are to split a sum of money and here one player suggests a division (the proposer) and the other can choose to accept or reject the offer (the responder). These roles shift between the players throughout the game so that both play the role of the proposer and the responder. The proposer can choose to divide the amount so that he proposes a fair offer but at the same time, he can choose between one or more offers that are considered unfair. If the responder chooses to accept the offer, they both get the allotted amount. If the responder rejects the offer, none of the players receive any money (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). The element of trust appears in that transferring an amount based on an expectation for it to be reciprocated can be argued to be related to trust in the social context. Hereby both elements of generosity and trust is included. It can however be argued that the Ultimatum Game assesses fairness sensitivity and punishment tendency in its purest form. However, these measures reflect forms of generosity and trust, for which reason this test can be used to interpret changes in these parameters.

When assessing the neural activity generated with this test with neuro-imaging techniques, it is evident that the same regions are activated as in the ToM. This is suggested to be due to the similarity in both tests concerns mentalizing with regards to cooperation and potential deception (Todorov et al., 2011). In response to unfair offers, brain areas related to cognition (dorsolateral prefrontal cortex) and emotion (anterior insula) were activated. Additionally, increased activity in anterior insula during rejected unfair offers suggests that emotion plays a vital role in decision-making (Sanfey et al., 2003).

A neurobiological approach

Social neuroscience is interested in investigating the underlying neural substrates of emotion and mood. However, there exists an approach in the field of psychology with a similar aim. The neurobiological approach has also been applied in investigating social cognition. Here the aim is elucidation of the genes, neural structures and neurotransmitter systems involved in social cognitive functioning. Social neuroscience comprises a great interest in

component processes of social cognitive processes as well as modulating behavioral responses such as memory, attention, motivation, decision-making and emotion have been investigated in this regard (Adolphs, 2001). The great interest in neurotransmitter effects on social cognition in the neurobiological approach has led to the conduction of experiment manipulating with certain neurotransmitter in order to affect the response on social cognitive test. The aims in this regard are contributing to the knowledge of how biology affects cognition, broadening our understanding of the human mind.

Neurotransmission and hormones

Vast amounts of research have been conducted with respect to hormones and social attachment and behavior. Especially the hormones vasopressin and OT have been investigated since they are both involved in social attachment and behavior (Carter, 1998). Studies with these hormones have shown that for instance treatment with OT will affect the cognitive state of the individual. There exists converging evidence that OT have prosocial effects. For instance some studies reported that a nasally administrated dose of OT has improved the ability of recognizing emotions in faces (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Leknes et al., 2013; Schulze et al., 2011). In other studies assessing verbal affective memory, intranasal administration of OT seems to produce a bias towards remembering a larger amount of positive words relative to negative words (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2008). This suggests that OT can affect emotion processing and social cognition.

Summary of part one

The first part of the thesis replies to the first research question regarding the contribution of cognitive neuroscience to the understanding of affective and social cognition. Here, the foundation and development of the field of cognitive psychology is elucidated stressing the importance of the contributions from Wilhelm Wundt and George Miller. Subsequently, it is described how this field has grown and now also include methods from the

field of neuroscience in aiding the understanding of affective and social cognition. In relation to this, the fields of cognitive neuroscience, affective neuroscience and social neuroscience are explained with respect to the specific interests they comprise. Consequently, it is elucidated how cognitive neuroscience has contributed to this current theory by broadening the understanding and definition of emotion and social cognition through research. In relation to this field of social cognitive neuroscience, it is explained how this science assesses social cognitive processes such as emotion recognition and ToM. The first part of the thesis also describes the neurobiological approach and how studies on hormones have shown to affect performance on tests regarding social cognitive processing.

Part two

In order to reply to the second research question, this part of the thesis contains a description of what the scientific literature can inform us about the effects of OT on affective and social cognition. This part will therefore begin with outlining some general effects of hormones and describe different classes of hormones. Subsequently, the OT system will be described along with its central and peripheral effects. The effects of OT will then be described in relation to the research conducted regarding affective and social cognition. In order to provide an overview of this research, a systematized review will be presented.

Hormones

Hormones play a vital role in brain function and alterations in hormone levels can produce changes in cognition and behavior and they affect aspects such as sleep, appetite, reproduction, caring for our children, cognitive abilities, emotions. A hormone can be defined as a chemical substrate that is distributed through the bloodstream by endocrine glands and into the specific parts of the body and has a regulating function on organs or tissues (Breedlove & Watson, 2013). Hormones function as a part of the body's chemical communication system and can be classified by their chemical structure. The chemical

structures of the hormones determine in which of the following three classes they belong: steroid hormones, amine hormones or peptide hormones. Steroid hormones consist of derivates of cholesterol and are easily dissolved in lipids allowing them to pass through membranes. Amine hormones are composed of an altered version of a single amino acid and hence they are small and simple types of hormones. Peptide hormones are molecules consisting of a string of amino acids. The division of hormones into classes is relevant since they differ in how they interact with various types of receptors. The hormones included in the peptide class include among others OT and OT-like hormones such as vasopressin. The hormone OT lies under the class of peptide hormones (Breedlove & Watson, 2013).

Oxytocin

The oxytocin system

The hormone OT is a neurohypophysial nonapeptide. The term nonapeptide means a peptide consisting of nine amino acids. OT is produced in the paraventricular and supraoptic nuclei of the hypothalamus and released from the posterior part of the pituitary gland mostly via exocytosis (Carter, 2014; Viero et al., 2010). OT can be administrated to the body either endogenous or exogenous. Endogenous OT is produced and released in the body either by central release or peripheral secretion. Exogenous OT refers to OT administrated to the body for instance by intravenous or intranasal administration (Neumann & Landgraf, 2012). Endogenous OT is released into the bloodstream from the axon terminals of magnocellular hypothalamic neurons. The posterior pituitary signals this release of OT as a response to various types of stimulation e.g. stress and birth which then accompanies behavioral and physiological effects. OT release accompanies both peripheral and central effects (Neumann & Landgraf, 2012). These effects will be outlined in the following.

Central effects

The central effects of OT are defined as the effects of this hormone in the brain (Neumann & Landgraf, 2012). The central effects of this hormone are therefore often described in relation to behavior. OT plays a vital role in social behavior in such caring for children, pair bonding, mating and the ability to form normal social attachments (Gimpl & Fahrenholz, 2001). Furthermore, OT modulates social preference, recognition and generates anxiolytic effects (Neumann & Landgraf, 2012). In relation to this, the levels of OT are important in nursing, and studies here have found that higher OT levels during pregnancy predict higher quality of maternal care postpartum (Feldman, Weller, Zagoory-Sharon, & Levine, 2007) and induces maternal behavior in relation to mother-infant relationships (Galbally, Lewis, Ijzendoorn, & Permezel, 2011). OT and attachment seem to interact with anxiety, where attachment and OT can suppress physiological stress response and subjective anxiety (Tops, Van Peer, Korf, Wijers, & Tucker, 2007). This is in line with findings in animal studies previously conducted showing that OT increases social behaviors and that both OT and social interactions reduces stress. The stress reduction is assessed in relation to the hypothalamic-pituitary-adrenal (HPA) axis where the activity was reduced. This is thought to be beneficial to the individual's health (Carter, 1998), since it results in physiological antistress effects (Uvnas-Moberg, 1998). The primary function of the HPA axis is to regulate stress response. The HPA axis system controls the secretion of glucocorticoid hormones such as cortisol. Cortisol plays an important function in stress response (Tsigos & Chrousos, 2002).

Furthermore, OT seems to be involved in memory and learning (Bruins, Hijman, & Van Ree, 1992; Gimpl & Fahrenholz, 2001). A single dose of 20 international units (IU) intranasal OT have shown to debilitate initial storage of verbal memory as well as the rate of storage but not for visual memory (Bruins et al., 1992). It is evident that this hormone plays a role in various types of behavior and is perhaps mostly known for its prosocial effects.

Peripheral effects

The peripheral effects of OT refer to the effects of this hormone occurring in the body, which here are defined as any effects occurring outside the brain (Neumann & Landgraf, 2012). Peripheral OT acts on the smooth muscle cell and facilitates milk ejection and uterine contraction during delivery. The role of this hormone during delivery gave rise to its name since OT in Greek means swift birth (Viero et al., 2010). During birth OT also facilitate the protection of the brain from hypoxia. Furthermore, this hormone has also shown to have contractile effects of the prostate gland in vitro (Bodanszky, Sharaf, Roy, & Said, 1992) hereby suggesting that OT is involved in ejaculation of prostatic secretions by contracting the prostate (Nicholson & Jenkin, 1994). Furthermore, this hormone serves as a regulatory component in conditions such as hypovolemia and hyperosmolarity and is released into the blood when signs of these conditions occur (Gimpl & Fahrenholz, 2001). OT has also shown to play a role in the functioning of a vast number of organs such as heart, testis, ovary, kidney and thymus. The latter being responsible for T-cell selection in relation to the immune system. Additionally, OT is involved in functions in cells and glands such as fat cells, pancreas and adrenal gland (Gimpl & Fahrenholz, 2001; Viero et al., 2010). Among the many effects of this hormone both central and peripheral, the effects that are essential in relation to this master's thesis are the central effects with respect to social behavior in normal, healthy female volunteers.

Pharmacological composition and intervention possibilities

Due to the behavioral effects of central OT, many researchers have shown interest in moderating the OT level and study behavioral effects in this regard. Knowledge of OT's pharmacological structure such as peptide sequence has enabled the synthetic production of this hormone in drug form (Viero et al., 2010). The amino acid sequence of OT is relatively short since it consists of nine amino acids. Figure 1 illustrates the chemical structure of this molecule. The sequence of this neurohormone is Cysteine-Tyrosine-Isoleucine-Glutamine-Asparganine-Cysteine-Proline-Leucine-Glycineamide and in

terms of structure, the cysteine residues forms a sulfur bridge (Viero et al., 2010).

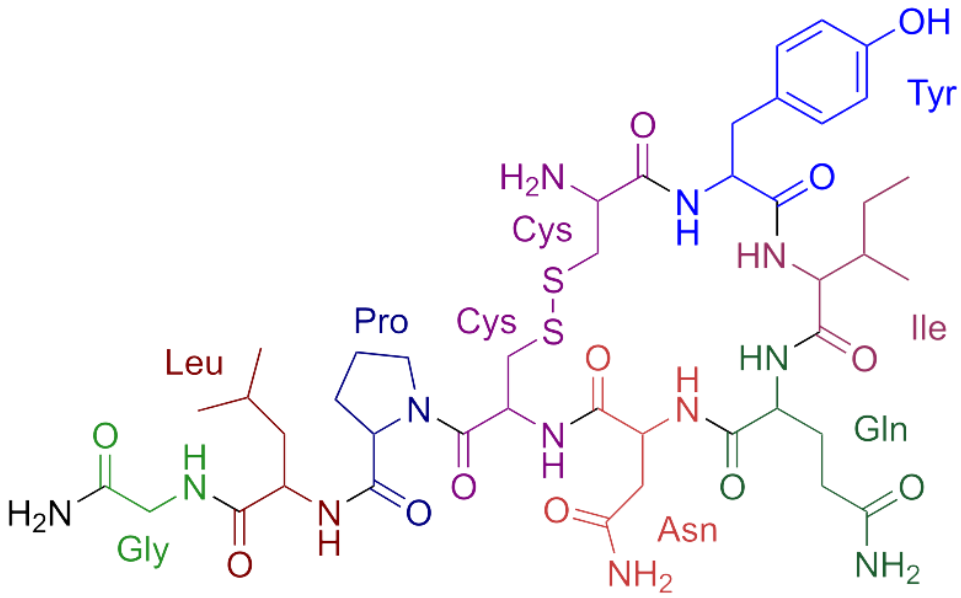

Figure 1 – The chemical structure of the oxytocin molecule. Picture adapted from www.paasp.net.

The synthetic form of OT has of course facilitated the possibility of pharmacological intervention. The possibilities are here oral, nasal and intravenous administration of the drug form. However oral administration would be a problematic choice for intervention since the nonapeptide can be decomposed by enzymes in the gastrointestinal tract (Viero et al., 2010). This leaves administration via intranasal and intravenous routes the most suitable candidates of these two intervention forms. Both intervention forms have been employed in studies assessing OT effects. However, both forms have received an extensive amount of critique by questioning the ability of this peptide to cross the blood-brain barrier (BBB) by exogenous administration (Gimpl & Fahrenholz, 2001). This questioning of the effects elicited by exogenous effects from intranasal OT is indicated in Figure 2. Nevertheless studies employing both intravenous infusion (Hollander et al., 2003) and intranasal administration (Kanat, Heinrichs, & Domes, 2014; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) of OT has provided an effect. The study, which gave rise to the current interest in OT as mediating prosocial behavior, will be presented in the following section.

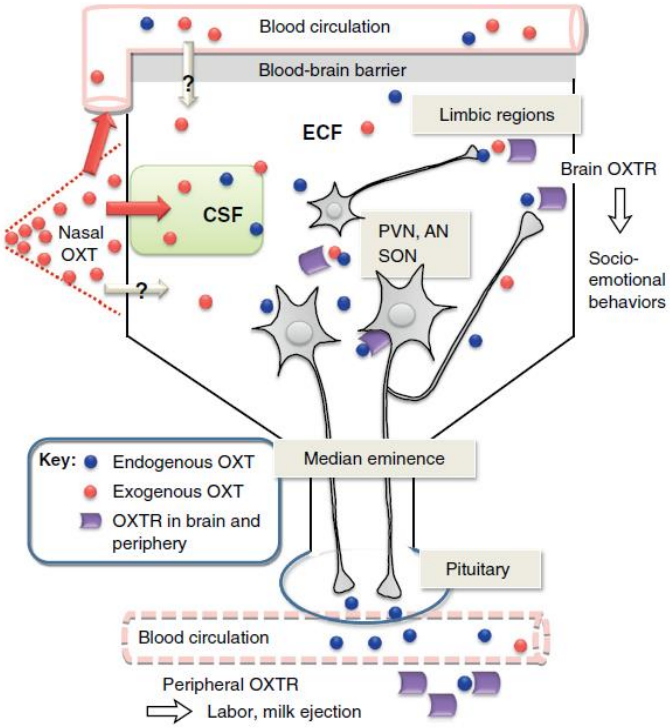

Figure 2 - This figure depicts the brain oxytocin system. Oxytocin (OXT) is released at the axon terminals of magnocellular neurons in the pituitary gland of the hypothalamus via exocytosis. Its release is activated by the pituitary gland due to stimulation such as stress, birth and suckling. The peripheral release of oxytocin can result in labor and milk ejection and central release affect socio-emotional behavior. Elevated levels of oxytocin can also be found in the extracellular fluid (ECF). The figure shows that intranasal administration of oxytocin enters the blood circulation and cerebrospinal fluid (CSF), however its ability to cross the blood-brain is questioned. Oxytocin binds to oxytocin receptors (OXTR) both in the in the brain and peripherally. The arrow shown under the brain OXTR indicates that oxytocin in the brain impacts socio-emotional behavior. Source of the figure: Neumann & Landgraf 2012.

Figure 2 presents both the exogenous and endogenous effects of OT. Here the ability of intranasal OT to directly permeate ECF as well as the BBB though the blood is questioned. However, it is clarified that both endogenous and exogenous OT is in the CSF and it is able to cross over to the ECF. Since a vast amount of research employs intranasal OT to modulate behavior, researchers have stressed this as being highly important to clarify (Gimpl & Fahrenholz, 2001).

In 2013, Striepens and colleagues investigated the levels of OT both in CSF through lumbar puncture and blood plasma subsequent to

intranasal administration. They found that plasma levels peaked after 15 minutes and decreased after 75 minutes. However, CSF only reached a significant level 75 minutes after administration. The level of OT in CSF increased 64% after 75 minutes. There was no correlation between plasma and CSF levels of OT. These findings indicate that intranasal administration of OT increase brain CSF concentrations. Since OT is able to cross ECF from the CSF, these elevated concentrations after systematized intranasal administration can hereby accompany behavioral changes (Striepens et al., 2012). Previously, a similar study was conducted by Born and colleagues (2002) with the OT-like hormone, vasopressin. Here intranasal administration also caused increased levels of the hormone in the CSF. This seems to provide evidence that intranasal OT is able to permeate the ECF via the CSF. Hereby this warrants for the use of intranasal administration of OT in studies assessing its modulatory effects on cognitive domains.

The beginning of the interest in intranasal oxytocin effects on affective and social cognition

In the recent years OT has received vast interest in the area of neuroscientific research (Kirsch, 2015). The increasing interest in OT and affective and social cognition can be attributed to groundbreaking study conducted in 2005, since this study showed modulatory effects of intranasal OT on the social cognitive domain known as trust behavior (Kosfeld et al., 2005). In this study, the participants (n=58) were divided in two groups; one receiving intranasal OT (n=29) and the other receiving placebo (n=29). Participants performed two experiments where one experiment assesses risk behavior and the other assesses trust behavior. In both experiments, the participants can win money according to how they behave in the test.

In the experiment assessing trust behavior, participants from both groups, OT and placebo, are randomly assigned to a role of either a trustee or an investor. Both the trustee and the investor are given 12 monetary units (MU) at the beginning of the experiment. The investor has the option of giving an amount of 0, 4, 8, or 12 MU to the trustee. The experimenter triples the amount of money chosen for the transaction. For instance, if the investor

chooses 12 MU then the trustee receives 36 monetary MU. Since the trustee initially has 12 MU, the total for this example is 48 MU. The trustee is informed by the investor's transaction and has to choose an amount to send back to the investor. The trustee can choose to honor the trust of the investor by dividing the money between them or keep a higher amount or the entire amount to himself. Each participant conducts this process four times with four randomly chosen interaction partners. In this experiment, a social risk component in implemented, since the investor does not know the behavior of the trustee. The dilemma of the investor is that he does not know if the trustee will share the amount or if the trustee will keep the entire amount himself.

In the risk experiment, all participants from both the OT and placebo group, play the role of an investor and have to choose an amount of money to invest. They are told that a computer will randomly give back an amount of the invested MU. Therefore, the experiment design is similar to the trust experiment; however the social component has been removed.

The results showed that the investors' behaviors do not differ between the OT and placebo groups in the risk experiment. Furthermore, there were no difference between the investors' behavior in the risk experiment and the placebo group investors' behavior in the trust experiment. However, a significant difference was found between the investors' behaviors for the OT and placebo group in the trust experiment. Here the participants who played the role of an investor and had received intranasal OT gave significantly higher amounts of transfers relative to the placebo group in the trust experiment. This suggest that OT increases trust in social situation but does not affect the ability to take risks in non-social situations (Kosfeld et al., 2005). Since previous findings suggests that humans normally show an aversion to take such monetary risks (Kahneman & Tversky, 1979; Rabin & Thaler, 2001), OT seems to modulate trust in social situations. This finding was groundbreaking with respect to neuroendocrine effects on social behavior, and therefore inspired other researchers to conduct similar experiments assessing the effects of OT on social behavior. The results from this study was in line with animals studies indicating prosocial properties of

the hormone (Carter, 1998) The modulation of social properties has since increased the interest in research of this hormone.

The mentioned study from Kosfeld et al. (2005) gave rise to an increasing number of studies assessing the modulatory effects of intranasal OT on affective and social cognition. A wide consensus now exists that OT modulates trust in humans, which is argued to account for the hormones prosocial effects such as social bonding both in humans and animals (Viero et al., 2010).

Systematized review on the literature of the effects of intranasal oxytocin on affective and social cognition

To address the question of the modulatory effects of intranasal OT on affective and social cognition, the empirical findings will be outlined in this section in a systematized review. Naturally, the vast numbers of studies conducted on the prosocial effects of OT vary in their designs. For comparisons reasons, the studies included in the review are selected on the basis that their design must be equivalent to the study design applied in the pilot study presented in this thesis. Therefore, inclusion criteria are listed in the following.

Inclusion criteria:

- Studies investigate the effects of OT
- Studies must employ intranasal administration of OT
- Studies must be double-blinded, randomized, placebo-controlled, crossover design
- The studied population must be healthy volunteers
- Studies must contain neuropsychological outcomes of affective and/or social cognition
- Studies must investigate the affective and social cognitive domains of emotion recognition, verbal affective memory, trust and empathy

Since the pilot study only includes healthy participants, studies on clinical and subclinical groups are excluded in the review. Furthermore, fMRI studies are only included if neuropsychological outcomes are the main outcome in the study design. These above-mentioned requirements for the designs of the empirical studies are incorporated in the employed search strings. The search string are illustrated in Table 1, where the requirements for the studies included in the review is phrased in a Boolean query (Zins, 2000). The selected databases for the systematized review are Web of Science and PsychInfo. Web of Science is a comprehensive database encompassing literature from a vast range of scientific disciplines including social sciences and humanities (webofknowledge.com). PsychInfo is an expansive database with peer-reviewed literature within the fields of mental health and behavioral sciences (apa.org). By employing these two databases, the thesis assesses peer-reviewed literature from a database covering a variety of disciplines. The two databases are selected since they provide both specificity and a broader span in the search, with the aim of increasing the possibility of identifying relevant studies.

Oxytocin	AND	Intranasal OR "nasal spray" OR "nose spray"	AND	Memory OR trust OR "emotion*" OR "facial expression" OR "facial expressions"	NOT	Schizophrenia OR depression OR autism

Table 1 – The table illustrates the employed search strategy for the review. This search strategy is incorporated to the databases PsychInfo and Web of Science.

As shown in Table 1, the search strategy for the articles for the review aims to identify articles investigating the modulatory effects of OT. The search strategy includes OT first and then the administration of the hormone has to be intranasal. Since the term "intranasal" also can occur as "nasal spray" and "nose spray", these terms are also incorporated into the search string.

Furthermore, the cognitive measures assessed in the scientific studies are often specifically outlined. For instance if a study assesses OT effects on memory, the article will list it as memory instead of the general term of neuropsychological measures. Thus, the specific cognitive measures relevant to this thesis are listed in the search string as memory OR trust OR emotion. Since facial expression can occur in both singular and plural forms, both are included in the search string. To avoid studies of clinical groups the exclusion function is employed in both databases, where it is manually selected that studies, which list schizophrenia OR depression OR autism in their topics cannot be included. Hereby, the search string entails that these words are not in the title or the keywords of the study. However, it does not exclude studies where the word is mentioned other places in the text. This is considered a strength since the word can be mentioned in the study of a non-clinical groups that e.g. suggest future directions for employing the study in certain clinical groups. When the search string is employed Web of Science provided 252 results. The search string on PsychInfo yielded 240 results. These results were combined and the duplicates of studies were removed. This process is illustrated in the prisma flow diagram in Figure 3. For the thesis, two versions of the review have been conducted. The systematized review presented in the thesis includes literature that obtains all the inclusion criteria listed above. In order to provide an overview of the studies assessing OT effects on affective and social cognition in general a larger review is also included. This review is enclosed in Appendix C and obtains all inclusion criteria except for the last. This general review of OT effects on affective and social cognition includes 36 studies. The studies included in Appendix C are found through the same process as the systematized review. The articles included in Appendix C are illustrated in the prisma flow diagram in Figure 3 as the 36 studies considered eligible.

The expanded review provides a greater overview of the studies of the modulatory effects of OT on social cognitive functioning. This review incorporates the same studies included as the first review as well as findings from additional studies that have assessed OT effects on other types of social cognitive functioning. It provides an overview of OT effects on parental

attachment, social awareness, eye-gaze, social stress, social memory and self-referential tasks in relation to words and faces. The expanded review is the enclosed Appendix C.

This small review therefore only employ studies assessing on the effects of OT on measures such as emotion recognition, verbal affective memory, trust and empathy. This review is presented in Table 2 and it comprises 21 studies. It is included in the thesis to provide an overview of the findings in this area. These findings will subsequently be compared to the results in the pilot study, since it assesses this type of social cognitive functioning. Therefore, the three types of studies included all assess OT effects on three domains of social cognitive functioning. These are verbal affective memory, emotion recognition and trust including empathy and generosity.

Types of studies included in the review

From the overview provided in the systematized literature review, it is evident that studies assessing emotion recognition comprise the majority of the studies. 21 out of the 36 studies (see Appendix C) have assessed the effects of OT on emotion recognition. OT effects on social awareness comprise 8 out of the 36 studies. Hereby, the OT effects on social awareness and emotion recognition constitute 29 out of the 36 studies and all but one of these studies reported modulatory effects of OT on this type of cognition. More specifically, these studies can be said to focus on affective cognition since they investigate emotion recognition and social cognition when assessing awareness in relation to social contexts. The effects of OT in verbal affective memory have not been studied to the same extent as other types of affective and social cognitive functioning, which is reflected in that only two of the studies assess OT effects on memory. One study assessed the effects of OT on social memory. Two studies assessed OT effects on parental attachment, one study examined eye-gaze and three studies investigated social stress. Furthermore, two studies assessed self-other differentiation (see Appendix C).

In the following, only the findings from the studies in the small review from Table 2 will be discussed. Only the studies included in this small review will be described, since the findings from these studies and their methods employed are most relevant to outline and compare in relation to the empirical study in this thesis.

The effects of intranasal oxytocin on verbal affective memory

The modulatory effects of OT have been tested on several types of affective cognition, however only a few studies have assessed OT effects on memory. The first study investigating OT effects on memory was conducted on implicit and explicit memory (Heinrichs, Meinlschmidt, Wippich, Ehlert, & Hellhammer, 2004). The authors employed three different memory tests. One was a word stem completion test assessing implicit perceptual memory, the other was a category-cued semantic association test assessing implicit conceptual memory and the third was cued recall test assessing explicit memory. The placebo group recalled a significantly larger amount of words that the OT group, which leads the authors to suggest that OT impair recall of words. This was evident for words with neutral meaning and reproduction-related words. In the test assessing implicit conceptual memory, the placebo group recalled a significantly larger amount of reproduction related words than the OT group. Therefore, the authors suggest that OT yields selective amnesic effects.

Subsequently, a study by Di Simplicio et al. (2008) investigated OT effects for recognition, categorization and recall of words. The results showed a trend for the OT group in recognizing a significantly larger amount of positive than negative words but the results were not statistically significant. Furthermore, in the memory test assessing recall of words, the OT group recalled a significantly larger amount of positive words than negative words. These effects lead the authors to suggest that OT modulates emotional processing by improving detection of positive social stimuli.

Conversely, another study assessing OT effects on verbal affective recognition have found OT to selectively improve recognition of

positive reproduction-related words (Unkelbach, Guastella, & Forgas, 2008). In this study, the OT group were faster at recognizing both positive sex-related and positive relationship words than the placebo group ($p<.05$). In relation to this, it is relevant to note that this study does not focus on memory. Instead, it focuses on recognition of words and can therefore not be directly compared to the other tests where memory is assessed. However, the study can aid the understanding of OT effects on word processing.

Emotion Recognition

Oxytocin improves emotion recognition

A known putative effect of OT is its ability to increase emotion recognition, however the following studies assessing emotion recognition show discrepant effects of OT (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). Some of the studies have in fact reported that OT seems to enhance emotion recognition abilities (Leknes et al., 2013; Schulze et al., 2011). For instance, a study by Domes et al. (2007) assessed emotion recognition by employing a test called Reading The Mind In the Eye, where the participants are to infer the emotional states of others. Results showed that OT significantly improved ability to infer emotional states of other. This effect of OT was also found in a study that investigated OT effects on a subclinical group and found that high alexithymia scorers increased their abilities in an emotion recognition test after administration of OT (Luminet, Grynberg, Ruzette, & Mikolajczak, 2011).

Oxytocin increases salience of social stimuli

Similarly, a study by (Lischke et al., 2012; Prehn et al., 2013) assessed emotion recognition by employed a design with dynamic facial expression, which means that the pictures varied in the emotional intensity they conveyed. Lischke and colleagues found that OT significantly increased emotion recognition ability by lowering the emotional intensity required for recognizing both positive and negative types of emotions. Prehn and colleagues also found that OT significantly lowered the required intensity for

recognizing all types of emotions expressed by both males and females, and they hereby suggest that OT increases salience of affective and social stimuli.

Conversely a study by Cardoso, Ellenbogen, and Linnen (2013) observed a decreasing effect in emotion recognition accuracy after OT administration. However, authors also argue that OT administration enhances the salience of social stimuli and hereby induce an "oversensitivity" in the interpretation of social stimuli for instance in emotional expressions. They argue that the enhancement of salience, which is modulated by OT is explanatory for the decreased emotion recognition accuracy. This OT effect of decreased accuracy was not found on tests with nonsocial stimuli.

Oxytocin generates a positive bias

Other studies found that OT increases processing of positive affective stimuli and hereby creates a positive bias. The above-mentioned study by Di Simplicio et al. (2008) assessed other social cognitive domains than verbal affective memory in their study. The study also investigated emotion recognition and found a general improvement in detection of positive social stimuli but not for emotion recognition. Correspondingly, a study by Domes, Sibold, Schulze, Lischke, Herpertz and Heinrichs (2013) reported that OT produced an attentional bias for happy faces compared to angry faces. Similarly, a study by Domes, Steiner, Porges, and Heinrichs (2013) did not find any OT effects on emotion recognition accuracy like Cardoso et al. (2013). Nevertheless, the authors of this study, which also assessed eye-gaze suggest, that OT modulates eye-gaze by remaining the increasing eye-gaze for happy facial expressions and decreasing eye-gaze for angry facial expressions. Hereby, the authors suggest that OT affects visual attention by increasing attention towards positive social signs. This study was replicated by Marsh, Yu, Pine, and Blair (2010) who also found that administration of OT improved recognition of positive facial expressions. The increase of processing of positive social stimuli is also found in a study by Guastella, Mitchell, and Mathews (2008) where OT increased encoding of positive social memories. A study by Tollenaar, Chatzimanoli, van der Wee, and Putman (2013) found that OT both increases eye-gaze cueing scores for

happy and angry facial expressions. In relation to this, a study by Kim et al. (2014) found that OT significantly reduced attention bias towards faces expressing negative emotions compared to placebo. This effect was particularly noticeable for the emotion disgust. Similarly, Ellenbogen, Linnen, Grumet, Cardoso, and Joober (2012) found that OT creates a positive bias by decreasing the engagement score for sad faces. Hereby, the effects listed above present changes in social information processing. Here, OT was found to create a positive bias by either increasing the processing of positive emotions or decreasing processing of negative emotions.

Oxytocin generates a negative bias

These reported effects of OT as increasing recognition and processing of positive social information is incoherent with other studies. These have reported that OT only increases emotion recognition accuracy for certain negative emotions such as fear (Fischer-Shofty, Shamay-Tsoory, Harari, & Levkovitz, 2010; Savaskan, Ehrhardt, Schulz, Walter, & Schachinger, 2008). A study by Guastella, Carson, Dadds, Mitchell, and Cox (2009) did not find any drug effects of OT compared to placebo with respect to emotion recognition. Here the participants were shown a variety of smileys with emotional expression and were to indicate whether these were expressing the same emotion of if one was discrepant. Instead, all participants despite drug intervention (placebo and OT) were faster and more accurate in detecting happy and neutral faces as opposed to angry faces.

The effects of intranasal oxytocin on empathy, generosity and trust

The modulatory effects of OT on trust have since the mentioned groundbreaking study by Kosfeld et al. (2005) been assessed by other researches. Results from this study showed that OT increases trust in humans and more specifically affect participants to take risk in social situations where money is included. Subsequently, studies have employed several variations of this paradigm to investigate OT effects on participants' behavior in

situations where monetary risk and social components are included. However, there is a discrepancy in what the authors argue that these paradigms assess. For instance, authors assessing variations of the paradigm, argue that they are assessing trust, empathy, compassion or generosity. Here, a wide perspective is employed, where the studies included assess OT effects on performance in tests with social components and/or monetary risks. Therefore, the paradigms in this section can be said to investigate altruistic or mentalizing behavior by employing various types of tests. For instance, a study assessing OT effects on the perception and ratings of faces found that OT increased perceptions of faces and more trustworthy and attractive (Theodoridou, Rowe, Penton-Voak, & Rogers, 2009).

Baumgartner, Heinrichs, Vonlanthen, Fischbacher, and Fehr (2008) conducted a study with a similar method as Kosfeld and colleagues assessing the OT effects in a trust game where the participant transfers money to another person and receive information that their trust will be breached 50% of the time. They also included a risk condition where the participant transfers money and is told that a computer will repay the transfer 50% of the time. The results were consistent with Kosfeld and colleagues' findings to the extent that the participants receiving OT showed significantly higher levels of trust than the placebo group when a social component was added to the game despite that both the risk and trust conditions yielded the same monetary risks (Baumgartner et al., 2008). Both studies reported that there was no difference between groups in the risk game, which did not include a social component.

In relation to these studies, OT effects on generosity have been assessed in a study that also included both a monetary and social incentives (Zak, Stanton, & Ahmadi, 2007). The test design included an Ultimatum Game test, where participants are assigned to the role of a decision-maker (DM1), who will divide the money, or a decision-maker (DM2), who can choose to accept or reject the division of the money between DM1 and DM2. If DM2 accepts the offer from DM1, then they both get the amount assigned by DM1. If DM2 rejects the offer, then neither of them receives money. The test therefore assesses fairness sensitivity and generosity. Both participants

with active and placebo treatment comprised the roles of DM1 and DM2. Results showed that the offers of participants in the role of DM1 were 21% larger in the OT condition compared to the placebo condition. Furthermore, generosity was 80% higher in the OT condition, since participants here accepted significantly lower offers than the placebo condition.

Radke and de Bruijn (2012) also found that OT administration affects behavior in relation to social norms in an Ultimatum Game context. However, they reported that the OT group offered a lower amount of money to their opponent compared to the placebo group, which suggests a decline in generosity. They also assessed the OT effect in a Dictator Game where the participants were to allocate an amount of money to their opponent. Here they found that participants in the placebo group offered the opponent a lower amount compared to the placebo group. Both the results from the Ultimatum Game and the Dictator Game hereby suggest that OT decreases generosity.

Bartz, Zaki, Bolger, et al. (2010) assessed the effects of OT on empathetic accuracy in healthy individuals that had completed an Autism Spectrum Quotient Questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) before the intervention. All participants were within the normal spectrum and did not have autism spectrum disorder. However, they found that participants with high autism quotient scores had improved empathetic accuracy after OT intervention. This suggests that OT improves the ability to infer and relate to the mental states of others.

Rockliff and colleagues (2011) assessed the effects of OT on compassion. More specifically, they assessed participants' self-reported abilities of Compassion Focused Imagery (CFI), which is the ability to imagine another mind being exceptionally compassionate towards oneself. It was also assessed how this ability interacted with feeling safe with others and self-criticism. Participants were instructed in CFI and guided in this process before assessment of this ability. They found that administration of OT significantly increased compassionate qualities compared to placebo ($p<.001$). They also found that participants who were lower in social safeness, attachment security, self-reassurance and higher in self-criticism reported a less positive experience of CFI under influence of OT compared to placebo.

This leads the authors to suggest that the experience of compassion and affiliation can be affected by attachment and self-perception (Rockliff et al., 2011).

Summary of the effects of intranasal oxytocin on social cognition

Three of the studies included in the review assessed verbal affective memory. One study found that OT significantly impaired recall of all types of words compared to placebo (Heinrichs et al., 2004). Two other studies found that OT increased the processing of positive words (Di Simplicio et al., 2008) and increased the ability to recognize positive relationship and sex related words (Unkelbach et al., 2008).

The reported effects of OT on emotion recognition are varying. Five of the studies included in the review reported that OT enhanced emotion recognition abilities (Domes et al., 2007; Leknes et al., 2013; Lischke et al., 2012; Prehn et al., 2013; Schulze et al., 2011). Three studies found that OT created a positive bias by increasing the processing of positive stimuli (Domes, Sibold, et al., 2013; Domes, Steiner, et al., 2013; Guastella, Mitchell, & Mathews, 2008) and one found that OT reduced the attention to negative stimuli (Kim et al., 2014).

Two studies reported that OT increased recognition of negative emotional stimuli (Fischer-Shofty et al., 2010; Savaskan et al., 2008). One study from the review reported no effects of OT (Guastella et al., 2009). Furthermore, one study found that OT decreased emotion recognition accuracy by increasing the salience of the social stimuli presented (Cardoso et al., 2013).

The classical study by Kosfeld et al. (2005) inspired other researchers to investigate the effects of OT of trust in humans. Like Kosfeld and colleagues, another study found that OT increases trust (Baumgartner et al., 2008). Furthermore, another study found that in relation to monetary investments, OT increases generosity in humans (Zak et al., 2007). Similar studies reported that OT increases empathic accuracy (Bartz, Zaki, Bolger, et

al., 2010) and improved ease of imagining compassionate qualities (Rockliff et al., 2011).

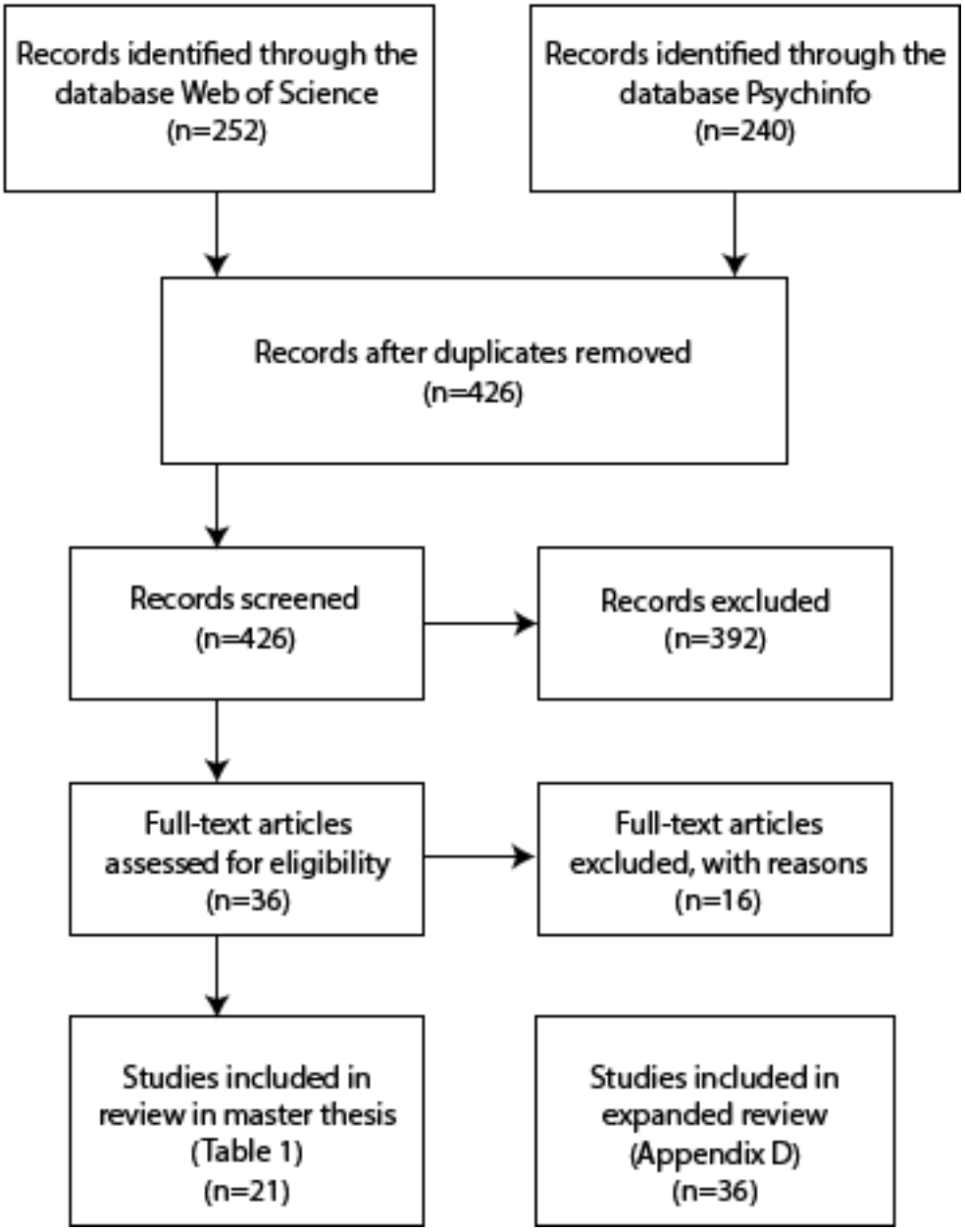

Figure 3 - Prisma flow diagram illustrating the screening process for the systematized review

Systematized literature review of literature on the effects of intranasal oxytocin administration on cognitive measures					
Reference	**Participants**	**Study design**	**Dose**	**Outcome measures**	**Primary findings**
Bartz et al. **2010 (a)**	27 males, (mean age 26.8 ± 7.0)	Randomized, double-blind, placebo-controlled, within-subject crossover.	24 IU	Autism spectrum Quotient questionnaire (AQ) Naturalistic empathetic accuracy test	AQ had a significant over-all ↓ effect on empathic accuracy. OT ↑ empathic accuracy for high AQ-scorers.
Baumgartner et al**. 2008**	49 males, (mean age 21.7 ± 2.5)	Randomized, double-blind, placebo-controlled, between groups	24 IU	Risk game with no social interaction. Trust game with social interaction where participants' trust was breached 50% of the times	Risk game: No differences between groups p=0.85. Trust game: OT treatment no changes in behavior when trust was breached 50% of the time. Placebo treatment ↓ trusting behavior. Difference between groups p=0.04.
Cardoso et al. **2013**	40 males, 42 females, (age range 18-30)	Randomized, double-blind, placebo-controlled, between groups	24 IU	Emotion Identification	OT ↑ ratings of facial stimuli as expressing emotional intensity. OT ↓ emotion recognition accuracy p<0.01
Di Simplicio et al. **2009**	29 males, (age range 18-30)	Randomized between-groups, double-blind, placebo-controlled design, between groups, groups were matched.	24 IU	Emotional processing (Facial expression recognition and memory, emotional categorization, memory and attention)	OT ↑ recalling of more positive than negative words (p=0.023). Trend for recognition of positive words compared to negative (p=0.073). No OT effect on word categorization accuracy, self-relevant words or recognition of emotional self-referential words

Domes et al. **2007**	30 males, (mean age 25.3 ± 2.2)	Double-blind, placebo-controlled, within-subject crossover	24 IU	Reading the Mind in the Eyes Test: ”Easy” and ”difficult” conditions	OT significantly ↑ inference of social cues for difficult items and not for easy items $p<0.006$.
Domes et al. **2013 (a)**	62 males, (mean age 24.0 ± 2.5)	Randomized placebo-controlled, double-blind, between groups	24 IU	Dynamic Affect Recognition Evaluation. Neutral face gradually changing into either anger or happiness	OT ↑ eye gaze for neutral and happy facial expressions but not for angry facial expressions. No effects of OT on emotion recognition accuracy.
Domes et al. **2013 (b)**	69 males, (mean age 24.0 ± 3.1)	Randomized placebo-controlled design, between groups	24 IU	Dot-probe task with angry, happy and neutral faces. Two conditions: long duration and short duration	OT produces attention bias for happy faces for short duration ($p=0.05$) but no effects were shown for the long duration exposure to facial expressions.
Ellenboge n et al. **2012**	OT: 13 males 15 females, (mean age 23.2 ± 3.3). Placebo: 14 males 15 females (mean age 23.6 ± 3.5)	Placebo-controlled, double-blind, between groups	24 IU	Dot probe design. Emotional face (sad, angry or neutral) signaling the likely location of the dot. Images shown for 750 ms, 200ms or 17ms	OT ↓ engagement score for sad faces at but not for angry faces in the 750 ms condition.
Fischer-Shofty et al. **2010**	27 males, (mean age 26.9 ± 3.5)	Randomized, double-blind, placebo-controlled, within-subject crossover	24 IU	Emotion recognition assessed with intensity morphed faces, 6 basic emotions, 100 frames during 10 sec.	OT ↑ recognition of fear but not other emotions. No difference between groups in reaction time of emotion-detection or for rating of mood.

Heinrichs et al. **2004**	38 males, (mean age 23.7 ± 3)	Randomized placebo-controlled double-blind, between groups	24 IU	Four phase memory test -'implicit perceptual test', implicit conceptual task' and 'cued recall test'. Mood state questionnaire	OT ↓ explicit recall performance across categories. Conceptual memory: OT group showed ↓ in ability to name words associated with reproduction. No effect of OT on mood states or implicit perceptual memory.
Kim et al. **2014**	31 females, (mean age 22.2 ± 2.2)	Randomized double-blind, placebo controlled, within-subject crossover	40 IU	Positive And Negative Affect Scale.Visual attention dot probe task. Behavioral Inhibition system/Behavioral Approach system questionnaires (BIS/BAS)	OT ↑ positive mood**.** OT specifically ↓ attention bias towards the faces showing negative emotion p=0.011. BAS-Drive positively correlated with OT on negative emotion p=0.007. No effect of OT on attentional bias towards happy faces.
Kosfeld et al. **2005**	66 males, (mean age 22.0 ± 3.4)	Randomized, double-blind, placebo-controlled, between groups	24 IU	Participants played role of investor. Risk game: told that computer randomly divides amount of invested money. Trust game: told another person divides the invested money.	Risk game: No significant group differences between the investor's behaviors. Trust game: OT ↑ the amount of transfer from the investor (p=0.035) suggesting that OT increases the trust for social situations both does not affect ability to take risk in non-social contexts.
Leknes et al. **2013**	19 males, 20 females, (mean age 26, age range 20-39)	Counterbalanced, double-blind, placebo-controlled, within-subject crossover	40 IU	Emotion recognition with implicit and explicit emotions (happy, angry and neutral) including rating of emotional intensity. Eye-tracker.	OT ↑ emotion detection of explicit and implicit emotional stimuli for happy (p=0.021) and angry (p=0.042) facial expressions.

Lischke et al. 2012	47 males, (mean age 26.09 ± 3.41)	Randomized, double-blind placebo-controlled, between groups	24 IU	Emotion recognition: neutral faces morphing into emotional faces: happy, angry, fearful, sad.	OT ↑ ability to recognize emotional expressions at lower intensity levels for all types of emotions (p=0.03). OT had no overall effect on recognition accuracy.
Marsh et al. **2010**	29 males, 21 females, (mean age 26.41, age range 20-40)	Randomized double-blind, placebo-controlled, between groups	24 IU	Morphed facial expressions.	OT ↑ emotion recognition only for happiness p=0.04. No effect of gender. No effect of OT on response bias and mood change.
Prehn et al. **2013**	47 males, (OT: n= 23, mean age 25.8 ± 3.4, placebo: n=24, mean age 26.4 ± 3.5)	Double blind, placebo-controlled, between groups	24 IU	Emotion recognition task (gradually morphing emotional intensity) Pupillometri	OT ↑ recognition for lower emotional intensity of angry stimuli p=0.010. OT generally ↑ pupil diameter p=0.047.
Radke & de Bruijn **2012**	24 males, (mean age 21.46 ± 1.93)	Randomized, double-blind, placebo-controlled, within-subject crossover	24 IU	Generosity assessed with Dictator Game and Ultimatum Game	OT ↓ generosity in both games
Savaskan et al. **2008**	18 males, 18 females, (mean age males 28.8 ± 1.7, mean age females 26.1 ± 1.3)	Randomized, single-blind, placebo-controlled, between groups	20 IU	Facial recognition memory test. Participant were to indicate if a face was a new or known (previously shown) face and identify emotional expression (happy or angry).	d' ↑ for OT group for angry faces p=0.03 but not for happy faces. Females had ↑ tendency for false alarms (p=0.02). OT ↓ false alarm rate (p=0.04). Total mean score showed no significance between groups.

Schulze et al. **2011**	56 males, (mean age 24.18 ± 3.12)	Randomized, double-blind, placebo-controlled, between groups	24 IU	Emotional face test: Participants indicate which emotion is shown (angry, happy or neutral) for 18, 35 or 53 ms.	d' ↑ for OT for all emotional stimuli $p<0.001$. OT ↑ emotion recognition for happy $p=0.005$. Both groups had ↑ d' for happy than angry faces $p<0.001$
Theodoridou et al. **2009**	48 males, 48 females (OT: n=51, mean age 21.1, placebo: n=45, mean age 21.9)	Double-blind, placebo-controlled, between groups	24 IU	Evaluation of trustworthiness and attractiveness of faces (both sexes) with neutral expression. Target face displayed until a response was made. Mood questionnaire.	OT ↑ perception of faces as more trustworthy and attractive $p=0.04$. Correlation between trustworthiness and attractiveness ratings for both groups $p<0.001$.
Zak, Stanton & Ahmadi **2007**	68 males, (mean age 21.8 ± 3.8, OT: n=34, placebo: n=34)	Double-blind, placebo-controlled, between groups	40 IU	Ultimatum Game and Dictator Game assessing generosity	OT ↑ generosity by 80% in tests with social components

Table 2. This table illustrates the small review conducted on the effects of intranasal oxytocin (OT) on affective and social cognition. It comprises 21 studies. It specifically includes studies on verbal affective memory, emotion recognition and trust including empathy and generosity. The first column includes the authors and publication year, which are listed in alphabetical order. In the second column, participants' mean age and standard deviation are presented in years with one decimal for all studies. The third column presents the study design and the fourth column outline the dosage administrated in intranasal units (IU). The fifth column indicates the measure employed and the sixth column provides the overall results.

Challenges regarding the literature on the modulatory effects of oxytocin on affective and social cognition

Dosage and effects of oxytocin

The most common dosage of OT in the studies mentioned in the review is 24 IU (see Appendix C). However, there is a discrepancy in dosage of OT in these studies, since other studies employed higher or lower doses, which could potentially be influential of the results. Four studies employed a dosage of 40 IU. These four studies have in common that they all found significant effects of OT on social cognitive measures. Here it is found to increase positive mood and decrease attention towards faces showing negative emotions (Kim et al., 2014). In another study employing 40 IU OT, investigators assessed empathic ability via perceived harm for victims of criminal offenses. Results showed that OT increased participants' perception of harm for the victims but did not increase their desire to punish the criminal offenders (Krueger et al., 2013). Furthermore, a study assessing generosity employed the same amount of OT. Here the investigators found that OT increased generosity by 80% (Zak et al., 2007). With respect to emotion recognition, the study employing 40 IU OT, reported that OT increased detection of both explicit and implicit emotional facial expressions for happy and angry faces (Leknes et al., 2013). Since these four studies found effects of OT, it raises the question of whether a higher dosage is required in order to produce more unambiguous robust effects in this type of intervention studies.

Similarly, other studies employing a higher OT dosage than the majority found an increase in social awareness on different social domains (Gallup & Church, 2015; Luminet et al., 2011) by employing 30 and 32 IU respectively. OT effects was found in all the studies administrating a higher dosage except for one study where OT did not modulate behavioral domains, however it decreased amygdala activity (Kirsch et al., 2005). The two studies

where a lower OT dosage was delivered reported ambiguous results. For instance, one study reported an increased ability to detect negative and not positive stimuli after administration of the hormone (Savaskan et al., 2008), and the found that OT increased positive rating of both social and non-social stimuli and decreased arousal when presented to threatening stimuli (Norman et al., 2011). These results also point to the fact that a higher dosage of OT will be most beneficial in providing clear and robust findings of OT, since some of the studies employing 24 IU or less show varying results. Hereby this will establish in the lacking consensus on OT effects were merely due to the dosage being too low of if the OT system is more complex than assumed.

Methodological considerations in administration of oxytocin

Nasal administration of oxytocin

In 2002, Born and colleagues argued that a so-called "transnasal approach" to the human brain is valid. They investigated the concentrations of different peptide in the CSF and blood after intranasal administration, including the OT-like peptide vasopressin. Intranasal administration of all peptides resulted in a significant increase in CSF levels of these peptides. However, the study does not clarify whether peptide uptake into brain tissue is possible. The authors advocate that intranasal administration of peptides have great potential, since it is non-invasive, it does not produce strong side effects and can produce substantial effects on the brain in small amounts (Born et al., 2002). Despite the promising findings concerning the prosocial effects of OT, some researchers however remain critical of these effects. They claim that there is an insecurity in determining the effects of OT due to its interactive effects with other hormones, as well as OT's stability and intricacies in the blood-brain barrier (Churchland & Winkielman, 2012). In relation to this, some have argued that the OT molecule is not able to cross the blood-brain barrier (Evans, Dal Monte, Noble, & Averbeck, 2014). Evans and colleagues argue that the peptide OT is unable to cross the blood-brain barrier and that it is still to be documented if it reaches the brain through

intranasal administration. However, they claim that the evidence of the modulatory effects of intranasal OT on social cognitive measures are converging. They explain that there exists three possible ways that intranasal administration of OT can affect social cognition. The first way is through diffusion to the central nervous system (CNS) where it can activate OT receptors. The second way is that it can affect behavior is by indirectly activating a central release of OT through peripheral mechanisms. Thirdly, the described indirect peripheral effects are assumed to produce a central release of OT, which then modulates behavioral effects (Evans et al., 2014). The authors hereby claim that there is a possibility of intranasally delivered OT to affect social cognition, but it does this by indirect mechanism rather than crossing the blood-barrier and hereby producing a direct behavioral influence.

Considerations of dosage and time window of oxytocin effects

Another factor that could potentially influence the modulatory effects of OT is that studies assess the effects with different doses and at different time points after administration. There is a wide consensus in the studies of employing 24 IU (see table 2). However, some studies administrate a smaller dosage (Savaskan et al., 2008) and some administrate a larger dosage (Zak et al., 2007). There is a probability that higher dosages of OT will produce more pronounced effects on affective and social cognition. Regarding the time-window of OT effects, the test designs could have the potential flaw that OT effects might be undetected because of the selected time point for testing. Here, the administrated hormone might not have reached significant levels yet or conversely that the optimum for testing the effects have passed. Striepens and colleagues (2012) determined that OT levels in the CSF were significantly higher up to 75 minutes after intranasal administration compared to the placebo group. The dose investigated here was 24 IU as employed in the majority of the studies assessing OT effects on social cognitive measures. For a discussion of the dosage and time window of assessing OT effects see the discussion section under *Dosage and time window of oxytocin effects*.

Methods and limitations in the presented study designs

In experimental research, where one variable is manipulated, we want the study design to be robust in order to generate valid and reliable data. Thus, the study design is relevant to have in mind when interpreting the results of the study. Here, the study designs from the review will be outlined in order to discuss the most optimal form of study design to employ in this type of experimental research. All 21 the studies included in the review have employed placebo-controlled study designs. The strength of placebo-controlled design is that it produces a comparable group to the group receiving the active compound, which is necessary in experimental research testing (Misra, 2012). Of the studies included in the review in Table 2, nine studies had a randomized design and two studies employed a counterbalanced design. Randomization is valuable in a study design in order to ensure that the unsystematized variation remains as low as possible. For study designs with repeated measures, a randomized study design eliminates practice effects and boredom effects that can occur in the second condition (Field, 2009) as well as confounding baseline variables (Misra, 2012). Of the total of 21 studies, 20 studies had a between groups study design and 7 of these had a within-subject crossover design. The between groups design comprise the limitations that the differences between groups can be caused by differences in the participants assigned to each group, which can interfere with the measuring of the effect of the intervention. Including a large number of participants can oblige this. In the within-subjects design, the difference between the two conditions can be caused by either the intervention or a difference in participants' performances in the conditions. However, the probable cause of the difference in conditions is the intervention, whereas the between-groups design is likely to produce considerable variance (Field, 2009). The within-subjects crossover study designs presents strengths to a study in that it allows the investigators to avoid potential confounders, which can be variations between individuals such as perception of and response to emotional stimuli. Hereby, this study design also enables investigators to compensate for unsuccessful randomization and demonstrate reversibility (Thiese, 2014). Furthermore, adding a double-blind procedure can strengthen

the study. In the review 24 studies had included a double-blind procedure in their design. Double-blinding in a placebo-controlled study is important in order to demonstrate causality. Hereby, neither the study staff, investigators or participants can have any expectations to the results that might influence the data (Misra, 2012).

There is an outweighing number of strengths to the randomized double-blind placebo-controlled, crossover study design. However, every study has its limitations. This type of study design can be time-consuming. The study design can be affected if participants withdraw from the study after participating in one condition since this compromises the crossover design. Nevertheless, compared to other designs, the level of evidence provided by a randomized double-blind placebo-controlled study designs is nearly 100%. Thus it is considered to be the gold standard in experimental research, since it has the advantage of being able to demonstrate causality (Misra, 2012). Thus, this type of study is employed in the empirical study.

Empirical study at NRU on the effects of oxytocin

In line with the above-mentioned strengths and limitations to various study designs, the empirical study has employed a double-blind, randomized, placebo-controlled, within-subject crossover study design, since this study design eliminates influence of confounding variables and hereby provides the most convincing research design (Misra, 2012). The dosis of OT employed in the study is selected due to the wide consensus in OT studies assessing social cognition of using 24 IU. This dosis is employed in 28 of the 36 of the studies in the expanded review (see Appendix C).

Summary of part two

This part of the thesis aims to answer the second research question and hereby illuminate what the scientific literature informs us about regarding the affective and social cognitive effects of OT. Here, the different classes of hormones are outlined and the peptide hormone OT is described in relation to its functioning in the body. Subsequently, the central and peripheral effects are explained. Furthermore, it is elucidated how the knowledge of the

pharmacological composition of this hormone has enabled synthetic production. The interest of assessing the modulatory social cognitive effects of OT began with a study conducted by Kosfeld and colleagues (2005), where they found that OT increases trust in humans. Since then, the interest has grown immensely, with many studies assessing various types of social cognitive functioning. In order to provide an over view of the literature in the area, a review has been conducted and presented in this part of the thesis. This is divided in an expanded review including 36 studies and a more specific review including 21 studies. The findings from the review of 21 studies are outlined in the thesis, since these studies assess the same types of social cognition functions as the empirical study. Therefore, the three types of social cognitive functioning investigated with OT are verbal affective memory, emotion recognition and trust including empathy and generosity. The results of the effects of OT on verbal affective memory are discrepant, but two of the studies found that OT increased processing of positive words. A large group of the studies assessing emotion recognition reported increased emotion recognition abilities after OT administration, however a broad consensus of this effect was not established across studies. The studies investigating different trust domains reported both that OT increased trust generosity and empathetic accuracy.

Part three

The third part of the thesis comprises an empirical study assessing the modulatory effects of OT on affective and social cognition. Since this study is conducted in collaboration with NRU, this research unit will be briefly introduced preliminary to the empirical study. Subsequently, the theoretical foundation of the applied test battery EMOTICOM and a verbal affective memory test are elucidated. Taking its starting point in the official protocol for the study, the participants and procedures are described. Following this, the measures and results are presented. Ultimately, topics covered in all three parts of the thesis are discussed.

Empirical Study

NRU

The empirical study for this master's thesis is conducted at NRU, Rigshospitalet in Copenhagen. The study in this master's thesis is conducted in relation to the project databases by the name of Center for Integrated Molecular Brain Imaging (CIMBI). The Lundbeck Foundation has provided NRU with a grant, which has enabled the CIMBI project to last from 2006 until 2015 (www.cimbi.dk). The OT empirical study is one of the last studies under this project. The aims of the research conducted under the CIMBI project include uncovering differences in behavior and personality between healthy individuals with respect to phenotypical variations relating to the serotonin systems.

The primary role for the cognitive psychology group called NRU-C is providing a cognitive, psychological perspective with respect to differences in cognitive functioning in psychiatric illnesses compared to healthy individuals as well as predicative aspects on drugs effects on the basis of personality and cognitive functioning. Hereby, the OT study, focusing on the predicative aspects of responses on affective and social cognitive tests on OT effects in individuals suffering from depression, falls entirely within the scope of NRU-C. The empirical study is essential on the basis that the method and study design are verified and potentially optimized before conducting the study on a larger scale with participants who are more sensitive. Naturally, the empirical study is also valuable in the sense that it provides a more or less certain idea of the drug effects on the applied cognitive measures. The empirical study included in this thesis is the pilot study from this project.

Theoretical foundation of EMOTICOM

The affective and social cognitive tests comprising the EMOTICOM test battery are similar to tests currently employed in neuropsychiatry and neuropsychology (Bland et al., 2016; Todorov et al., 2011). Individual responses on the tests assessing affective and social cognition have been

investigated by employing neuroscientific techniques such as neuropsychological testing and brain scans. The vast amount of research in relation to neuroscientific investigation of affective and social cognition processing has provided converging evidence with respect to the neural substrates of these cognitive processes as well as provided evidence for a separation of social cognition and non-social cognition (Todorov et al., 2011). Due to the nature of the test design in the pilot empirical study, the focus is on the affective and social cognitive, psychological neuroscientific research with respect to the tests in the study. In the following, a description of the theoretical framework for each test included in the empirical study will be presented.

Methods

Participants and procedures

The information in this 'Participants and procedures' section are taken from the study protocol (see enclosed appendix B), which have been approved by the Scientific Research Ethics Committee of the Capital Region (In Danish: Videnskabsetisk Komité Region Hovedstaden) under the protocol number H-15004506 on June 9th 2015. The study has also been approved by the Danish Data Protection Agency (In Danish: Datatilsynet).

Recruitment

After the necessary approvals for the conduction of the study, links for recruitment to the study were established on the websites www.nru.dk and www.forsoegsperson.dk. The websites allow participants to sign up for the study and read the criteria for inclusion and exclusion. In connection with this, they have to answer questions regarding their mental and physical health in order to determine if they meet the inclusion and exclusion criteria for the study. This information is delivered to a database at NRU from which the participants are recruited. Prior to including participants in the study, they are

contacted via telephone and screened in order to ensure that they do in fact meet the criteria for inclusion and exclusion.

Inclusion criteria

- Healthy, fertile females between 18 and 45 years of age.

Exclusion criteria

- Psychiatric disorder (DSM-IV Axis and WHO ICD-10 diagnostic classification).
- Current or previous neurological disorder including traumatic brain injury and/or severe somatic disorder.
- Consumption of any medication that can be presumed to affect the test results.
- Non-fluency in Danish.
- Distinct visual or auditory impairment.
- Pregnancy and breastfeeding.
- Use of systematic, hormone-based contraceptives.
- Irregular menstrual cycle and/or menstrual cycle with a duration shorter than 23 days or longer than 35 days.
- Alcohol or drug abuse
- Allergy to any of the ingredients in the drug used in the study
- Declining information about health condition in the case of signs of somatic disorder in connection with the study

Intervention

The investigational program for the study includes the following:

- Health assessment and history
- Collection and analysis of biological material
- Completion of questionnaires
- Intervention with OT 24 IU and placebo in crossover design
- Neuropsychological assessment

- Psychophysiological measurements such as skin conductance, blinking reflex, pulse and respiration.

Assessment of current health and health history

The assessment of current health and health history include obtaining detailed information of potential previous disorders, hereditary predispositions, use of tobacco and alcohol, as well as a short psychiatric interview screening for psychiatric disorders. Furthermore, a doctor or medical student will conduct a clinic somatic and neurological assessment.

Collection and analysis of biological material

Collection of biological material will be conducted both for the pilot study and the main study. However, in the pilot study the biological material collected will be limited to saliva samples and the main study will include both collection of blood and saliva samples.

Questionnaires

The participants are to fill out questionnaires regarding trait and state. The trait questionnaires are filled out by the participants at home before meeting up for the interventions. The trait questionnaires include the Aggression Questionnaire, Barratt Impulsiveness Scale 11, Edinburgh Handedness Inventory, Highly Sensitive Person Scale, The Revised NEO Personality Inventory, The Online Stimulant and Family Assessment Module, Parental Bonding Instrument (one for each parent), Positive Life Events, Stressful Life Events, Sensation Seeking Scale and Temperament and Character Inventory. There will be two intervention days – one for OT and one for placebo in randomized order. For both intervention days, the participants have to fill out state questionnaires including The Major Depression Inventory, The Perceived Stress Scale, The Pittsburgh Sleep Quality Index, The Profile of Mood States and The Symptoms Checklist Revised.

Intervention with oxytocin and placebo

Each participant will on one of the intervention days receive 24 IU synthetic OT provided by six puffs of a nasal spray containing 6.7 micrograms OT per dose with the equivalence of 4 IU per dose. The pharmaceutical name for the synthetic OT employed in the study is Syntocinon. On another intervention day, which is randomized in order, the participant will receive a placebo intervention. The placebo intervention consists of an isotonic saline solution. All participants will be thoroughly instructed in using the nasal spray and supervised when using the product. This is in order to ensure standardization with respect to the intervention.

Neuropsychological assessment

The neuropsychological assessment for the pilot study will differ from the main study. In the main study this assessment will consist of a test-battery that is a standard neuropsychological assessment procedure at NRU. This test-battery comprises a variety of cognitive measures, which are carefully selected to fit the type of research conducted at NRU. These cognitive measures are employed in neuropsychological assessment internationally, however the cognitive measures also include a test developed by the psychology group at NRU. The tests included in the battery are in the enclosed appendix A where they are explained in detail. Here they are briefly outlined and only the test developed by the psychology group at NRU, called the Verbal Affective Memory Task-26, is described in detail in the 'Methods' section. The full test battery employed in the main study comprise the following tests: Reynolds Intellectual Screening Test, Simple Reaction Time, Emotional Face Recognition Task, Trail Making Test, Design Fluency Test from D-KEFS, Word Fluency, Symbol Digit Modalities Test, Letter-Number-Sequencing from WAIS-III, Emotional Go/NoGo Task, Cambridge Gambling Task, and Verbal Affective Memory Task-26. In addition to the standard test battery at NRU, the neuropsychological assessment in the main study also includes five selected tests from the newly developed EMOTICOM test battery. Since the modulatory effects of OT on affective and social cognitive measures are assessed, the EMOTICOM tests measuring these

types of cognition will be employed in the time window where the effects of OT are expected to occur. The cognitive measures in the pilot study is limited to Verbal Affective Memory Task-26 and the five selected EMOTICOM tests. The tests from the EMOTICOM test battery include the Face and Eyes Emotional Recognition Task, Emotional Intensity Morphing Task, Moral Judgment, ToM, and Ultimatum Game.

Measures

Collaboration on the EMOTICOM test battery

During my internship at NRU, this pilot study has evolved from the stage of a project idea to the stage of conduction. The empirical study is led by MD. PhD. Vibe G. Frøkjær at NRU. The study is conducted in collaboration with Cambridge Cognition Group, England who has developed a new test battery by the name of EMOTICOM (Bland et al., 2016). This test battery is the first of its kind focusing exclusively on affective and social cognitive functioning (ibid.) and it is developed with the aim of evaluating treatment effects on motivational, emotional, and social function in neuropsychiatry (see overview of tests in the enclosed appendix A). The entire test battery is computerized and the participant is to reply in each test by using the keyboard or the touchscreen. The tests in the test battery are divided in categories with respect to the mentioned aims. The test battery is divided into four categories. The first category **Emotion Processing** comprises tests such as Face and Eyes Emotional Recognition Task, Emotional Intensity Morphing Task, Face Affective Go/NoGo Task, Word Affective Go/NoGo Task and Emotional Memory Recognition Task. The tests in the first category all focus on recognition of specific emotional stimuli. The second category **Motivation and Reward** includes the tests Reinforcement Learning Task, Monetary Incentive Reward Task, New Cambridge Gambling Task and Progressive Ratio Task. The tests in this category assess risk taking and decision making often in settings including monetary rewards. The third category **Impulsivity** contains the tests Delay Discounting and 4 Choice Reaction Time Task. These tests assess visual attention as well as presence of premature responses. The

fourth and last category comprises tests assessing **Social Cognition** with the five tests called Moral Judgment, ToM, Prisoner's Dilemma, Ultimatum Game and Social Urn Task. The tests in the social cognition category all have in common that they assess the ability to identify with others in either an information sampling situation or in a situation involving cooperation.

NRU and EMOTICOM

The psychology unit at NRU is particularly interested in cognition and NRU in general is interested in neurobiology and neuropharmacology. Concerning neuropharmacology, one of the specific aims is to predict outcomes of pharmacological interventions especially in relation to brain disorders (www.neuropharm.eu). Therefore, the influence of OT on cognition is a relevant area of research to NRU, especially with the new methods of assessing cognitive functioning with EMOTICOM. The tests from the EMOTICOM test battery, which are included in the empirical study at NRU, constitute four tests. They are selected from the categories of Emotion Processing and Social Cognition, since previous research indicates that OT can affect these cognitive domains (see part 2 of this thesis). The reason for minimizing the testing to include five tests is the limited time window regarding the effect of OT. Within this time window the selected EMOTICOM test and the verbal affective memory test will be conducted. These tests will be described in the following.

Tests included in the empirical study

Previous studies have studied the modulatory effects of OT on social cognitive neuropsychological measures (see Table 2). One of the aims for the empirical study is to investigate OT effects on a novel set of affective and social cognitive neuropsychological tests. Since there is a strong indication of the prosocial effects of OT, the study only employs tests assessing social cognitive functioning. By employing a novel set of social and affective neuropsychological tests, the empirical study aims to contribute to knowledge concerning the effects of OT on various social and affective stimuli (see Appendix B). Additionally, the choice of exclusively including social and

affective cognitive tests is due to the limited time window of OT effects. A study assessing the levels of OT in the CSF, found that levels had significantly increased after 75 minutes after administration of 24 IU and at 60 minutes for 40 IU (Born et al., 2002; Striepens et al., 2012). Another study investigated the levels of and OT -like peptide, arginine vasopressin. Here, 40 and 80 IU of the peptide was given resulting in significantly increased CSF levels 30 minutes after administration. The peptide was still present in significantly elevated levels in the CSF 100-120 minutes after administration (Born et al., 2002). In their article Striepens and colleagues (2012) suggest that depending on dosage, an effect of OT will occur 60 minutes after administration and be likely to increase further similar to the study by Born and colleagues (2002). These results seem to have inspired studies assessing OT effects in their planning of the neuropsychological testing. 16 of the 21 studies included in the systematized literature review commenced the neuropsychological testing 40-50 minutes after administration of OT. For instance, Ellenbogen and colleagues (2012) commenced the testing 45 minutes after OT administration. The testing lasted for 70 minutes.

Since there is no study specifically assessing the pharmacokinetic properties of OT regarding the time window of OT effects, this remains uncertain. Due to the uncertainty of the time window of effects, the tests included in the empirical study exclusively assess affective and social cognition. This also presents a limitation in that, since OT effects on cold cognitive tests are not investigated.

Description of the employed EMOTICOM tests and outcomes measures

Face and Eyes Emotional Recognition Task

The Face and Eyes Emotional Recognition (FEER) Task belongs to the Emotion Processing category in the test battery. The FEER task assesses the ability to identify emotions in facial expression and in the expression of eyes. In the Face Condition of the tests, a picture of a face is shown for 250 ms to the participant and subsequently the picture is covered up with a mask as

shown in Figure 5. The participant has to determine which emotion this face was expressing choosing from the emotions happy, sad, fear and anger as illustrated in Figure 6. These emotions are written in four separate bubbles on the screen and the participant has to press the computer screen to indicate their answer as shown in Figure 6. The facial expressions in the pictures are morphed in order to elicit different intensities of emotional expression and the test includes ten intensities for each of the four emotions. Hereby, the test has varying difficulty levels and is sensitive since it does not only assess the ability to distinguish emotions but also the ability to recognize emotions expressed at different intensities. Furthermore, this test also includes a condition where the participant must decide the age of the face as being either child, young adult, middle aged or older adult. These choices appear in the bubbles instead of the emotions as depicted in Figure 6. The test developers validated these tests in an English population. The Face Condition of the FEER test had an intraclass correlation coefficient of 0.86 and the Eyes Condition had an ICC of 0.74 (Bland et al., 2016). Thus the ICC of the Face Condition is considered to be excellent and for the Eyes Condition the ICC is good (Cicchetti, 1994).

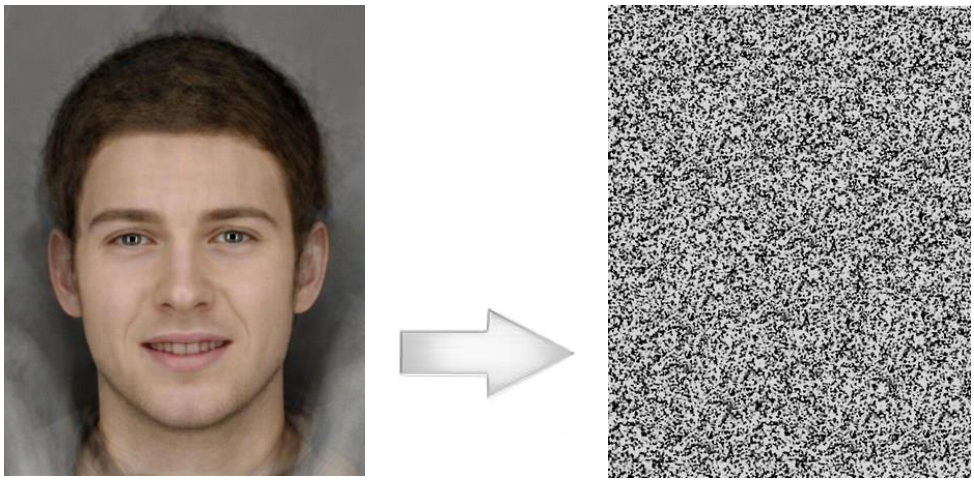

Figure 4 - This picture is part of the FEER test and here the participant must identify the emotion expressed in the face. There are 10 intensities of any emotion, this picture show an intensity of 8 on the happiness scale. The picture of the face is shown for 250 ms seconds and is then covered by a mask. Pictures are adapted from the test and Appendix A.

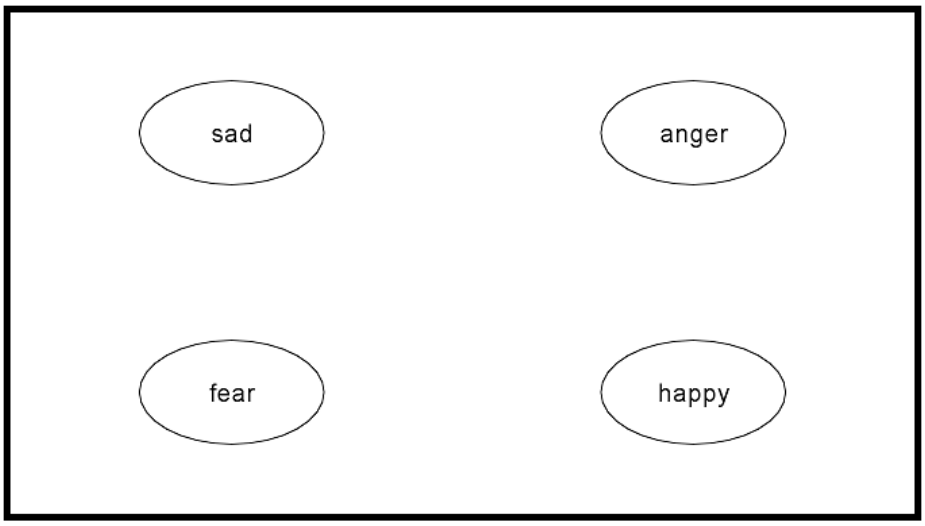

Figure 5 - This picture is part of the FEER Task and here the participant must identify the emotion. These bubbles appear subsequently to the picture and the mask and here the participant must choose which of the four emotions (sad, anger, fear and happy) was expressed. Picture is adapted from the FEER Task.

For the Eyes Condition of this FEER Task, the participant has to identify the emotion expressed in the eye region of the face as shown in Figure 7. The test design is the same as the Face Condition, where a picture is shown for 250 ms and is then covered by a mask before the participant has to press one of the bubbles on the screen indicating which emotion was present (Figure 6). Here, the stimuli have also been morphed, so that the eyes vary in the emotional intensity they are expressing. There are ten emotional intensity levels in this condition as well. The original test description can be found in Appendix A.

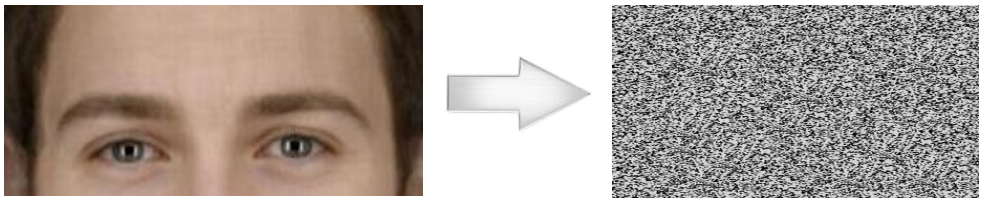

Figure 6 - This picture is part of the FEER test and here the participant must identify the emotion expressed in the eyes. There are 10 intensities of any emotion, this picture show an intensity of eight on the happiness scale. The picture of the eyes is shown for 250 ms and is the covered by a mask. Pictures are adapted from the test and Appendix A.

For the FEER Test from the EMOTICOM test battery the selected outcomes are reaction time, hit rates and false alarm rates. The hit rates and false alarm rates are employed to produce one combined measure called d'. This measure is from signal detection theory, which combines detection theory with statistical decision theory (Harvey, 2003). Eliminated the response criteria liberal conservative. d' reflects a person's actual sensitivity. The higher d', the more sensitive a person is.

The d' measure was originally invented by Green and Swets in 1966 (Green, 1966) and in the following years it was particularly employed in the growing research of operant behavior (Nevin, 1969). The d' measure indicates how well the participant can discriminate a signal from the noise (Brown & White, 2005). The d' is an index of response accuracy, which combines hit rates and false alarms to provide a complete measure where response bias is accounted for. The higher the d' value, the better the participant is at discriminating the signal from the noise (Brown & White, 2005). More specifically, when applying d' for this test, the measure indicates how well the participant can discriminate the emotion shown in the face from other emotions.

Emotional Intensity Morphing Task

The face can either begin with the highest degree of emotional intensity and then decrease or begin with the lowest degree of emotional intensity and then increase. The first condition is referred to as the descending condition and the latter the ascending condition. There are 15 levels of emotional expression in each condition. When the developers assessed the test reliability of the conditions in the test, the ICC of the ascending condition is excellent (ICC=0.80) and the ICC of the descending condition is considered to be good (ICC=0.73) (Bland et al., 2016). Before the face is shown, the participant is instructed in whether they should press the space button when they SEE the emotion or when the NO LONGER SEE the emotion. The EIM task assesses five emotions, so the face will express either happiness, sadness, fear, anger or disgust. The test design for this test is illustrated in Figure 8. The outcome measures include intensity level needed for detection of emotion for both the

ascending and descending conditions. Response latency is also an outcome measure. The original test description can be found in Appendix A.

Figure 7 - This figure illustrates the test design of the EIM task. Here the participant is to indicate when the emotion is present. The blue arrow indicates time since the face in morphed and gradually changes into depicting another degree of emotional intensity. The participant is to press the button when he is able to see the emotion. The picture is adapted from Appendix A.

Ultimatum Game

The Ultimatum Game assesses punishment tendency and fairness sensitivity. The psychometric properties showed good test reliability (ICC=0.73) (Bland et al., 2016). In this test, the participant plays against an opponent, which consists of a computer generated response style related to a certain face. Before the test begins, the participant can press a picture the opponent they would like to play against. The participant completes what they think is a skill-based task, which gives a certain amount of money depending on performance. The task is not skill-based, since the programming of the test predetermines the outcome. The participant is presented with the amount of money they have won as well as how much their opponent has won (see Figure 9). They then take turns to divide the money between them. The participant has four choices of dividing the money (see figure 10). The participant can choose to divide the money in the ratio 80/20, 70/30, 60/40 or 50/50. When the division of money is made the opponent can choose to accept or reject the offer. When the opponent divides the money, the participant can also choose to either accept or reject the offer. The opponent have different response styles requiring that the participant use his mentalizing ability in

imagining the next move of the opponent or trying to deceive the opponent and gain the most money. The outcome measures are response latency, percentage of accepted offers and breakpoint of no longer accepting an offer. The original test description can be found in Appendix A.

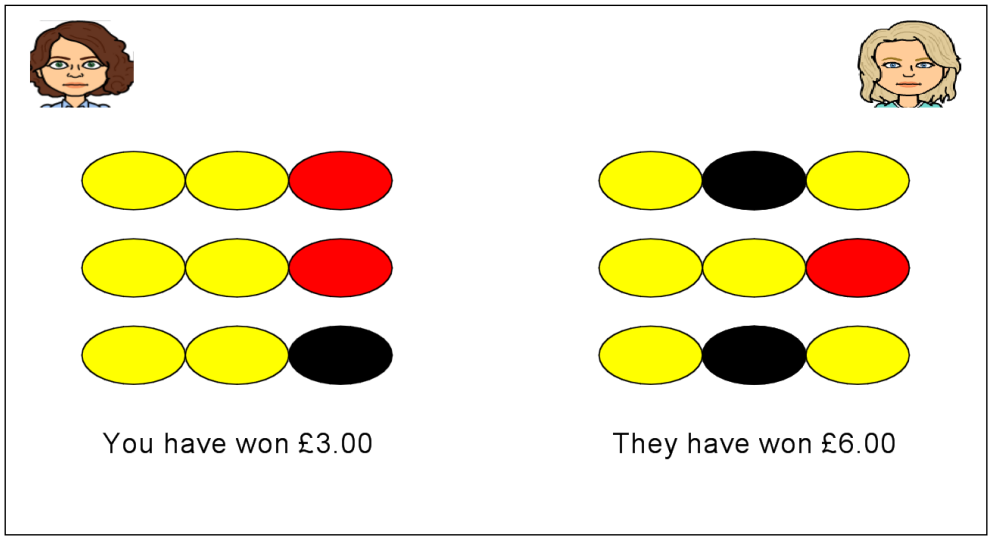

Figure 8 - The picture depicts part of the Ultimatum Game. In this particular situation, the participant must decide how to divide the money between him and his opponent. Pictures are adapted from the test.

Figure 9 - The picture depicts part of the Ultimatum Game. In this particular situation, the participant must decide how to divide the money between him and his opponent. Pictures are adapted from the test.

For this thesis, the participants' acceptance rates for unfair offers of money were calculated. The acceptance rates are corrected for the number of times the offers are presented to the participant. More specifically, the offers of 40, 35, 30, 25 and 20 percent of the money was offered twice as frequently as the offers of 50 and 10 percent. Since the idea was to test whether the OT influenced acceptance towards unfair offers, the 50/50 split of the money was not included in the calcutations.

Verbal Affective Memory Test

The Verbal Affective Memory Test is developed and validated by psychologist at NRU (Jensen et al., 2015). The psychometrics properties of this test were assessed in a study with Danish healthy adults and showed satisfactory results. The test is designed for assessing memory biases in affective cognition. These memory biases can for instance be found in individuals woth Seasonal Affective Disorder. There are two versions of this test. One version includes 24 words and is called VAMT-24 and the other revised version includes 26 words. The revised version called VAMT-26 is employed in this empirical study. The words include positive, negative and neutral words. Danish adults aided the categorization of these words rating the valence of 210 monosyllabic, non-taboo and frequently used Danish words. This test is inspired by the English memory tests Rey Auditory Verbal Learning Test (Schmidt, 1996) and California Verbal Learning Test (Yi, 2011). However this test employs visually presented words, where each word is displayed on a computer screen for 750 ms with 750 ms intervals between words where a cross is displayed. The participants are told that a list of words will appear individually on the screen and that he or she should try to retain as many words as possible. The list of words is presented to the participants and followingly the particpant is asked to recall the words by saying them, while the experimenter registers the words recalled. This process is repeated so that the partcipant sees and recalls the target word list five times in total. After testing the immediate recall of the target list, an interference list is presented one time where the participant is again asked to retain as many words on the list and recall them afterwards. Subsequently, the participant is

asked to recall words from the first list again without being presented with the words again in order to obtain a score for short term memory. As a surprise after 30 minutes conducting other tests, the participant is asked to recall as many words from the first list as possible, which yields a score for long term memory. This test has a total of 10 outcomes. This includes immediate recall, short term memory, long term memory and the three valences, positive, negative and neutral as well as total number of mistakes. For this empirical study, the outcome with total number of mistakes is not included.

Hypotheses for effects of oxytocin on performance on applied tests

Verbal Affective Memory Test

Studies assessing OT effects on memory have shown that OT enhanced recall and recognition of positive words (Di Simplicio et al., 2008; Unkelbach et al., 2008) memory of emotional words whereas only one study reported selective amnesic effects on explicit recall performance (Heinrichs et al., 2004). Therefore, the hypothesis regarding word valences in that a larger amount of positive words will be recalled compared to negative and neutral words in the VAMT-26 test.

Emotion Recognition Test

A majority (six) of the studies assessing emotion recognition found an improvement in accuracy and processing (Domes et al., 2007; Leknes et al., 2013; Lischke et al., 2012; Prehn et al., 2013; Schulze et al., 2011), and four studies specifically reported increased processing of positive stimuli (Domes, Sibold, et al., 2013; Domes, Steiner, et al., 2013; Guastella, Mitchell, & Mathews, 2008; Marsh et al., 2010) or created a positive bias by reducing attention to negative stimuli (Kim et al., 2014). Therefore, the hypothesis for the emotion recognition test is that the OT group will recall a larger amount of words especially positive words compared to the placebo group. Since no

studies reported significant OT effect on reaction time, the hypothesis in that OT will only affect the above-mentioned parameters.

Emotional Intensity Morphing Task

Studies conducted on the effects of OT on recognition of emotional expression show that participants receiving placebo recognize emotional expressions at lower intensities than participants receiving placebo (Lischke et al., 2012; Prehn et al., 2013). Therefore, I hypothesize that participants in the empirical study will need a lower threshold for emotion recognition and thus will have a shorter reaction time for this test.

Ultimatum Game

Since studies have shown that OT increases trust in humans (Baumgartner et al., 2008; Kosfeld et al., 2005) and betting in relation to games/tests with monetary rewards. I hypothesize that participants who have received OT will accept a higher number of unfair offers than participants who have received placebo.

Data acquisition

In line with the placebo-controlled, crossover study design described in the Methods section, each participant conducted the affective and social cognitive tests twice, one for the OT condition and one for the placebo condition. This acquired data will be presented in the following for the Face and Eyes Emotion Recognition Task, Emotional Intensity Morphing Task, Ultimatum Game and Verbal Affective Memory Test-26.

However for the Emotional Intensity Morphing Task, there is some missing data for the first intervention days for the first two participants, due to technical difficulties with this test, which was subsequently corrected. Therefore, there are two missing sets of data for the placebo condition for this test and the results are interpreted with this in mind.

Data analysis

The data analysis was conducted with the statistics program IBM SPSS Statistics for Windows, version 23.0[1]. In the following, the test design will be outlined as well as the assumptions with respect to the inferential data analysis. Subsequently, the outcomes for each test will be described.

Parametric and non-parametric tests

The choice of parametric and non-parametric test depends on whether or not the data set is normally distributed. When choosing a parametric test, the underlying assumption for this choice is that the data is normally distributed. Conversely, when choosing a non-parametric t-test, the underlying assumption is that the data is not normally distributed (Field, 2009).

Assumptions for parametric tests include addivity, linearity, normality, homogeneity of variance and independence. If these assumptions for the test are violated, it will create sources of bias. This means that the test chosen is a poor model fit for the data and therefore can create a bias in the test statistics and p-values. More specifically, it could bias confidence intervals, standard errors and parameter estimates e.g. effects sizes (Field, 2009). In order to avoid these biases, the data is tested for whether or not it is normally distributed and on the basis of this result, a parametric or non-parametric test is selected.

The tests conducted analyzing normality in SPSS is the Kolmogorov-Smirnov and the Shapiro-Wilk tests. As an example of this is shown in Table 2 where the reaction time for the reaction time for the emotion anger is assessed for normality. None of the tests are below statistical significance, indicating that the null-hypothesis of the tests non-normal distribution should be rejected. For the example in Table 3, this means that the scores on tests are normally distributed and a parametric test would be suitable for this dataset. The tests of normality are conducted for every outcome for all tests included. However not all test scores were normally distributed.

[1] Reference: IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	Df	Sig.	Statistic	Df	Sig.
FERT. Mean RT angry face 1	,250	10	,077	,862	10	,080
FERT. Mean RT angry face 2	,188	10	,200*	,911	10	,291

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tabel 2. This table represents the tests conducted assessing normality in SPSS. In this example, the outcome Reaction Time (RT) for the emotion anger is analyzed for normal distribution. This is one of the outcomes EMOTICOM test Face and Eyes Emotion Recognition (FERT) and from the Face condition of this test. In this example, the distribution of the results for the emotion angry is both analyzed for the group 1 (active) and group 2 (placebo).

Repeated measures ANOVA

An analysis of variance (ANOVA) is a statistical test, which assesses whether or not the means of several groups are the same. The strength of employing this analysis is that it has a lower probability of producing type 1 errors compared to conducting several t-tests. ANOVA assesses overall experimental effects and does therefore not inform us about which groups were affected. However, it can provide information about interaction effects. The *F*-ratio that ANOVA produces reflects the ratio of the models to its error by comparing the systematic variance to the unsystematic variance in the data. The larger the *F*-ratio, the larger the probability is that the groups have different means. If the *F*-ratio is lower than 1, this will represent a non-significant effect (Field, 2009).

Assumptions for ANOVA

The choice of parametric and non-parametric test depends on whether or not the data set is normally distributed. When choosing a parametric test, the

underlying assumption for this choice is that the data is normally distributed. Conversely, when choosing a non-parametric t-test, the underlying assumption is that the data is not normally distributed. Assumptions for parametric tests include addivity and linearity, normality, homogeneity of variance and independence. If these assumptions for the test are violated, it will create sources of bias. This means that the test chosen is a poor model fit for the data and therefore can create a bias in the test statistics and p-values. More specifically, it could bias confidence intervals, standard errors and parameter estimates e.g. effects sizes. In order to avoid these biases, the data is tested for whether or not it is normally distributed and on the basis of this result, a parametric or non-parametric test is selected (Field, 2009).

The tests conducted analyzing normality in SPSS is the Kolmogorov-Smirnov and the Shapiro-Wilk tests. As an example of this is shown in Table 2 where the reaction time for the reaction time for the emotion anger is assessed for normality. If the result is statistically significant, it indicates that the null-hypothesis of the tests non-normal distribution should be rejected. This is not the case for the example in Table 2, which means that the scores on the test are normally distributed and a parametric test would be suitable for this dataset. The tests of normality are conducted for every outcome for all tests included. However, a few of the test scores were non-normally distributed. This would typically require the use of non-parametric tests. However since there is not counterpart to a repeated-measures ANOVA and since it is a robust test (Field, 2009; Glass, Peckham, & Sanders, 1972), this parametric test is selected. Therefore, it is important to address how the broken assumption of normality can affect the test results and have this in mind when interpreting the results. Other assumptions such as sphericity will not be an issue, since the study design only employs two conditions (Field, 2009).

Multiple comparisons

The following data analysis entail ANOVA and pairwise comparisons in the form of post hoc t-tests. Since the thesis only includes a pilot study, an

explorative approach to the data is selected. Therefore, paired samples t-tests are subsequently conducted. These t-tests will assess if there are significant differences in test performances of the OT and placebo group.

In the subsequent data analysis, multiple comparisons are conducted in the post hoc t-test in relation to the ANOVA. In order to avoid conducting type I errors, the Bonferroni correction is employed to adjust the *p*-values and keep the alpha level at .05 across all comparisons. All the reported *p*-values in the following for the post hoc tests are adjusted with the Bonferroni correction unless otherwise is specified.

For the paired samples t-tests conducted subsequent to the ANOVA, a less stringent correction of multiple comparisons is employed. This type of correction is based on the Bonferroni correction, however the Holm-Bonferroni is a sequentially rejective version (Holm, 1979). Each test was analyzed in concordance with the hypotheses and the family-wise alpha level was set at .05 for all tests. The Gaetano calculator was employed to aid the Holm-Bonferroni correction following this procedure, the p-levels for each test were ranked with the lowest p-value first to the highest (Gaetano, 2013).

Results

Repeated measures design

The potential differences between the groups can be caused by either systematic or unsystematic variation. Researchers want the difference between the groups to be due to systematic variance since this refers to the effect of the experimental manipulation. An unsystematic variance will be due to errors that can be difficult to account for such as differences in ability or that the test in conducted at different times of the day or by various researchers testing the participants. This creates noise in the test results. The unsystematic variation can be diminished by a test design that is carefully prepared. For the repeated measure design, the unsystematic variance is reduced due to the elimination of group differences apart from the

intervention (Field, 2009). Therefore, this design is a strength of this study. Furthermore, for this design we implemented a double-blinded randomized control. A double-blinded study, where neither the participants nor the test conductor know which intervention has been given, will reduce the effects of expectation of the intervention, which can influence test results. The randomization is a strength since the study hereby reduces practice effects and boredom effects of the test, since the order of the placebo and OT intervention conditions is counterbalanced so that an equal amount of participant receives OT as the first condition as the amount of participant receiving placebo as the first condition (Field, 2009). Since the groups are identical for both conditions, due to the crossover-design, it is appropriate to conduct a repeated measures test. Therefore, the data is analyzed with a repeated-measures ANOVA in SPSS. Subsequently, the data is assessed with paired samples t-test to outline any possible significant differences between groups.

Descriptives

For this pilot study, 10 female participants were recruited. They have a mean age of 23.9 with a standard deviation of 4.74. Information about education was assessed by obtaining the number of years of achieving education (7-12 years) and the degree of education from 1 (no vocational degree) to 5 (>4 years academic education with prior high school degree included). These numbers are added to provide an education score. The mean education score of the participants is 16 with a standard deviation of 1.9.

Verbal Affective Memory Test - 26

Immediate recall of words

The means of the two groups (active vs. placebo) on the immediate recall of words in the Verbal Affective Memory Test – 26 (VAMT-26) is depicted in Figure 11. The figure also shows error bars indicating Standard Error of the Mean. The standard error of the mean indicates the spread in the sample (Field, 2009), which here is the spread of the mean scores included for each

test for both the active and the placebo group. This measure is chosen to give a descriptive outline of the two groups both in relation to the means and standard error of the mean. The descriptive statistics indicated that the OT group recalled a higher amount of words compared to the placebo group in the immediate recall condition, which is depicted in Figure 11. The repeated ANOVA revealed that there were no interaction effects of treatment on memory for immediate recall of words $F(2, 36) = 1.054$, $p = .359$, $\eta^2 = .055$. There was a significant difference of the recall of word valences within the immediate recall category words $F(2, 36) = 76.9$, $p < .001$, $\eta^2 = .810$. Pairwise comparisons revealed that a significantly higher amount of neutral words was recalled compared to positive $p < .001$ and negative $p < .001$ words. Post hoc paired samples t-tests showed no significant differences between the OT and placebo group on the scores for immediate recall of words.

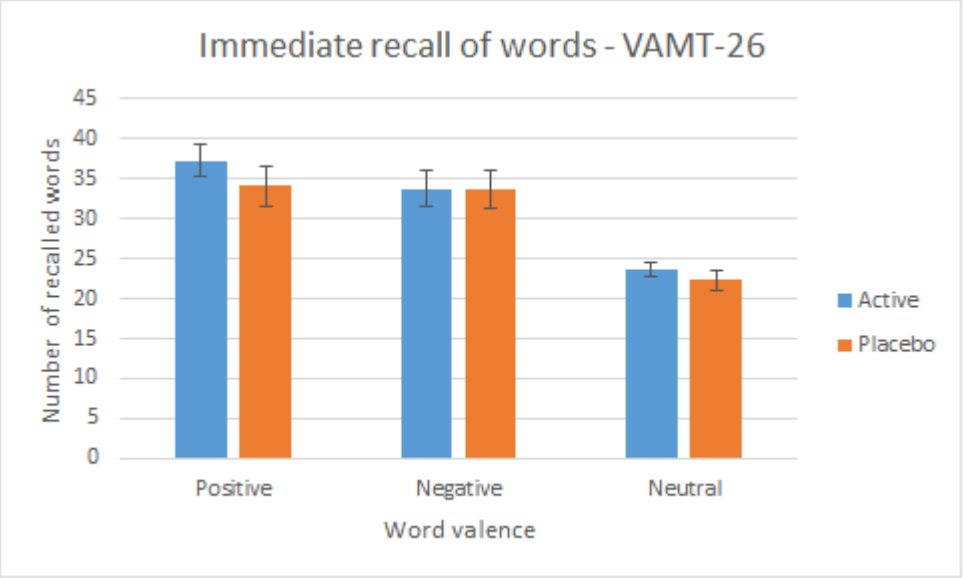

Figure 10 - The bars show number of words recalled in the immediate recall of words memory category of the VAMT-26 for both the oxytocin and placebo group. The number of words recalled is shown for the three word valences, positive, negative and neutral and for the total number of words recalled across valences. Error bars depict Standard Error of the Mean. Results were non-significant.

The mean number of recalled words for each group for the short term memory category is depicted in Figure 12. When analyzing the interaction of group and scores on the short term memory category, this was non-significant $F(2, 36) = .028$, $p = .972$, $\eta^2 = .002$. The descriptive statistics (Figure 12) show

that the active group recalled more words than the placebo group in the short term memory category. There was a significant difference of recall of words for the type of valence within the short term memory category $F(2, 36) = 16.51$, $p < .001$, $\eta^2 = .478$. Pairwise comparisons revealed that a higher amount of neutral words were recalled compared to positive $p < .001$ and negative words $p < .001$. When conducting a paired t-test it shows that this difference was statistically significant $p = 0.025$. After correcting for multiple comparisons for this test, the p-value for the group group differences for the short term memory were borderline significant (p=.075).

Short term memory

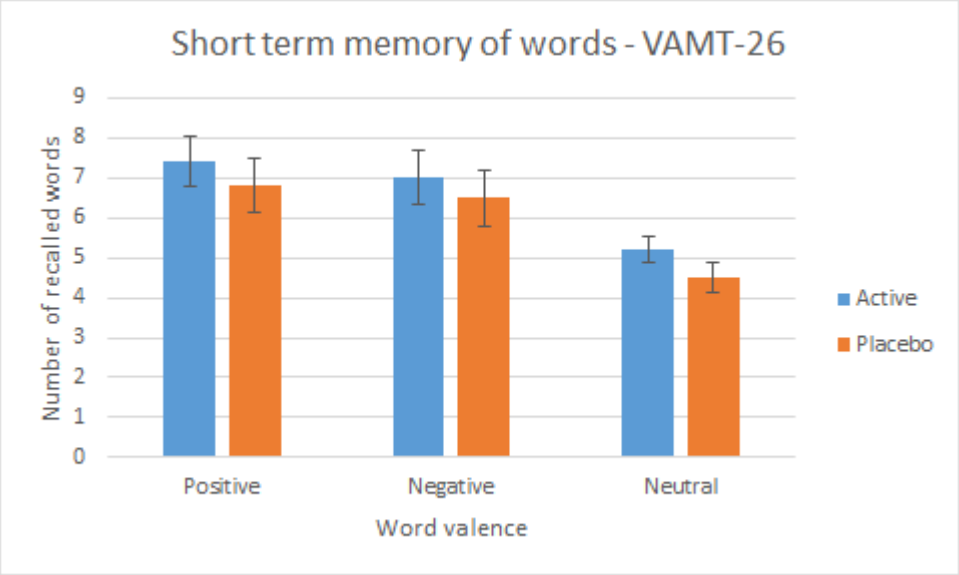

Figure 11 - The bars show number of words recalled in the short term memory category of the VAMT-26 for both the oxytocin and placebo group. The number of words recalled is shown for the three word valences, positive, negative and neutral and for the total number of words recalled across valences. Error bars depict Standard Error of the Mean.

For the memory category called delayed recall of words in the VAMT-26, the mean number of words is illustrated in Figure 13. There were no significant interaction between group and number of words recalled for the delayed recall memory category $F(2, 36) = .607$, $p = .550$, $\eta^2 = .033$. Results also showed significant differences in the valence of words recalled in this category $F(2, 36) = 22.72$, $p < .001$, $\eta^2 = .558$. Pairwise comparisons revealed that a larger

amount of neutral words was recalled compared to positive $p < .001$ and negative $p < .001$ words. The active group recalled more positive words than the placebo group as shown in Figure 13. Here the placebo group recalled slighty more neutral and negative words than the active group. Paired samples t-test conducted post hoc show no significant differences between the two groups for this memory category.

Delayed recall of words

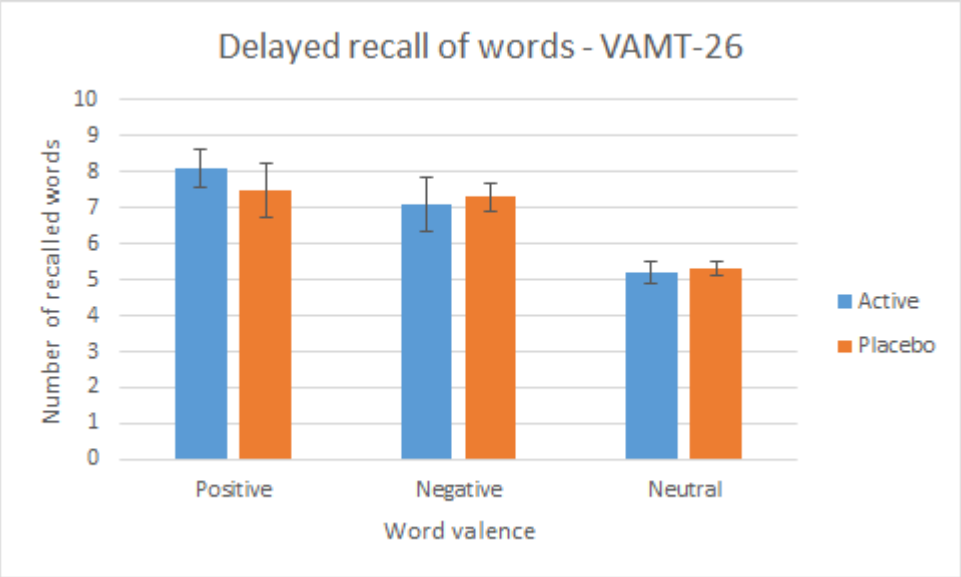

Figure 12 - The bars show number of words recalled in the delayed recall of words memory category of the VAMT-26 for both the oxytocin and placebo group. The number of words recalled is shown for the three word valences, positive, negative and neutral and for the total number of words recalled across valences. Error bars depict Standard Error of the Mean. Results were non-significant.

Figures 14a and 14b illustrates the differences between the group across all three memory categories. Mauchly's test of sphericity specified the assumption of sphericity was violated for the main effect of categories $X^2(2) = 44.44$, $p < .001$. Therefore, the Greenhouse-Geisser correction of degrees of freedom are reported (ε=.519). The results indicated that there was no interaction effect of group on the three different word categories $F(1.04, 18.68) = .358$, $p > .05$, $\eta^2 = .020$. There was a significant difference in amount of words remembered across the categories $F(1.04, 18.68) = 534.71$, $p < .001$, $\eta^2 = .967$. Pairwise comparisons revealed that both groups remembered a

significantly larger amount from the immediate recall category compared to the short term category $p < .001$ and the delayed recall category $p < .001$. The active group recalled more words than the placebo group for the categories immediate recall and short term memory, however only the differences in the short term memory category were borderline statistically significant (p=0.057). This significance was not present after correcting for multiple comparisons.

Recall of words for all memory categories

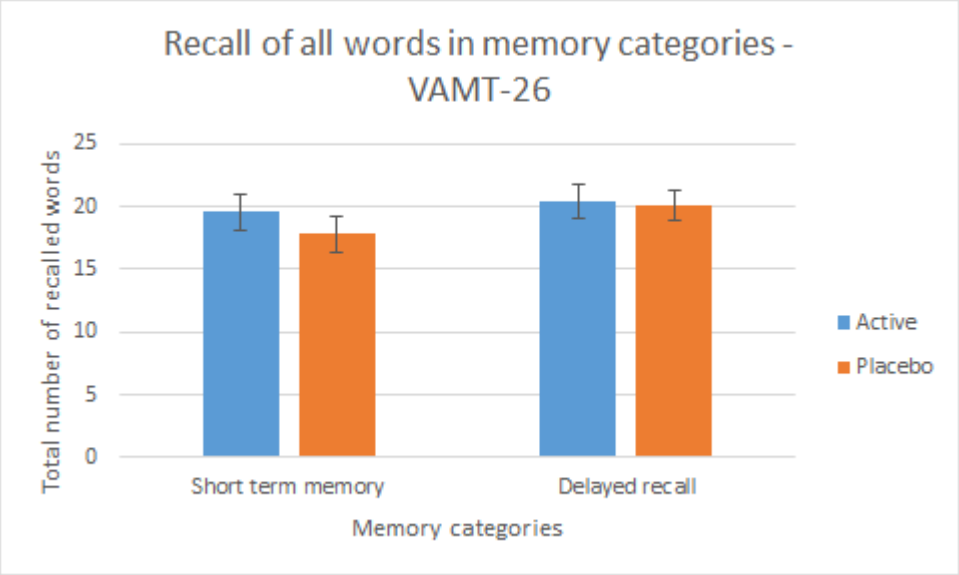

Figure 13a - The bars show number of words recalled aross all three memory categories of the VAMT-26 for both the oxytocin and placebo group. The number of words recalled is shown for the immediate recall, short term, and delayed recall memory categories. Error bars depict Standard Error of the Mean.

As depicted in Figures 14a and 14b, the active group recalled more words than the placebo group for the categories immediate recall and short term memory. The paired samples t-test revealed that this difference was borderline significant for the short term memory category (p=0.057). When adjusting for multiple comparisons with Bonferroni, the result was not significant at the $p < .05$ level.

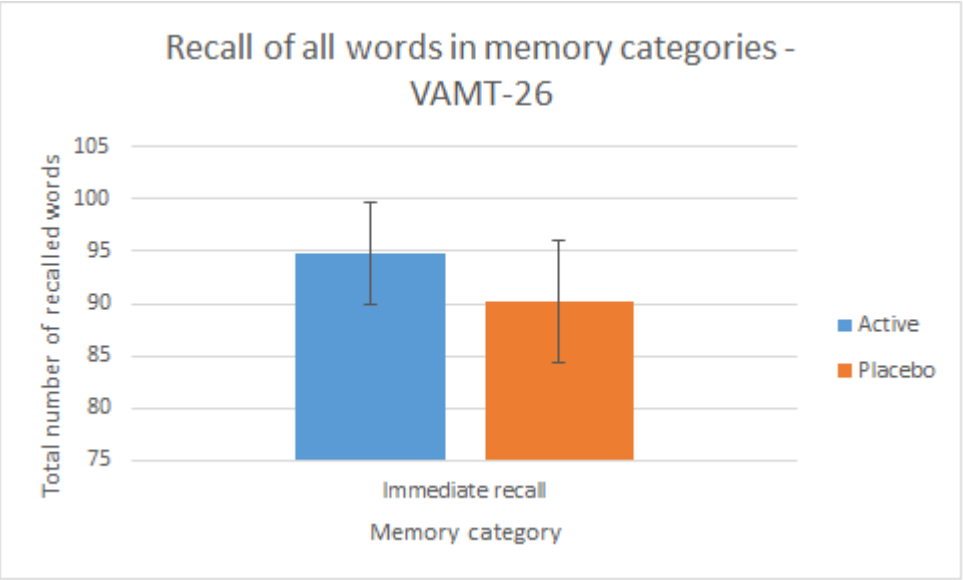

Figure 14b - The bars show number of words recalled aross all three memory categories of the VAMT-26 for both the oxytocin and placebo group. The number of words recalled is shown for the immediate recall, short term, and delayed recall memory categories. Error bars depict Standard Error of the Mean. Results for this category was non-significant.

Face and Eyes Emotion Recognition Task

For this task, the two conditions were combined. This entails that the d' and reaction time scores contain a combined mean from the Face Condition and the Eyes Condition.

d'

As shown in Figure 15, the placebo group was better at identifying the emotions happy, sad and anger. The active group (OT) was better at recognizing fear. However, results from the ANOVA showed that there were no statistically significant differences between treatment and emotion recognition ability $F(3, 54) = .150$, $p > .05$, $\eta^2 = .008$. There was a significant difference in the d' scores for the emotions presented $F(3, 54) = 2.87$, $p < .045$, $\eta^2 = .138$. Pairwise comparisons revealed that the d' was higher for fear compared to sad, however the result was only borderline significant $p = .052$. Paired samples t-test showed no statistically significant differences for group in ability to recognize emotions $p > .05$.

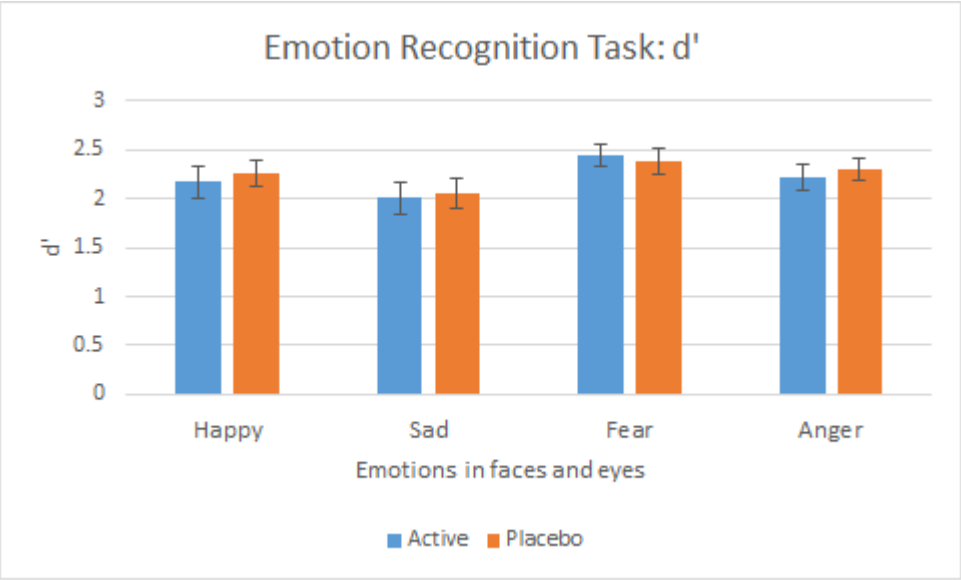

Figure 14 - The bars show the d' values for the recognition of the emotions happy, sad, anger and fear in the Emotion Recognition Task. The d' values are shown for both the oxytocin and placebo group. Error bars depict standard error of the mean. Results were non-significant.

The results depicted in the histogram in Figure 16 indicatethat the placebo group was faster at detecting the emotions happy, sad and fear compared to the active group. Mauchly's test indicated that the assumption of sphericity was violated for the main effect of reaction times $X^2(2) = 11.73$, $p < .05$. Therefore the Greenhouse-Geisser estimates were employed to correct the degrees of freedom (ε=.747). There was no significant main effect of group and emotion recognition ability F=(2.08, 37.5) = .711, $p > .05$, $\eta^2 = .038$. The results show that the ability to recognize emotion was affected by the emotion presented F=(2.08, 37.5) = 61.61, $p < .001$, $\eta^2 = .774$. Post hoc analyses of pairwise comparisons of emotions revealed that participants had a significantly higher reaction time for sad than for happy $p < .001$, fear $p < .001$ and anger $p < .001$. Therefore, participants were significantly slower at detecting the emotion sad compared to the other emotions. Post hoc t-test revealed no significant differences between groups.

Reaction time

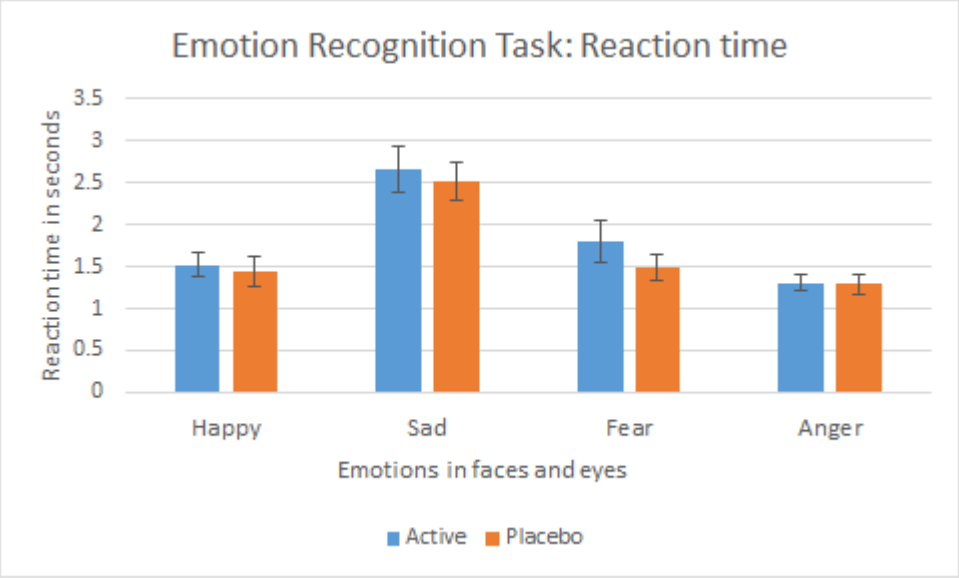

Figure 15 - The bars show the reaction times measured in seconds for recognition of the emotions happy, sad, anger and fear in the Emotion Recognition Task. The reaction times are shown for both the oxytocin and placebo group. Error bars depict Standard Error of the Mean. Results were non-significant.

Emotional Intensity Morphing Task

The bars in the histogram in Figure 17 depict the intensity levels at which the emotions are recognized in the ascending condition of the Emotional Intensity Morphing Task. The results indicate that the active group perform slightly better than the placebo group for all emotions expect for sad anger, since the active group recognize the emotions happy, fear and disgust at lower intensity levels. The effect of treatment on emotion recognition was not significant $F(4, 72) = .969$, $p > .05$, $\eta^2 = .029$. There was a significant difference in recognition of specific emotions $F(4, 72) = .969$, $p < .002$, $\eta^2 = .029$. Post hoc tests revealed that participants were able to identify anger at lower intensity levels than disgust $p < .05$. Post hoc t-test showed no significant differences between groups.

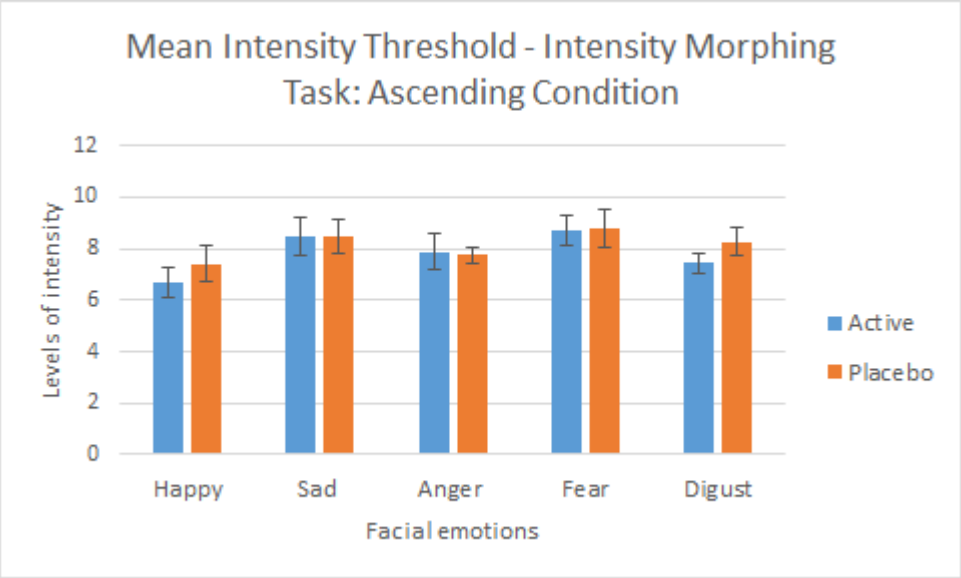

Figure 16 - The bars present a group mean of the intensity levels required for recognition of the emotions happy, sad, anger, fear and disgust in the Ascending Condition of the Emotional Intensity Morphing Task. The required intensity levels for emotion recognition are shown for both the oxytocin and placebo group. Error bars depict Standard Error of the Mean. Results were non-significant.

The bars in Figure 18 show that the active group requires lower intensity of emotional expressions to identify emotions in the descending condition. This is the case for the emotions happy, sad and anger. For the emotions fear and disgust, the placebo group was better at identifying emotional expressions. Mauchly's test showed that the assumption of sphericity was violated $X^2(9) = 19.79$, $p < .05$ when comparing treatment with emotion. Therefore, the Greenhouse-Geisser correction was employed (ε=.706). Results show that there was a non-significant effect of treatment on emotion recognition ability $F(2.82, 50.83) = 1.84$, $p > .05$. Furthermore, the analysis also showed a significant difference in recognition of emotions $F(2.82, 50.83) = 2.87$, $p < .05$. Pairwise comparisons revealed that participants recognized faces expressing disgust at a significantly lower intensity level than happy faces $p < .05$.

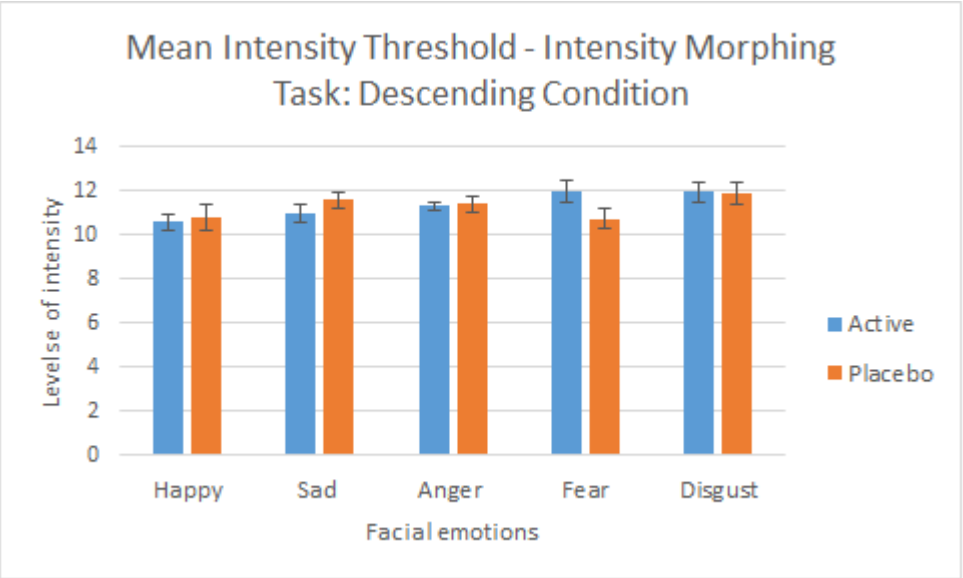

Figure 17 - The bars present a group mean of the intensity levels required for recognition of the emotions happy, sad, anger, fear and disgust in the Descending Condition of the Emotional Intensity Morphing Task. The required intensity levels for emotion recognition are shown for both the oxytocin and placebo group. Error bars depict Standard Error of the Mean. Results were non-significant.

Overall, the descriptive statistics for both conditions in the task indicated that the OT group on average required a lower level of the emotional intensity to determine the emotion expressed in the face compared to the placebo group.

Ultimatum Game

As Figure 19 depicts, the active group accepted of unfair offers of 40, 20 and 10 percent of the money more frequently that the placebo group. The descriptive statistics indicate that the placebo group accepted 35 and 30 per cent of the money more frequently that the active group.

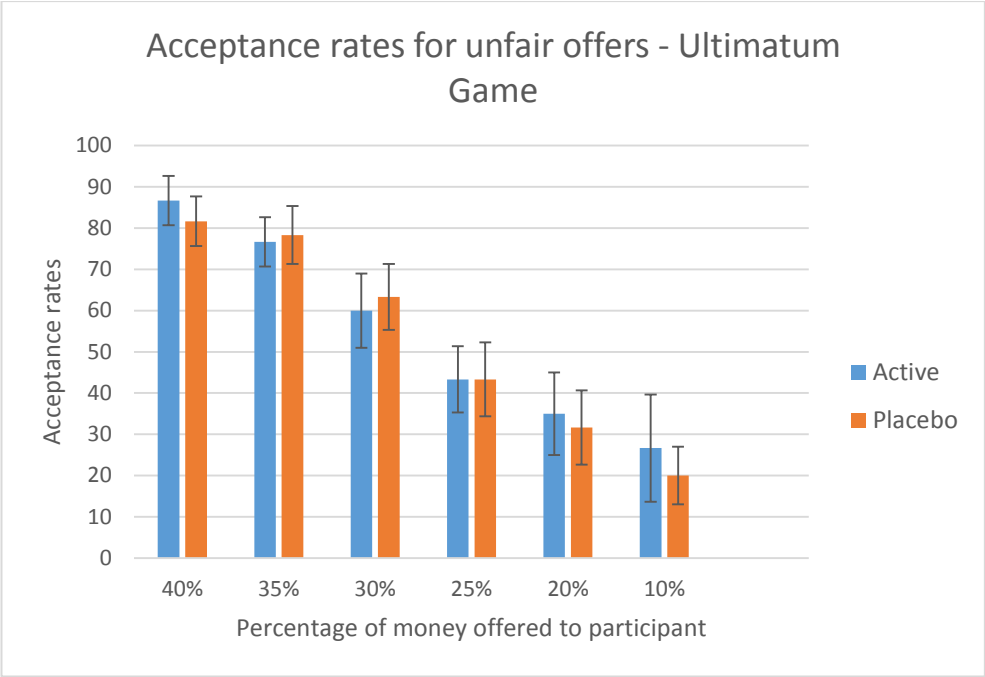

Figure 18 - The bars display the acceptance rates for each of the six unfair offers presented to the participants (40, 35, 30, 25, 20 and 10 percent) in the Ultimatum Game. The acceptance rates are shown for both the oxytocin and placebo group. Error bars depict Standard Error of the Mean. Results were non-significant.

Figure 20 also depicts the acceptance rates for both groups in the Ultimatum Game. Here the slopes for acceptance rates are shown. The acceptance rates decrease in line with the amount offered to the participant as shown in both Figure 19 and Figure 20. Figure 20 provides a different overview of the acceptance rates and here it is evident that the slopes do not decrease as much for the small offers for the active group as for the placebo group. However, this difference is not statistically significant $F(5, 90) = 0.209$, $p = .958$, $\eta^2 = .011$. Pairwise comparisons revealed that there was a significant difference between numbers of accepted offers. Here the acceptance rates for the offers of 40% and 35% of the amount was accepted significantly more frequently compared to offers of 30% $p < .001$, 25% $p < .001$, 20% $p < .001$, and 10% $p < .001$. Post hoc t-test revealed no statistically significant differences between groups.

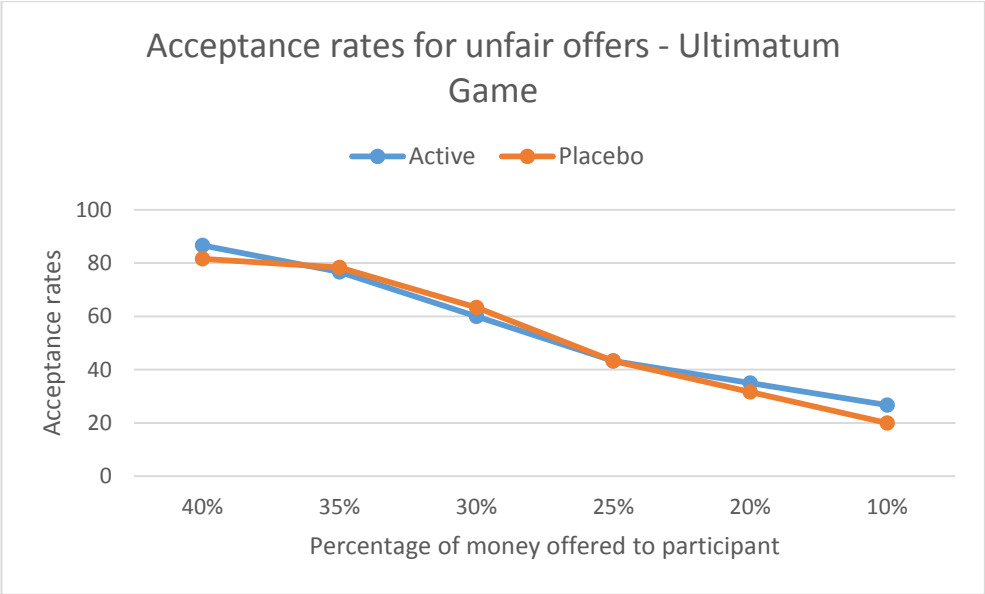

Figure 19 - The lines display the acceptance rates for each of the six unfair offers presented to the participants (40, 35, 30, 25, 20 and 10 percent) in the Ultimatum Game. The acceptance rates are shown for both the oxytocin and placebo group. Error bars depict Standard Error of the Mean. Results were non-significant.

Discussion

This section encompasses a critical discussion concerning the modulatory effects on OT on affective and social cognition. Here, it is discussed how the dosage of OT and time window of its effects might influence the results on the cognitive measures. Subsequently, the effects of OT are also discussed in relation to the empirical study. Here, the interpretation of the results from the study is discussed. Furthermore, the results from the empirical study are discussed in relation to the EMOTICOM test battery with respect to its properties and challenges. Afterwards, the modulatory effects of OT are discussed in relation to the discrepancies in the findings of studies investigating this. This also includes discussing the potential bias in the publication of results regarding OT effects on affective and social cognitive functioning. Moreover, this section considers how social and affective cognition can be appreciated as a spectrum and the possibility of OT as creating an oversensitivity towards affective and social stimuli.

Dosage and time window of oxytocin effects

Time window for effects of oxytocin compared to test procedure

As mentioned in section *Tests included in the empirical study*, a more extensive understanding of pharmacokinetic properties of intranasally administrated OT has yet to be established. Especially more knowledge is required about the duration of the central effect of the administrated OT is present. This will ensure more reliability in terms of the testing procedure. For instance, if the effect of OT only lasts for two hours, there is no use in having a three hour long test battery. In relation to this, it can be considered problematic that the vast majority of the studies included in the review (see Table 2) do not report the duration of the neuropsychological testing. For this reason, it creates an uncertainty of whether the effect of OT was still present when testing for its effects on cognition. Therefore, more knowledge on

pharmacokinetic properties of OT could improve the strength of the study designs considerably.

For instance, Theodoridou and colleagues (2009) initiated the neuropsychological testing 25 minutes after OT administration for half of the participants. The other participants began testing 45 after intervention. The authors tested whether there was an effect of time in relation to the results and they did not find any (Theodoridou et al., 2009). However, intranasally administrated OT is estimated to significant elevated CSF levels 30 minutes after administration (Born et al., 2002). Therefore, one can argue that 5 minutes of testing before the estimated effect of OT occur might not be substantial enough to create significant differences in results compared to the testing 45 minutes after administration.

Conversely, the study conducted by Cardoso and colleagues (2013) commenced the neuropsychological testing 120 minutes after administrating OT. Therefore, it can be questioned if the effects of the administrated OT were still present. They reported that OT lowered accuracy of detection emotion, which they argue is due to OT increasing the salience of social stimuli. Based on the uncertainty of the time window of OT effects, more research is required in order to determine whether OT produces an oversensitivity to social stimuli.

Since most of the studies included in the review Table 2 conduct the testing 40-50 minutes after OT administration, it seems that these researchers have been inspired by the study by Born and colleagues (2002) assessing the effect of the OT -like peptide, vasopressin. However, Striepens and colleagues (Striepens et al., 2012) demonstrated the effect of 24 IU OT in only present in significantly elevated levels in the CSF after 75 minutes. This raises a critical question to most of the studies included in the review. At the same time, another study similar to that of Striepens and colleagues would be highly relevant in order to establish a more valid understanding of the OT effects. Therefore, more research is warranted regarding the pharmacokinetics of OT to determine its increase as well as decrease after nasal administration. This will improve the robustness of studies regarding the modulatory effects of OT on affective and social cognitive measures.

Dosage of oxytocin

As previously mentioned, most of the studies assessing the effects of OT on affective and social cognition employed a dosage of 24 IU. Previous work with the OT -like peptide, arginine vasopressin, demonstrated that dosage highly affect the time before increased levels of the peptide in the CSF (Born et al., 2002). Here 40 IU of arginine vasopressin caused elevated levels in the CSF after 10 minutes compared to 24 IU causing elevated levels 60 minutes after administration. This suggests a more rapid effect when neuropeptides are administrated in higher doses. Three of the studies included in the review, employed a dosage of 40 IU (see Table 2). In the study by Kim and colleagues (2014) they found that 40 IU OT reduced attentional bias towards negative stimuli. Leknes and colleagues (2013) reported that 40 IU of OT enhanced recognition of covert emotional stimuli. In their study investigating OT effects on cognition, Zak and colleagues (2007) found that 40 IU of OT increased trust by 80 percent compared to the placebo group. In the study by Kim and colleagues, the neuropsychological testing commenced 45 after OT administration. Leknes and collegues conducted the testing 50 minutes after administration and Zak and colleagues began testing after 60 minutes. The study by Striepens and colleagues (Striepens et al., 2012) indicates that the central effects of OT will only occur 75 minutes after administration. However, this is when 24 IU is administrated and therefore it is uncertain if the effects of OT can occur more rapidly when administrating a higher dosis. Thus, there is an uncertainty in whether a high dosis can modulate OT effects faster and this can therefore be seen as a challenge in the test design. Furthermore, it is uncertain how much OT is required to pass into the brain in order to modulate behavioral effects. Some authors argue that OT is rapidly degraded in the brain tissue and this hereby creates and uncertainty on the duration of the possible effects of intranasally administrated OT (Leng & Ludwig, 2016). Additionally, more knowledge about dosage and effects is required since there might not be a linear relationship between dosage and effects. Moreover, knowledge about optimum of OT dosage is still required in order to provide the most suitable effects of OT. Despite the fact that the studies report modulatory effects of OT on domains of affective and social

cognition, more research concerning the pharmacokinetic properties of OT is required in order to determine its modulatory effects with a higher degree of certainty.

Publication bias

Another critical point to be made about the modulatory effects of OT is that there can be a publication bias favoring the studies that can report OT effects. The dramatic increase of interest in the modulatory effects of OT on affective and social cognition has led to many studies investigating this. In relation to this, some scientists argue, that the reason for the publication bias might be due to insufficient knowledge of OT's pharmacokinetic properties, essential methodological and statistical issues and lack of replication efforts (Lane, Luminet, Nave, & Mikolajczak, 2016; Leng & Ludwig, 2016). They argue that this could result in multiple conducted OT studies with null-findings, which have never been published. The authors also argue that many of the studies are statistically underpowered. Hereby, they stress the importance of publishing studies with null findings so that the modulatory effects of OT on social cognition is overestimated (Lane et al., 2016)

Empirical study and EMOTICOM tests

Interpretation of results of empirical study

There are several point to take into consideration when interpreting the results from the empirical study. First, it is a pilot study, indicating that it does not have the same statistical power as the main study. The main study aims to include 45 participants in order to obtain a power of .8 while maintaining the α-level at .05 (see Appendix B). Since the pilot study included 10 participants it cannot obtain a statistical power that is approximate to the main study. Therefore, the main study will provide more certainty on the modulatory effects of OT compared to the pilot study. Despite the fact that the data from the pilot shows borderline significant differences after correction for multiple comparisons, these results might not reflect actual effects of OT on affective memory. Conversely, the null findings from the pilot study does not ensure that there are no effects of OT on the other cognitive domains assessed. When the main study is conducted it will yield clearer results regarding the effects of OT on the four tests assessing affective and social cognition. Conceivably, it could elucidate the effect is found in the pilot study.

In relation to the interpretation of the statistical results, it is also noteworthy the sub-facets within each test in handled as independent from the other sub-facets. For instance, a person who is skillful in recognizing happy faces might also very well be skillful in recognizing sad faces. Therefore, the tests seem to be intercorrelated. Furthermore, the assessed population is healthy individuals and some studies suggest that OT does not produce pronounced effect in individuals within the normal spectrum of social cognitive functioning compared to sub-clinical and clinical groups (Bakermans-Kranenburg & van IJzendoorn, 2013; Bartz, Zaki, Bolger, et al., 2010; Ishak, Kahloon, & Fakhry, 2011).

Other authors agree that OT effects depend on degree of psychopathology but suggest that OT administration enhances the salience of social stimuli and hereby induces an “oversensitivity” in the interpretation of social stimuli for instance in emotional expressions (Shamay-Tsoory & Abu-

Akel, 2016). For instance, they argue that the enhancement of salience OT produces is explanatory for the decreased emotion recognition accuracy. When interpreting this in relation to the results on the affective memory tests in the empirical study, it might be that participants attribute a affect to neutral words when they are presented along with emotionally valenced words and hereby increasing memory of these words. However, this is only speculative due to the low statistical power in the pilot study. In relation to the pilot, it also seems relevant to discuss the employed tests from the novel EMOTICOM test battery and the challenges they might present.

EMOTICOM tests as representing real-life stimuli

Social economic exchange games such as the Ultimatum Game are argued to be valuable as sensitive biomarkers of pathological human social cognition. Additionally, these games are claimed to provide computerized, objective measures of both normal and pathological cognitive functioning. Hereby, computerized tests are already available as a diagnostic tool enabling a broader understanding and better treatment for psychiatric disorders (Kishida, King-Casas, & Montague, 2010). Therefore, the EMOTICOM test battery aims to provide a simpler game design with respect to the Ultimatum Game, making it more suitable for neuropsychological testing (Bland et al., 2016). There is an increasing interest in neuroscience for a computerized, quantitative assessment of social cognitive functions (Parsons, 2015), which is accommodated with the EMOTICOM test battery (Bland et al., 2016). In order to reflect real life situations, it is argued that presenting dynamic stimuli is important (Parsons, 2015). The EMOTICOM test battery provides a test encompassing dynamic stimuli via the Emotional Intensity Morphing Task (Bland et al., 2016). In relation to this, it seems relevant to discuss whether computerized tests depicting social interactions can provide knowledge of how individuals will react in real-life setting outside the test room.

Despite the technological developments improving the ecological validity of neuroscientific assessment of social and affective cognition, some remain critical of the utility of the employed tests (Todorov et al., 2011). James Rilling argues in Todorov et al. (2011, pp. 217-218) that

the elicitation of the neural systems occurs due to a so-called anthropomorphization. This means that humans reflexively attribute personality to computer-generated faces and social interactions presented by the computer. In order to assess the neural activation further and aid the understanding of social cognition, neuroimaging studies have been conducted. Studies in this field have specifically investigated the neural correlates activated by these tests (Todorov et al., 2011, p. 79). In relation to Ultimatum Game, it shows that this type of neuropsychological test elicits the same type of neural response both when the participant is playing against humans and computer partners. This warrants for the ecological validity of the test and hereby the utility of this test in neuropsychological assessment. Following this hypothesis, it is interesting to investigate whether the neuropsychological tests assessing social cognition are able to generate the same responses as produced by real life situations. If cognitive neuroscience is able to produce tests that resemble real life social situation more than they currently do, this will improve the ecological validity of the test. However, it is noteworthy that this test did not elicit the same amount of activation in the anterior insula when playing against a computer compared to a human opponent. Contrary, to the argument of the ecological validity of this test, this instead suggests that human opponent provides a more effective way of activating this neural system (Sanfey et al., 2003).

Since these tests are not as potent as real life stimuli, this warrants for more research in virtual reality, which could possibly accommodate this problem by providing more potent real life stimuli. Recent developments in technology have however enabled a setting resembling the real life situations in a more accurate way than neuropsychological tests have previously achieved. This setting is provided by virtual reality. Neuroimaging could here be employed again to assess whether virtual reality tests invoke the same neural responses and therefore determine if these tests would be more ecologically valid. A more life-like experience as for instance pictures of actual individuals instead of cartoon figures could decrease distancing between the participant and the computerized opponent. Hereby, this could

enhance emotional engagement and affective experience in the test session (Parsons, 2015).

The concluding remarks for this discussion is therefore that the neuropsychological tests employed in social neuroscience seem to activate the same neural systems that are recruited in real life social interactions. Therefore, they are efficacious in producing the same neural responses as in real social situations, however they are not as potent. The tests employed in neuroscience hereby seem to inform us about social cognition in a quantifiable and measurable way. However, further development and optimization is needed. This warrants for more research in virtual reality, which could possibly accommodate this problem by providing more potent real life stimuli.

Conclusion

This thesis aims to elucidate the modulatory effects of OT on affective and social cognition. In order to elaborate on this, a tripartite structure is employed in the thesis through three research questions. First, it is described how a cognitive neuroscientific perspective contributes to the understanding of affective and social cognition. Here, the emergence of cognitive psychology as a scientific field is outlined including its basic concepts and ideas. Subsequently, the fields of cognitive neuroscience, social cognitive neuroscience and affective neuroscience are outlined. It is described how research in neuroscience has enabled the distinction of affective and social cognition from non-social cognition. This warrants for a distinction of social cognitive neuroscience from cognitive neuroscience. In relation to this, it is argued that research in cognitive neuroscience has provided a broader understanding of affective and social cognitive domains. Research on the domains of emotion, emotion recognition, trust and affective memory are outlined.

Secondly, it is investigated what the scientific literature can inform us about the effects of OT on affective and social cognition. Here, general effects of hormones are briefly described and the central and peripheral effects of OT

are outlined. It is described that the hormone OT does not only facilitate birth and lactation, it is also shown to modulate social and cognitive functioning such as improved ability to infer mental states of others. This part also comprises a systematized review, which includes 21 studies that assess the modulatory effects of intranasal OT on affective and social cognitive domains. Specifically, it is assessed how OT modulates performance on memory, emotion recognition and trust in healthy participants. Although there is a wide consensus in the studies that OT modulates social cognition, the findings seem to be equivocal. However, there is an overweight of studies reporting increased emotion recognition abilities after administration of intranasal OT. Furthermore, studies suggest that intranasal OT increases trust as well as empathic accuracy.

Thirdly, the thesis presents an empirical study that investigates the modulatory effects of OT on performance on tests assessing memory, emotion recognition and trust. In the discussion section the methodological difficulties concerning the administration of OT is discussed. Here it is argued that there is a lack of knowledge on the pharmacokinetic properties of OT, which could have pronounced effects on the test results since there is no established knowledge about the effect of dosis and the time window of OT effects.
Most of the studies assessing OT effects on affective and social cognition are designed based on the pharmacokinetics of the OT-like hormone vasopressin. However, since there is no certainty that OT has the same pharmacokinetic properties it creates an uncertainty in the interpretation of the results. Though studies point towards the ability of OT to modulate affective and social cognition, more research concerning the effects of OT and its pharmacokinetic properties are warranted to establish a wider consensus of these effects.

Third, the thesis aims to empirically elucidate how OT modulates performance of tests assessing trust, memory and recognition of emotional faces in healthy participants. It does so by incorporating results from an

empirical study conducted at NRU. In the empirical study, it is assessed how OT affects these affective and social cognitive functions. The study is conducted with a randomized, double-blind, placebo-controlled, within-subject, crossover study design. The study employs tests from a novel test battery called EMOTICOM, assessing emotion recognition, emotion recognition for different emotional intensities and trust. It also included a test of affective memory. Results show that oxytocin might modulate affective memory, however since the study is a pilot study, more research is required for a higher degree of certainty of this effects. No effects of OT is found to either type of emotion recognition nor trust. The discussion section encompasses a critical discussion of dosage of OT and time window for its effects in relation to conductance of neuropsychological testing. Here, it is stressed that more research on the pharmacokinetic properties of OT is warranted in order to obtain more robust study design without the current methodological challenges. Knowledge about the pharmacokinetic properties of OT will hereby aid in determining its modulatory effects.

Future directions

The prospects of oxytocin as pharmacological treatment

A vast amount of research have also been conducted on the effects of intranasal OT on individuals with psychopathologies especially autism (Carter, 2014; Guastella et al., 2013). This research of the effects of intranasal OT on individuals with psychopathologies that encompass difficulties in social skills have further contributed to the knowledge of this hormone on affective and social cognition. Here, it can be argued that social cognition can be seen as a spectrum and that OT can aid individuals who are less socially proficient in improving social skills (Bartz, Zaki, Bolger, et al., 2010; Guastella et al., 2010; Leknes et al., 2013). For instance, the research in this area is expected to broaden the understanding of OT's role for trust adaptation

in psychopathologies such as autism and social phobia (Baumgartner et al., 2008). Furthermore, several reviews conducted on the research in this area has led the understanding of OT as prospect with respect to pharmacotherapeutic treatment for individuals suffering from schizophrenia, social anxiety, postnatal depression, obsessive-compulsive problems, borderline personality disorder, post-traumatic stress and especially autism (Bakermans-Kranenburg & van IJzendoorn, 2013; Feldman, 2012; Guastella et al., 2013; Ishak et al., 2011; Kirsch, 2015). A recent study from 2013, has assessed the long-term effects of OT on children with autism spectrum disorder (ASD) (Tachibana et al., 2013). The participants in this study were all males aged 10 to 14 years and with an IQ between 20 and 101. Six of the eight participants improved their social skills with respect to social interaction and communication and caregivers of five of the included participants reported enhanced quality of reciprocal communication as being a result of OT (Tachibana et al., 2013). This study found a tendency in improvement of social interaction and communication after long-term treatment with OT. These results suggest OT as a promising pharmacological treatment. The treatment prospects of OT on youth with ASD has been further supported by a study conducted in 2010 where the short-term effects of the hormone were assessed (De Dreu, Baas, & Boot, 2015). By conducting a randomized, placebo-controlled, crossover design, they found that OT significantly improved emotion recognition assessed with Reading The Mind In The Eyes Test for 60% of the participants compared to the placebo condition. This study point towards a possibility to improve emotion recognition with OT in children with ASD and hereby enable an improved understanding of social cues, which can lead to higher quality of social interactions (De Dreu et al., 2015). The study by Guastella et al. (2013) employed a dose of 18 IU and 24, however the study by Tachibana et al. only employed a dose of 8 IU increasing to 16 IU after two months and the 24 IU after a subsequent two months. The differences in the doses employed and the results of the studies could indicate that the study design from Tachibana et al. could benefit from increasing the dose of OT. The research area of OT effects of youth with ASD could benefit from establishing a balance between the dose of OT, which will

be safe for the children and a dose that will be sufficient in producing a possible effect of the hormone. If these criteria are met, then OT could become a possible pharmacotherapeutic treatment improving social skills of children and adolescents with ASD.

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Enclosed appendixes:

Appendix A – Original EMOTICOM test descriptions from Cambridge Cognition Group

Appendix B – Protocol for the Oxytocin Project

Appendix C – Review on the literature of the effects of intranasal oxytocin on social cognition comprising 36 studies

Figures:

Figure 1: Oxytocin molecule structure.

http://www.paasp.net/news/discussions-in-social-media/oxytocin-does-bond/ (accessed Feb. 9th, 2017)

Websites:

APA:

http://apa.org/search.aspx?query=psychinfo (accessed Feb. 9th, 2017)

Biopac:

https://www.biopac.com/application/psychophysiology/ (accessed Apr. 19th, 2016)

CIMBI:

www.cimbi.dk (accessed Apr. 19, 2016)

NRU:

www.nru.dk (accessed Apr. 19, 2016)

Oxytocin chemical structure:

https://pubchem.ncbi.nlm.nih.gov/compound/oxytocin#section=Top

(accessed Apr. 19th , 2016

Web Of Science:

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