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The relationships of empathy, oxytocin, and depression

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I hereby certify that all material in this final year project which is not my own work has been identified and that no work is included for which a degree has already been conferred on me.

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Abstract

Empathy, oxytocin, and depression are three subjects that are widely researched. Empathy means experiencing or understanding the emotions of an individual who is being observed. Oxytocin has frequently been shown to have a connection to lactation and labor. Depression is a common sickness that results in malfunctioning, suffering, and a shorter life. The mutual relationship and connection of all three has received limited research. The aim of this essay is to explore how they all relate to one another, to see what neural areas of involvement they have in common, and finally to see if there is a potential to administer oxytocin in order to alter empathy and/or depression. The sources used are published literature on the topics, found in for example Google Scholar and Worldcat. What was found was that both emotional and cognitive empathy have a positive relationship with oxytocin. Emotional empathy has in most research a positive relationship with depression while cognitive empathy seems to have a negative relationship with depression. Depression has a negative correlation with oxytocin. The neural areas of common involvement were amygdala, hippocampus, and cingulate cortex. Future research should look at how empathy, oxytocin, and depression affect each other, and why this happens. It is also important to look at the possibilities of affecting a neural area involved in empathy, oxytocin, and/or depression in order to make an impact on any of these factors.

Key words: emotional empathy, cognitive empathy, oxytocin administration, plasma oxytocin depression, neural areas

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Introduction

A lot of research on empathy, oxytocin, and depression exists. Findings of the effect that oxytocin has on mentalization in depressed individuals compared to healthy have been presented by Pincus et al. (2010), and they may be the first to explore this correlation. There is an abnormal ventral limbic and paralimbic activity in depressed individuals, and these neural areas are the same areas that are involved in mentalization. The administration of intra-nasal oxytocin affected neural areas involved in mentalization, and also improved this ability (Pincus et al., 2010)

This introduction will provide presentations of empathy, oxytocin, and depression coupled with further information of their connection to each other. A definition of empathy proposed by two leading researchers in the area, namely Decety and Jackson (2004), consists of referring to empathy as shared neural representations, self-awareness, mental flexibility, and emotional regulation. These functions are all represented by a number of brain areas (Decety & Jackson, 2004). As early as 1980, there was a research paper on the multidimensional nature of empathy. This multidimensional view consists of dividing empathy into cognitive and emotional components (Davis, 1980). Barraza and Zak (2009) mentions that empathy relates to many pro-social behaviors (Barraza & Zak, 2009). For example, dispositional empathy (a term described later on in this paper) is likely to be positively correlated with the willingness to volunteer (Davis et al., 1999). Also, empathic concern (Verhaert & Van den Poel, 2011), a function of emotional empathy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009), positively affects decisions to donate to charity (Verhaert & Van den Poel, 2011).

A subject that has been linked to empathy in research is oxytocin. Scatamburlo et al. (2007)

mention that oxytocin is a nanopeptide (Scantamburlo et al., 2007), and it is located in the paraventricular and supraoptic nuclei of the hypothalamus (Lee, Macbeth, Pagani, & Young, 2009). Like empathy (Barraza & Zak, 2009), oxytocin is also positively correlated with some pro-social behavior (Bartz et al., 2010), as well as attachment behaviors in mammals. It is a likely cause of ones responses to affective states of other humans. It exists in brain areas like amygdala and cingulate cortex, which are commonly known to be involved in emotions and social behaviors. In humans, oxytocin mediates behaviors like partner preference, social interaction, parental care, social approach, and trust (Barraza & Zak, 2009). It has been found that oxytocin increases activation in empathy related neural networks (Feldman, 2012).

Oxytocin seems to have a role in depression. Von Knorring, Von Knorring, and Waern (2013) say that depression is a sickness bringing malfunctioning, suffering, and shortening of life for the diseased (Von Knorring et al., 2013). Symptoms of depression such as social withdrawal, reduced appetite, and cognitive impairments have been linked to a worsened oxytocin function (Scantamburlo et al., 2007), and intra-peritoneal administration of oxytocin has been found to reduce depressive-like behavior (Slattery & Neumann, 2010).

There exist findings regarding the relationship of depression and empathy and we will present examples of what has been found. Nicolas, DeSilva, Prater, & Bronkoski (2009) saw that emotional empathy, namely empathic family stress, had a positive relationship with depression (Nicolas et al., 2009), and Inoue, Tonooka, Yamada, & Kanba (2004) found a positive correlation between major depression and cognitive empathy, namely Theory of Mind (ToM) (Inoue et al., 2004).

Following questions will be of focus:

Are oxytocin levels positively correlated with emotional and/or cognitive empathy?

Does administration of oxytocin heighten emotional and/or cognitive empathy?

Is depression positively related to emotional and/or cognitive empathy?

Is oxytocin negatively correlated with depression?

Does administration of oxytocin lower depression?

These questions will be answered in order to explore how oxytocin, depression and empathy is connected and interact with each other, and if there may be a possibility of altering the oxytocin levels to affect empathy and/or depression. This paper will, in order to answer these questions, consist of information about how different types of empathy and outcomes of empathy, different types of depression, and administration or internal level of oxytocin are related to each other. There is a need from researchers working in the field of empathy, depression, and oxytocin, for knowledge on the relationship between these three subjects. Schreiter, Pijnenborg, and aan het Rot (2013) writes that social functioning seems to be negatively related to depression, and empathy that is a part of sociality is there for an important aspect of focus in research. Abnormalities in empathy functioning may be a contributing factor in the development of depression (Schreiter et al., 2013). It is also important to see how oxytocin affects depression, to find if it is possible to use oxytocin in treatment of depressive symptoms (Pincus et al., 2010). Regarding the importance to find connections of oxytocin and empathy, an important question is for example if oxytocin can be used to treat autism (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). The purpose of this article is to compile what already exists in research on empathy, depression and oxytocin. This will result in a greater understanding of the relationships among them, as well as more insight in how one can affect them.

The paper will have a psychological and neurological perspective. A presentation of empathy, oxytocin, and depression, at different sections, will take place after the introduction. There will be a focus on neural aspects of these, to be able to correlate the neural areas they have in common. Thereafter, a presentation of the recent findings regarding the relationships of empathy and oxytocin will be put forth, followed by empathy and depression, as well as depression and oxytocin. Next is a presentation of research looking at all three aspects to see what they present and conclude. Both empirical and theoretical research shall be reviewed to find the answers of the questions of the paper presented above. There will also be a review of methods used in these researches. Last, there will be a conclusion and discussion of the findings, resulting in an inference from these.

Of interest will be articles containing information about empathy, depression, and oxytocin. A focus will be placed on how these three are connected to each other coupled with the differences in neurology in the client as a result of lower or higher levels of empathy, depression and oxytocin. Worldcat, Psych info, Web of science, Google Scholar and Medline will be used for reviewing studies on empathy, depression and oxytocin.

First of all there will be a presentation of empathy.

Empathy and its neural correlates

Empathy is an emergence of similar emotions as the person being observed (Preston & De Waal, 2002), or an understanding of the emotions of the individual being observed (Singer et al., 2004), as a result of perceiving the situation of this individual (Preston & De Waal, 2002). A common way of describing empathy is that it enables us to understand what others are feeling. Emotions such as happiness, sadness, and pain is understood in terms of how it feels for another person (Singer et al., 2004). It plays a big role in the sharing of experiences, needs, and goals, across individuals (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003). As mentioned earlier, empathy can be divided into emotional and cognitive aspects (Davis, 1980). What will follow next is a description of these two aspects of empathy.

Emotional empathy

When it comes to emotional empathy, it is described as the degree to which an individual feel someone else's emotions (Schreiter et al., 2013). Emotional empathy involves experiencing the feelings that you observe in another individual, or having an emotional reaction to the feelings you observe in this individual (Rodrigues, Saslow, Garcia, John, & Keltner, 2009). Following concepts are related to emotional empathy. Shamay-Tsoory et al. (2009) say that emotional contagion is a part of emotional empathy (Shamay-Tsoory et al., 2009), and a result of both emotional and cognitive empathy. The difference when comparing empathy to emotional contagion is that emotional contagion includes an emergence of similar emotions as the individual being observed, as

a result of perceiving the emotions of this individual. Empathy on the other hand does as mentioned occur due to the situation of the individual being observed (Preston & De Waal, 2002). The emotional contagion system is thought to be an important part of the ability to empathize emotionally, and mirror neurons are possibly the neural base for this (Shamay-Tsoory, 2011). A term frequently used is empathic concern. This is when compassion gives you motivation to give support to another person (Schreiter et al., 2013). This is a component of emotional empathy (Shamay-Tsoory et al., 2009). Goetz, Keltner, & Simon-Thomas (2010) defines compassion as the feelings that emerge when you perceive a suffering individual, that in turn lead to a desire to help that individual. It does not mean an experience of the similar feelings as the suffering individual, as is the case with empathy (Goetz et al., 2010). Personal distress, often referred to as empathic distress, can be a result from experiencing empathy (Decety & Ickes, 2011), and it is the self-directed feelings like getting upset or worried that arise when viewing someone in need. It often results in trying to decrease one's own negative feelings (Batson, Fultz, & Schoenrade, 1987) by withdrawing from the stressor, since there is a an awareness of the distinction between the feelings oneself has and the feelings of someone else. This in comparison with sympathy and compassion that often leads to motivation to relieve the distress of the person in need, which can be seen as a pro-social behavior (Decety & Ickes, 2011). One often feel personal distress in situations like for example a loved one getting sick (Monin, Schulz, Feeney, & Cook, 2010). It is a concept used in research and it refers to feeling anxiety and discomfort when seeing someone having a negative experience (Erlanger, 1998). It does not involve feeling distress for another person, or same as another person, but because of another person (Decety & Ickes, 2011). A baby crying when hearing another baby crying is thought to be a reaction of empathic distress (Sagi & Hoffman, 1976) and Davis (1980) tell us that a baby experiences empathic distress when seeing another baby in distress. When a baby later develops a perspective-taking ability, the empathic distress will transform into compassion and sympathy (Davis, 1980). Personal distress is also an important component of emotional empathy

(Shamay-Tsoory et al., 2009). A last concept that is a part of emotional empathy is emotional

recognition and this is the ability to recognize emotional expressions (Shamay-Tsoory et al., 2009).

See Figure 1 for clarification of the components of emotional empathy.

There are a couple of theories regarding the emotional empathic systems functioning. For

example, the perception-action hypothesis sees it as perception of a behavior that induces

representations for that behavior, leading to output to the motor areas which in turn leads to

appropriate responses to this behavior being prepared and carried out. The simulation theory, in

comparison, proposes that neural states are activated during an observation, to match how one

would feel in the situation observed. This is due to social information processing, and it is thought

by some that mirror neurons is involved in this process of emotional contagion (a term described

later on in this paper), motor empathy, and imitation. Motor empathy is when one automatically

mimic or mirror behaviors such as facial expressions, vocalizations, or movements (Blair, 2005).

Mirror neurons are a set of neurons that are activated when performing an act as well as seeing

someone else perform the same act. These neurons are located in the inferior frontal gyrus (IFG),

the inferior parietal lobule (IPL) (Shamay-Tsoory, 2011), and the ventral premotor cortex known as

area F5. The mirror neuron system is important in understanding actions, intentions, and mental

states of others (Decety & Ickes, 2011). There is strong evidence for the role that the IFG has in

emotional contagion and emotional recognition. One hypothesis say that mirror neurons in the IFG

are involved in converting perceived facial expressions to neural activity suitable for making similar

expressions (Shamay-Tsoory, 2011). The IPL is thought to be active in self-other distinctions. The

ventral premotor cortex is increasingly activated in both imitating and perceiving emotional

expressions and hand movements. Both imitating and perceiving emotional expressions lead to

increased activation in the amygdala and insula. It may be that mirror neurons is an important

component for the ability to empathize with others by holding the capacity for understanding other

people's emotions. The insula could be of importance in making emotional representations to achieve this. It has been found that the ability to emotionally empathize is positively correlated with higher activity in mirror neurons in the IFG, as well as emotion representation in the amygdala. This means that mirror neurons may be involved in the ability of feeling what others feel, by mirroring others emotional responses (Decety & Ickes, 2011).
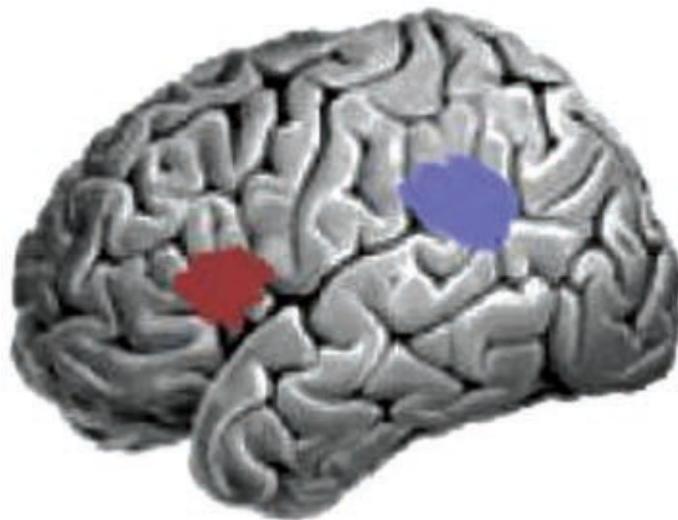
 (Shamay-Tsoory, 2011).

Much research provides support for the notion that the IFG is involved in emotional empathy (Shamay-Tsoory, 2011). Jabbi, Swart, and Keysers (2007) has for example looked at the IFG activation when perceiving positive and disgusted faces (Jabbi et al., 2007), and Schulte-Ruther, Markowitsch, Fink, and Piefke (2007) looked at IFG activation in emotional recognition (Schulte-Ruther et al., 2007). Research has also been on IFG activation during experience of emotional empathy for people suffering from threat or harm (Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008). Lesions in the IFG have been shown to affect emotional contagion (Shamay-

Tsoory, 2011).
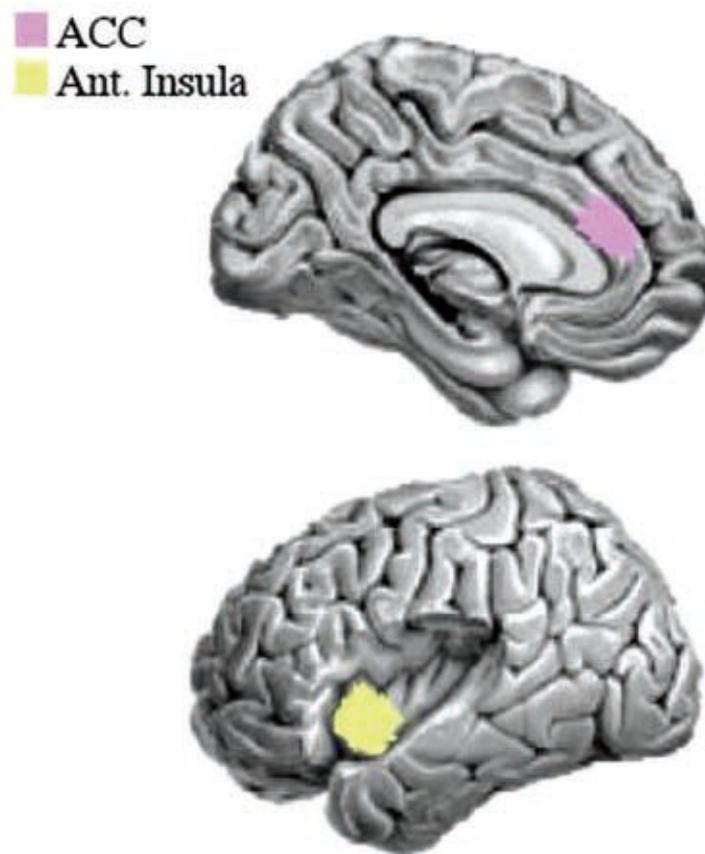
(Shamay-Tsoory, 2011).

Regarding emotional empathy to pain, anterior cingulate cortex (ACC) and the anterior insula are more active during the observation of pain but also during exposure to own pain. The judgment of how intense the pain is for someone else is based on the other person's facial expressions, and the increased neural activity positively correlated with how the observed pain of another person is rated based on severity. It is believed that the neural activity in response to pain is similar to the neural activity in response to other peoples pain (Shamay-Tsoory, 2011).
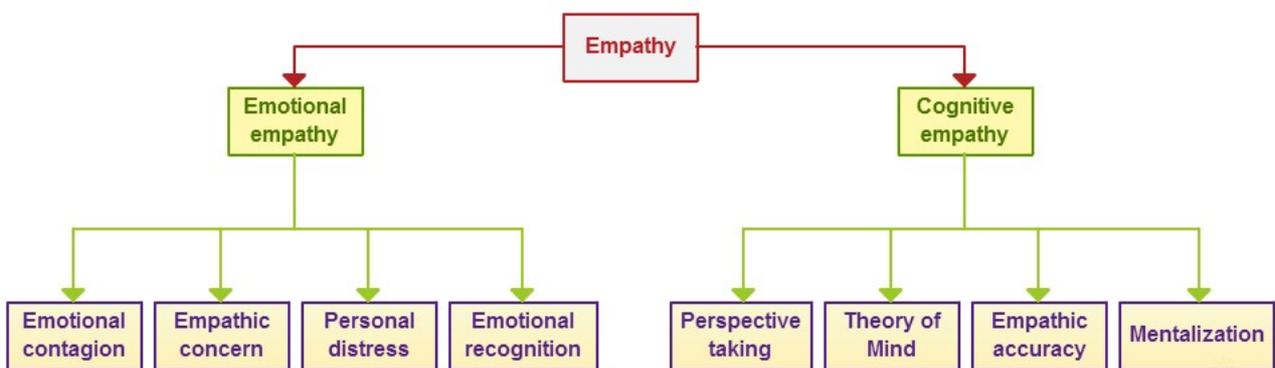
Cognitive empathy

Cognitive empathy is described as perspective taking, ToM, and empathic accuracy. Perspective taking is the ability to understand where others stand (Schreiter et al., 2013), which is also known as role-taking. This means trying to understand another person's cognitive and emotional state (Rodrigues et al., 2009). ToM is the attribution of mental states to self and others in order to understand that there are differences between your own and others mental states (Schreiter et al., 2013). According to Shamay-Tsoory (2011) there is a differentiation between affective and cognitive ToM in that affective ToM is an emotional form of mentalizing where one makes inferences about others emotions, and cognitive ToM is an ability to make inferences about others beliefs. Both affective and cognitive ToM is a part of cognitive empathy (Shamay-Tsoory, 2011). Empathic accuracy is the understanding of others mental states by viewing others behaviors (Schreiter et al., 2013). There is another concept related to cognitive empathy, called mentalization (Shamay-Tsoory et al., 2009). Pincus et al. (2010) tell us that mentalization is the ability to affectively and cognitively attribute the mental states of others. It is a higher order ability than ToM in the fact that it involves better care-taking. ToM is in comparison an imagined involvement with another person (Pincus et al., 2010). See Figure 1 for clarification of the components of cognitive empathy.

As previously mentioned, cognitive empathy is the ability to infer mental states on others, and to take others perspective. This ability involves ToM. The following brain regions have been shown to be involved in ToM: the medial prefrontal cortex (mPFC), superior temporal sulcus (STS), temporoparietal junction (TPJ), and temporal poles. Lesions in the ventromedial PFC (vmPFC) are related to deficits in cognitive empathy (Shamay-Tsoory, 2011), namely affective ToM (Decety & Ickes, 2011). The TPJ is active when creating theories about others brief mental states, and the mPFC is involved in prescribing the more permanent traits and qualities of both self and others.

Although, it has recently been proposed that the vmPFC is needed for the affective functions of ToM, and that the activity in the dorsolateral PFC is related to cognitive empathy. The medial temporal lobes, including the hippocampus, are involved in ToM. This means that autobiographical memories, meaning the capacity to remember memories from the past, play a role in inferences of others mental states. Self-other differentiation is thought to be an important part of cognitive empathy. This is based on the fact that people having ToM impairments such as those with autism have an impaired self-other distinction, and that they have no difference in the activation in vmPFC in response to self and others. Healthy individuals on the other hand have a different level of activation when comparing responses in vmPFC to self and others (Shamay-Tsoory, 2011).

Figure 1. The multidimensional nature of empathy. Emotional empathy with its sub-components to the left, and cognitive empathy with its sub-components to the right.

Concepts similar to empathy

There are some concepts that are similar, or often confused with emotional and cognitive empathy, but actually defines something else. Dispositional empathy is referred to as the tendency to use the capacity of empathy, and it can be a use of either emotional or cognitive empathy (Perez-

Albeniz & de Paul, 2003). It is also known as the tendency to react to others experiences (Davis, 1983). Interpersonal distress is a term used when situations with another person or other persons invoke for example upsetting feelings or feelings of anger, as in one experiment where they asked participants to tell about an interpersonal situation in which they got angry or upset (Gratz et al., 2011). Another article explains interpersonal distress as the distress experienced from exhibiting different interpersonal behaviors (Gunn, Troxel, Hall, & Buysse, 2014). Sympathy is a concept often confused with empathy, and sympathy is a state of feeling sorry for an individual based on the distress which that individual is experiencing (Preston, & De Waal, 2002). Experiencing empathy can in the end lead to sympathy, meaning sorrow or concern for someone based on that person's emotions or situation. It often leads to trying to decrease the suffering of the other person. Many scholars use sympathy and empathy to describe the exact same thing, but sympathy is the emotional reaction that results from perceiving someone's emotions or situation, an emotional reaction that is different from the emotional reaction of the individual being observed (Decety & Ickes, 2011).

The two different but interacting systems

The emotional empathic system, as compared to the cognitive, has been shown to be the ability developed earliest. The cognitive system is a more advanced system. The emotional system exists in rodents, while in comparison the cognitive system only is found present in chimpanzees and humans. In chimpanzees, only elementary aspects of cognitive empathy like ToM has been found. Also, babies show emotional empathic abilities earlier than they show cognitive empathic abilities (Rodrigues et al., 2009).

Cognitive and emotional empathy is thought to be operated by different systems. There lies support for this in studies of autism finding that there is a distinction between the two in this disorder (Rodrigues et al., 2009), meaning that one aspect of empathy may be intact while another shows impairments (Shamay-Tsoory, 2011). Emotional empathy may consist of simulation processing, while ToM processing is what underlie cognitive empathy. Emotional and cognitive empathy are run by different but interacting neural networks. Areas involved in cognitive empathy are the areas involved in ToM (mPFC, STS, temporal poles, and ventromedial cortex), and areas involved in emotional empathy are those that mediate emotional experiences (amygdala, insula, and the IFG) (Decety & Ickes, 2011). In regard to this, there is a possibility that the oxytocingeric system modulates emotional empathy, and that the dopaminergic system modulates cognitive empathy (Rodrigues et al., 2009).

Empathy does as mentioned seem to have some kind of connection to oxytocin (Shamay-Tsoory, 2011). This connection leads me to present information regarding oxytocin to further evaluate what it is and what connection it has to depression and empathy. What will follow is information of this nanopeptide.

Oxytocin and its neural correlates

Oxytocin is involved in social and emotional processing in the body and brain (Rodrigues et al., 2009). It is well known for its role in labor, and has been found involved in pair-bonding, and social attachment (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Lee et al. (2009) say that oxytocin is most known for its role in parturition and lactation but it is also involved in behaviors like learning, anxiety, feeding, pain perception, social memory, sexuality, trust, and aggression. It may also play a role in autism and schizophrenia. There are sexual differences as well as species differences in oxytocin distribution, and this is thought to explain some variations in behavior (Lee et al., 2009).

Oxytocin consists of nine amino acids, and is very similar to vasopressin with only two amino acids that differ them apart (Lee et al., 2009). Oxytocin is as mentioned a nanopeptide located in the hypothalamus but it has also been found in neural areas like the striae terminalis, amygdala, septum, and hippocampus. This supports the notion that oxytocin is involved in neurotransmission, psychogenic stress, and anxiety (Scantamburlo et al., 2007). Psychogenic stress is for example behavioral, cognitive, or physiological changes in a person, aimed at changing or conforming to a stressful event (Dimitroglou et al., 2003). In animal research it has been found that oxytocin has stress-decreasing and stress-inhibiting effects (Scantamburlo et al., 2007). These effects may alleviate pair bonding (Gimpl & Fahrenholz, 2001). It may also be that is can enhance positive social interactions. Studies of oxytocin in humans are scarce but some findings support that oxytocin has stress-attenuating effects in humans. There has also been research showing the anti-depressive effects of oxytocin in humans (Scantamburlo et al., 2007). Oxytocin is both a hormone and a neurotransmitter, released into the brain and the bloodstream. It can be found in the heart,

uterus and spinal cord (Rodrigues et al., 2009).

Gimpl & Fahrenholz (2001) tell us that oxytocin is used to prompt labor, and it is involved in the initiation and maintenance of lactation, as well as milk ejection. A pulsation of oxytocin seems to be related to ejaculation, and the prostate has been found to have a higher concentration of oxytocin than plasma. Oxytocin has also been found in the kidney, thymus, pancreas, and adipocytes. In rats, oxytocin has been found associated with spontaneous erections. There is an increase in pressure in the arteries following injection of oxytocin in rats. It has been found that in rats, oxytocin exists in a high concentration in for example the aorta, vene cava, and atria. Also, in rats, oxytocin fibers have been found in the dorsomedial hypothalamic nucleus, thalamic nucleis, dorsal and ventral hippocampus, subiculum, entorhinal cortex, medial and lateral septal nuclei, amygdala, olfactury bulbs, mesencephalic central gray nucleus, substantia nigra, locus coeruleus, raphe nucleus, nucleus of the solitary tract, and dorsal motor nucleus of the vagus nerve (Gimpl & Fahrenholz, 2001).

Oxytocin receptors have been found in hypothalamic neurons and astrocytes. In the brain of rats, oxytocin receptors have been found in cortical areas, basal ganglia, the limbic system, thalamus, hypothalamus, brain stem, and spinal cord. A significant difference between female and male rat brains have not yet been found. In humans and no other species, oxytocin receptor bindings is present in the pars compacta of the substantia nigra. This means that the oxytocin system may be involved in basal ganglia functions like motor function. Estrogen and glucocorticoids have an effect on the oxytocin receptors. Oxytocin is known to mediate aggressive and affiliative behavior in many species, and it has been found that rats with dysfunction of the oxytocin gene exhibit less aggressive behavior. Research on prairie voles show that intra-cerebroventricular administration (Gimpl & Fahrenholz, 2001), a type of drug administration that is able to reach the brain (Cook,

Mieure, Owen, Pesaturo, & Hatton, 2009), of oxytocin alleviated the formation of pair bonds

(Gimpl & Fahrenholz, 2001).

Depression and its neural correlates

Depression can occur in all ages, and it is after puberty more existing in females. During a lifetime, the risk of having depression is 36 percent among women and 23 percent among men (Von Knorring et al., 2013). The symptoms consist of gloominess, lack of interest, lack of energy, fatigue, lack of self-esteem, guilt, self-blame, suicidal thoughts, cognitive dysfunction, psychomotoric repression or agitation, sleeping problems, and appetite problems. The length of a depressive episode can vary from a month to seven years. Both suicide and death by accident is a higher risk among those suffering from it, as well as sicknesses like cardiovascular disease (Von Knorring et al., 2013). Up to 20 percent of the US population suffer from milder forms of depression and it is almost twice more common in females than males. Depression is often thought of as a stress-related disorder with episodes occurring in the presence of stress. Despite this, stress is generally not the cause since most people do not become depressed after stressful experiences and those who do have quite mild stresses. This is proof for a view that sees depression as an interaction of genes and environment. 40-50 percent of the risk of having depression is genetic, making it as heritable as type II diabetes, hypertension, and asthma. Even so, to this day it has not been any certainty of what genes are abnormal in depression vulnerability (Nestler et al., 2002). Depression is easily confused with sadness. The difference between the depression and sadness is that sadness is a normal and time-limited reaction to a loss while depression is recurring and disruptive (Leventhal, 2008).

A diagnosis of a depressive disorder could be defined as minor or major. A major depressive disorder (MDD) involves a minimum of five symptoms of depression, including anhedonia. These symptoms are listed in The Diagnostic and Statistical Manual of Mental Disorders, edition IV and all five symptoms have a duration of at least two weeks for it to be classified as MDD (Hart et al.,

2012). Anhedonia is a lack of interest or pleasure in activities previously seen as rewarding (Treadway & Zald, 2011). Minor depressive disorders consists of two to four symptoms (including anhedonia) of depression present for a minimum of two weeks, listed in The Diagnostic and Statistical Manual of Mental Disorders, edition IV (Hart et al., 2012). It is normal for people having minor depressive disorder to experience impairments in social participation, and vocational functioning, as well as having increased health service utilization, lower perceived health, and an increased risk of developing MDD (Hart et al., 2011). Minor depression seems to be a milder form of major depression in terms of severity. For a diagnosis of minor or major depression, a requirement is that the symptoms significantly impair an individual's functioning (Fils et al., 2010). Bipolar depression is a disorder consisting of phases of depression and phases of mania (Baldessarini, Vieta, Calabrese, Tohen, & Bowden, 2010). People suffering from bipolar depression spend 3 times as much time in the depressive phase as in the mania phase (Berk et al., 2011).

MDD patients have been shown to have volumetric differences in subcortical brain regions such as the amygdala and ventral striatum, as well as in cortical regions such as the anterior cingulate cortex, orbitofrontal cortex and prefrontal cortex. These changes is thought to originate from abnormal functioning of the hypothalamic-pituitary-adrenal (HPA) axis (Aan het rot, Mathew, & Charney, 2009). The HPA axis is a neuro-endocrine system regulating release of cortisol, involved in the stress-response (Nieuwenhuizen & Rutters, 2008). It has also been found that patients with MDD possibly have lesser levels of glutamate in the prefrontal cortex. This show that glutamate toxicity may have a role in the biological symptoms of MDD (Aan het rot et al., 2009).

Individuals suffering from MDD have consistently been observed to have an excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis (Plotsky, Owens, & Nemeroff, 1995). Rodents that are separated from their mothers early in life show differences in the HPA axis

functioning, similar to those differences seen in humans with MDD (Nestler et al., 2002). Many

with MDD also have an increase in the cortisol concentration (Arborelius, Owens, Plotsky, &

Nemeroff, 1999). This increase in cortisol may be toxic to hippocampal neurons, resulting in

cognitive dysfunctions (Nestler et al., 2002). In animal models there are reductions in the birth of

new neurons in hippocampus due to stress, which could be related to the smaller left hippocampus

seen in some individuals with MDD (Bremner et al., 2000; Nestler et al., 2002).

Nestler et al. (2002) talk about the common treatments methods, and tell us that medication

is useful for about 80% of the diseased, while psychotherapy can make improvements in people

with mild to moderate depression. The most effective way of treating depression is often by

combining medication and psychotherapy. In the past, mechanisms of antidepressants were found.

Tricyclic antidepressant medications inhibit serotonin or norepinephrine re-uptake transporters,

while monoamine oxidase inhibitors inhibit monoamine oxidase. Antidepressants discovered

through these findings, and most used today are serotonin-selective re-uptake inhibitors, and

norepinephrine-selective re-uptake inhibitors (Nestler et al., 2002).

Nestler et al. (2002) say that many brain regions are likely to be abnormal in people with

symptoms of depression, with support from measures of changes in for example blood flow and

anatomy (Nestler et al., 2002). Changes in the brain of people with MDD have been found in areas

like hippocampus, striatum, amygdala, thalamus, and regions of prefrontal and cingulate cortex

(Manji, Drevets, & Charney, 2001), but some of these findings have been contradictory. Different

brain areas contribute to different aspects of depression. Neocortex and hippocampus are thought to

affect cognitive aspects of depression like memory and feelings of worthlessness, hopelessness,

guilt, and suicidality. The striatum and amygdala are thought to affect emotional memory, and to in

turn have a role in anhedonia, and anxiety. Hypothalamus is thought to have a role in depression

because of the symptoms of problems with sleep, appetite, energy, and interest in sex and other pleasurable activities. Nucleus accumbens, amygdala, and hypothalamus, which are involved in reward, fear, and motivation, are highly likely to be involved in depressive symptoms (Nestler et al., 2002).

Hippocampus has as mentioned a role in depression, and this brain area is known for its involvement in memory and learning. The symptoms of depression have been found to affect memory and learning, but these are only a few of the functions impaired in depression. Many other brain areas, like nucleus accumbens, hypothalamus, and amygdala, may be impaired since they are involved in domains that are often dysfunctional in depression. These domains are motivation, sleep, appetite, energy level, circadian rhythms, and responses to pleasurable stimuli. The neocortex is also a likely candidate of involvement in depression, in feelings of for example worthlessness, hopelessness, guilt, and suicidality (Nestler et al., 2002).

What will follow next is a presentation of the relationships of empathy and oxytocin, empathy and depression, and depression and oxytocin. The findings of empathy and oxytocin are presented first.

The relationship of empathy and oxytocin

The findings regarding the relationships of empathy and oxytocin have differences, but the aspects of empathy measured are varied, with personal distress, empathic concern, dispositional empathy, empathic accuracy, cognitive empathy, emotional empathy, and emotional recognition being measured. Research differs on oxytocin being administered intra-nasally, or measured through blood draw. This explains some of the conflicting findings but the results will be examined more thoroughly.

Emotional empathy

One study aimed at finding if experiencing empathy, namely personal distress and empathic concern (Barraza & Zak, 2009) which are both aspects of emotional empathy (Shamay-Tsoory et al., 2009), led to higher oxytocin levels. They did this because there is a lack of research on brain mechanisms behind the experience of empathy. They measured oxytocin through blood draw. Empathy toward others and personal distress was measured by letting the participant view a video of a father, and his son who suffered from cancer. What was found was that watching the emotional video increased oxytocin with 47% compared to those in the control group. A positive relationship was found between oxytocin level, and amount of experienced empathy. This relationship was stronger in women than men. Dispositional empathy and empathic concern, as measured by the Interpersonal Reactivity Index (IRI), predicted a spike in oxytocin. They saw that personal distress seemed to decrease oxytocin release, and self-reported empathy was positively correlated with

personal distress (Barraza & Zak, 2009). IRI is a subjective 28 item survey with 4 sub scales

measuring different dimensions of empathy (Davis, 1980). It is one of the most popular self-report

measures of empathy. It measures both cognitive and affective components, including perspective

taking, fantasy, personal distress, and empathic concern (Grynberg, Luminet, Corneille, Grèzes, &

Berthoz, 2010), and it includes statements like "when I see someone who badly needs help in an

emergency, I go to pieces" to measure empathic distress (Ghorbani, Bing, Watson, Kristl Davison,

& LeBreton, 2003).

In other words, empathic concern heightened the oxytocin release, while personal distress

lowered the oxytocin release. Empathic concern and personal distress are according to Shamay-

Tsoory et al. (2009) both aspects of emotional empathy (Shamay-Tsoory et al., 2009) but

hypotheses say that oxytocin release is decreased in personal distress due to the distress that is felt

because of another person. Oxytocin has by Scatamburlo et al. (2007) been found to have stress

decreasing effects (Scantamburlo et al., 2007), so perhaps it is a lack of oxytocin that provides

higher personal distress. Schreiter et al. (2013) say that in empathic concern, compassion motivates

to help an individual in need, and no personal distress is mentioned to be involved (Schreiter et al.,

2013), so this may reflect the increase in oxytocin.

Intra-nasal administration of oxytocin has been shown to increase emotional empathy, found

by measuring cognitive and emotional empathy by using the Multifaceted Empathy Test (MET)

(Hurlemann et al., 2010). MET is a collection of photographs of people in emotional situations.

These are viewed by the participant and the participant infer the mental states of the people in the

photographs to measure cognitive empathy. The participants also report their emotional reactions to

the photographs to measure emotional empathy (Dziobek et al., 2008). This finding of emotional

empathy and oxytocin suggests that the system that releases oxytocin regulates emotional empathy,

but not cognitive. Cognitive empathy is thought to be modulated by dopamine (Schamay-Tsoory, 2011). Although, other findings that are presented below point to a positive correlation between oxytocin and cognitive empathy as well. It could be that oxytocin differentially affect separate components of cognitive empathy.

These findings show that emotional empathy seems to be positively correlated with intra-nasal oxytocin administration. Empathic concern, which according to Shamay-Tsoory et al. (2009) is a component of emotional empathy (Shamay-Tsoory et al., 2009), is shown to be positively correlated with higher oxytocin levels in the blood.

Cognitive empathy

Bartz et al. (2010) performed a study on the effects of oxytocin on empathic accuracy (Bartz et al., 2010), which is a component of cognitive empathy (Schreiter et al., 2013). Oxytocin was intra-nasally administered and empathic accuracy was measured by letting the participants view five emotional videos, and indicating how positive or negative they thought that the people in the video felt. They found that oxytocin increased empathic accuracy, but only in individuals with higher score on the Autism Spectrum Quotient (AQ) (Bartz et al., 2010). The AQ is a measure of autistic-like behavior (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). Bartz et al. (2010) view their finding as consistent with the notion that oxytocin may increase the perceived salience of social cues. If this is true, oxytocin would only benefit those who are less attuned to social information meaning those individuals who have difficulties making appropriate appraisals of social cues. These are for example individuals with higher scores on the AQ (Bartz et al., 2010).

Shamay-Tsoory et al. (2013) found that administration of oxytocin intra-nasally can increase empathic responses to pain of an out-group. Specifically they found that when they administered oxytocin to Jewish Israelis, the empathic responses to the pain of Palestinian Arabs was significantly heightened. They found this by asking the individuals to report the pain intensity of the individual being watched (Shamay-Tsoory et al., 2013), so in other words they measured cognitive empathy.

This is in accordance with the finding of Kosfeld et al. (2005) that showed how intra-nasal oxytocin administration enhances trust. This is due to a greater willingness of engaging in interpersonal interaction that could mean a social risk, following intra-nasal oxytocin. This was found through having participants play a trust game in which they play for money. In this game, one participant transfers an optional sum of money to the opponent and this sum is tripled by the experimenter. The opponent can thereafter choose between keeping the money and giving it back (Kosfeld et al., 2005).

Also in line with the findings of Shamay-Tsoory et al. (2013) is what Domes et al. (2007) found. The saw that intra-nasal oxytocin administration is related to improved ToM ability. Reading the Mind in the Eyes Task (RMET) was used in this experiment (Domes et al., 2007). The RMET consists of photographs of faces where only the eyes are visible, used for showing how well one can attribute emotions of the faces being viewed (Pincus et al., 2010). ToM is a component of cognitive empathy (Schreiter et al., 2013), which is thought to impact the beliefs that out-group members can have complex emotions (Shamay-Tsoory et al., 2013).

These findings show positive relationships of intra-nasal oxytocin and cognitive empathy. According to this, oxytocin seem to heighten cognitive empathy.

Oxytocin is in research shown to have a connection to depression. Some findings of oxytocin reducing depression are shown (Scantamburlo et al., 2007). What will follow is a presentation of research regarding these two.

The relationship of oxytocin and depression

Conflicting findings exist regarding the relationship of depression and oxytocin. Oxytocin administration has in following research been intra-peritoneal, and intra-nasal. Plasma oxytocin, serum oxytocin, and salivary oxytocin has been measured. OT-immunoreactive neurons in the thalamus has been measured, as well as oxytocin-expressing neurons in the hypothalamus. These different methods of measurement are considered when searching for the different relationships of depression and oxytocin, and it may be what causes the contradictions.

The findings on plasma oxytocin in depressed patients are scarce, but they exist. More research is needed to find out if oxytocin could be of therapeutic benefit in those depressed patients with for example anxiety, and lack of social attachment. Half of patients with MDD suffer from anxiety disorder, so oxytocin could perhaps be of significance in therapy for these individuals as well as for individuals only suffering from anxiety (Slattery & Neumann, 2010).

Oxytocin has in research been shown to have anti-depressive, as well as stress reducing effects (Scantamburlo et al., 2007). Arletti and Bertolini were the first to show such an effect with findings of intra-peritoneal oxytocin administration reducing immobility time in the forced swim test (Slattery & Neumann, 2010) where mice are put in a water filled tank where the time swimming is recorded. An increase in floating instead of swimming is classified as an increase in depressive-like behavior (Norman et al., 2010). Stress is somewhat positively correlated with depression (Nestler et al., 2002).

A recent study found that depressed mothers showed less salivary oxytocin (Feldman, 2012),

with depressive symptoms found by clinically interviewing to determine axis I disorders, and oxytocin extracted from the saliva of the participants (Thompson, Parker, Hallmayer, Waugh, & Gotlib, 2011).

Another study saw that higher plasma oxytocin was related to postpartum depression symptoms in women. Postpartum depression was measured with the Edinburgh Postnatal Depression Scale, and blood samples were taken to measure plasma oxytocin (Skrundz, Bolten, Nast, Hellhammer, & Meinlschmidt, 2011).

Twelve majorly depressed individuals in a study had reduced levels of plasma oxytocin, and this is according to themselves in accordance with their previous findings of oxytocin abnormalities in depression. DSM-IV criteria was followed to find if subjects were depressed, and plasma oxytocin was measured by taking blood samples. Oxytocin decreases the stress-response, and the reduction of oxytocin in those with depression could possibly result in the up-regulated HPA system that is often found in depression. This abnormal HPA system could be the cause of the increase in oxytocin, in order to accomplish better mood and well-being (Scantamburlo et al., 2007).

Serum oxytocin is shown to be lower in patients with major depression and bipolar disorder than controls. Serum oxytocin was measured by taking blood samples, and depression was measured with Hamilton Depression Rating Scale that with 17 items measures symptoms of depression. They say that similar results have been presented earlier, and they also mention a possible connection of the HPA system with the oxytocin system. Increased HPA activity is thought to be related to decreased oxytocin release, and symptoms of depression such as loss of appetite, and reduced sexual and social behavior may be connected to the decreased oxytocin in those suffering from depression since oxytocin seems to be related to bonding and sexual behavior

(Ozsoy, Esel, & Kula, 2009).

This finding is consistent with what Anderberg & Uuvnäs-Moberg (2000) found in their research. When measuring depression with BDI, and oxytocin by taking blood samples, they saw a correlation between lower levels of oxytocin and higher scores of depression. This research measured females with fibromyalgia syndrome, a chronic pain disorder (Anderberg & Uuvnäs-Moberg, 2000). It is hypothesized that in depression, the neurohypophyseal system is of abnormal functioning. The neurohypophyseal system is involved in the releasing of oxytocin into the bloodstream and is also a part of the stress response (Ozsoy et al., 2009).

Another study saw a negative correlation of plasma oxytocin and depressive symptoms in patients with MDD (Scantamburlo et al., 2007). Looking at this, plasma oxytocin seems to be related to some symptoms of MDD (Slattery & Neumann, 2010). There is also findings of oxytocin being positively related to improvements of sexual dysfunctions, sleep disturbances, and anhedonia, symptoms. These are symptoms that are commonly present in depression (Neumann & Landgraf, 2012).

Plasma, serum and salivary oxytocin are in these findings shown to have negative relationships with depression, and administration of oxytocin seems to have anti-depressive effects. What will follow next are some research result that could be seen as opposing.

One study of women found that when performing an image session of affiliation, higher plasma oxytocin concentrations was found in participants with MDD. The oxytocin concentrations during the session positively correlated with symptom severity. During the image session, there was

also a dysregulated oxytocin release in the patients with MDD (Cyranowski et al., 2008). This could all mean that oxytocin may be associated with sociality in depressed patients (Slattery & Neumann, 2010).

Here, plasma oxytocin concentrations was higher in those with MDD, compared to previous findings presented where concentrations were lower, but this was during an image session of affiliation so that may very possibly have had an impact on the result.

Another study found that oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus have been found to be increased in patients with major depression and bipolar disorder, when performing postmortem examinations (Purba, Hoogendijk, Hofman, & Swaab, 1996). This is hypothesized to be the cause of the dysregulation of the HPA system found in individuals suffering from major depression. Another hypothesis is that there is an increase in oxytocin-expressing neurons as a result from the dysregulated HPA system (Scantamburlo et al., 2007).

A postmortem study of patients with major depression and bipolar depression found a 23% increase in the quantity of oxytocin-immunoreactive neurons in the paraventricular nucleus of the thalamus. This is thought to be connected to activity in the HPA axis (Purba et al., 1996).

These two findings present the amount of neurons in thalamus and hypothalamus, so it does not necessarily reflect the oxytocin amount. The findings of oxytocin having anti-depressant effects are about the oxytocin level in the blood so when considering if the level of oxytocin has anti-depressive effects it seems as if it does since neurons cannot tell the ending result of the oxytocin amount. Perhaps there are more neurons as a compensation for a lower level of plasma and serum

oxytocin in depression.

Earlier in this paper, it was mentioned that anhedonia is a part of depression. Administration of oxytocin into the ventral tegmental area, ventral subiculum, and posteromedial cortical nucleus of the amygdala in mice has been shown to result in increased dopamine release in nucleus accumbens. This support the hypothesis that oxytocin has rewarding properties since in drug abuse there is also an increase of dopamine release in this area. This suggests that oxytocin application and release results in a positive hedonic state, thereby possibly able to decrease the severity of anhedonia in patients with MDD (Slattery & Neumann, 2010).

There is a possibility that negative early-life events can be a cause of the differentiation in the activity of the brain oxytocin system, and that this is resulting in mental disorders. The support for this lies in the research of men who had experienced negative parenting, who showed lower sensitivity to basal plasma cortisol-reducing effect of intra-nasal oxytocin. Also, oxytocin can increase feelings of attachment security in males with insecure attachment that could lead to MDD. Findings promote that oxytocin could have beneficial effects for at least some majorly depressed individuals. The possibility is that administration of oxytocin to majorly depressed individuals may promote positive social interactions and lead to improvements from depression (Slattery & Neumann, 2010).

Something being discussed in research is if depression has some kind of connection with empathy. A connection seems to exist (Schreiter et al., 2013), so research on this topic will now be presented.

The relationship of depression and empathy

Aan het Rot et al. (2009) tell us that structural and functional abnormalities in frontal brain areas have been linked to MDD (Aan het Rot et al., 2009) and this is hypothesized to be the cause of difficulties in concentration and decision making. They think that these abnormalities in the frontal brain areas also could lead to in impairments in cognitive empathy (Schreiter et al., 2013).

The findings of the relationship of empathy and depression are conflicting, but research tend to look at different aspects of empathy. Empathic distress, empathic concern, perspective taking, emotional empathy, and ToM are considered in the following section.

Emotional empathy

Findings are showing that higher levels of depression seem to be associated with higher levels of empathic distress (Nicolas et al. 2009). According to Shamay-Tsoory et al. (2009), empathic distress is a component of emotional empathy (Shamay-Tsoory et al., 2009). For example, Nicolas et al. (2009) found a significant positive relationship between empathic family stress, and depression. As empathic family stress increased, so did the depressive symptoms. They describe empathic family stress as the worry and stress that arise due to the problems of a family member (Nicolas et al., 2009). In other words basically the same description as empathic distress. Nicolas et al. (2009) measured depressive symptoms with The Center for Epidemiologic Studies Depression Scale (CES-D) (Nicolas et al., 2009). This is a 20-item self-report scale of symptoms present within the last week (Radloff, 1977). To find the empathic family stress levels, they used the

Neighborhood and Family Questionnaire which is a self-report questionnaire consisting of 85 items about neighborhood, relationships, and help-seeking behavior. They selected a sub scale of 10 items that would measure stress in health, relationships, work, and legal problems of family members and found relationships between empathic family stress and depression based on this (Nicolas et al., 2009).

TABLE 6
Correlation Matrix for Empathic Family Stress, Depression, and Acculturative Stress

Measure	1	2	3
1. Family stress	—		
2. Acculturative stress	.18*	—	
3. Depression	.22*	.32**	—

Note.
*$p < .05$.
**$p < .01$.

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(Nicolas et al., 2009).

Ghorbani et al. (2003) found a relationship between higher empathic distress and higher levels of depression. Empathic distress and depression were also indicators of personality maladjustment. For measuring depression they used Costello and Comrey's 14-item depression scale, and for measuring empathic distress they used the IRI (Ghorbani et al., 2003). The 14-item depression scale is a part of the Scales for Measuring Depression and Anxiety. It is a self-report questionnaire assessing higher or lower levels of depression by measuring items of depressive tendencies like "when I wake up in the morning I expect to have a miserable day" (Costello & Comrey, 1967).

Schreiter et al. (2013) has found that many articles find no correlation between empathic concern (Schreiter et al., 2013), told by Shamay-Tsoory et al. (2009) to be a component of emotional empathy (Shamay-Tsoory et al., 2009), and depression neither in subjective nor objective

measures. They did however present one article by other researchers who looked at the relationship between emotional and cognitive aspects of empathy and depressive symptoms in medical students (Schreiter et al., 2013). These researchers found that lower empathic concern was correlated with more depressive symptoms in women (Thomas et al., 2007) so higher scores of depressive symptoms is in other words related to lower scores on the emotional aspects of empathy when considering that Shamay-Tsoory et al (2009) see empathic concern as a part of emotional empathy (Shamay-Tsoory et al., 2009). Schreiter et al. (2013) tell us that this is one of few articles that may show a gender difference in the correlation of low empathic concern and depression (Schreiter et al., 2013). To find the correlation, they used the Primary Care Evaluation of Mental Disorders (PRIME-MD), to measure depressive symptoms, and the IRI to measure empathic concern, and perspective taking (Thomas et al., 2007). The PRIME-MD is a two item survey (Spitzer et al., 1994).

Table 2. Empathy and Markers of Distress

	Mean cognitive empathy score				Mean emotive empathy score			
	Men	P value	Women	P value	Men	P value	Women	P value
Burnout								
Emotional exhaustion*								
Low (<=18)	19.8	0.183	21.3	0.634	21.7	0.009	24.6	0.076
Moderate	19.6		20.2		21.0		23.5	
High (>=27)	18.9		21.2		20.2		24.0	
Depersonalization*								
Low (<=5)	20.4	0.002	21.5	0.017	22.4	<0.001	24.7	<0.001
Moderate	19.5		20.6		21.2		24.0	
High (>=10)	18.1		19.9		18.9		22.5	
Personal accomplishment†								
High (>=40)	20.7	<0.001	22.5	<0.001	22.6	<0.001	24.9	<0.001
Moderate	18.7		19.9		20.4		23.6	
Low (<=33)	18.6		19.5		19.7		23.2	
Depression								
Screen negative (n=241)	19.6	0.583	21.8	0.013	21.3	0.476	24.9	0.001
Screen positive (n=294)	19.3		20.5		20.9		23.5	

*High score on this scale is indicative of burnout.
†Low score on this scale is indicative of burnout.

(Thomas et al., 2007).

A second article that Schreiter et al. (2013) present that shows a correlation of empathic concern and depression is one by Gawronski & Privette (1997). They have found a significant

correlation in women, where more depressive symptoms was correlated with higher levels of empathic concern. In this experiment, the participants were only women, and only women working in health care. They measured empathy by using the Mehrabian and Epstein Questionnaire Measure of Empathic Tendency (Gawronski & Privette, 1997) which is a measure of emotional empathy (Mehrabian & Epstein, 1972). They measured depressive symptomatology using the adapted Zung Self-rating Depression Scale (Gawronski & Privette, 1997) that measures depressive symptoms (Adogwa et al., 2012).

One research show that individuals with MDD have significantly less empathy as measured by using the Toronto Empathy Questionnaire (TEQ) (Cusi, MacQueen, Spreng, & McKinnon, 2011). The TEQ is a self-report questionnaire consisting of 16 items rated on five point scale, measuring primarily emotional empathy (Spreng, McKinnon, Mar, & Levine, 2009). These individuals also had less empathic concern as measured by the IRI. These correlations had occurred despite that the levels of the depressive symptoms were low. Emotional empathy seems to be impaired in majorly depressed individuals, and this impairment may worsen the depression (Cusi et al., 2011).

The findings here are contradictory, with research showing a positive correlation with empathic distress and depression in men and women, and emotional empathy being positively correlated with depression, while empathic concern has shown both a negative and a positive correlation with depression in women.

Lee, Brennan, and Daly (2001) also found that less life satisfaction was correlated with higher emotional empathy, with emotional empathy measured by using the Mehrabian Emotional

Empathy Scale. This scale includes statements like "the people around me have a great influence on my moods" with the possibility to rate from very strong disagreement to very strong agreement. Life satisfaction was measured with Life Satisfaction Index Z that includes 13 items of overall life satisfaction that is rated by the participant. They conclude that the result may be because of the caregiver's inability to detach themselves from the problems of the ones they take care of (Lee et al., 2001).

Cognitive empathy

Schreiter et al. (2013) tell us that there are very conflicting research findings on the relationship between depression and scores on the IRI sub-scale of perspective taking, with perspective taking being a part of cognitive empathy. Some studies found no correlation, and some studies found a negative correlation. Regarding subjective measures, there are conflicting findings of impairments of cognitive empathy in depression (Schreiter et al., 2013). Lee (2009) was one of those to find no correlation. He found that that perspective taking had no correlation to depression, and he also found that perspective taking had a positive relationship with empathic concern, but a negative relationship with personal distress. Depression was measured by using The Beck Depression Inventory (BDI) (Lee, 2009), which is a 21-item self-report questionnaire that measures the severity of depression (Segal, Coolidge, Cahill, & O'Riley, 2008), and IRI was used to measure perspective taking, empathic concern, and personal distress (Lee, 2009).

Grynberg et al. (2010) used the same measures as Lee (2009) but found a negative correlation between depression and perspective taking (Grynberg et al., 2010).

Table 2
Pearson-moment product correlations between alexithymia, empathy, anxiety and depression scores.

Factors	DDF	EOT	TAS-20 total	PD	EC	F	PT	STAI-T	BDI-13
DIF	.57***	.25***	.83***	.32***	−.07	.12**	−.14***	.54***	.45***
DDF	–	.30***	.83***	.22***	−.12**	−.01	−.18***	.32***	.25***
EOT		–	.63***	.02	−.24***	−.21***	−.37***	−.05	.06
TAS-20 total			–	.25***	−.18***	−.01	−.28***	.42***	.35***
PD				–	.22***	.18***	−.06	.52***	.28***
EC					–	.32***	.33***	.03	−.01
F						–	.16***	.13***	.08
PT							–	−.14***	−.13**
STAI-T								–	.69***

Note: DIF = difficulty identifying feelings; DDF = difficulty describing feelings; EOT = externally-oriented thinking; PD = personal distress; EC = empathic concern; F = fantasy; PT = perspective taking. STAI-T = trait anxiety; BDI-13 = depression. All correlations refer to the whole sample, except for the BDI-13 (French sample only).
** $p < .01$.
*** $p < .001$.

(Grynberg et al., 2010).

Ghorbani (2003) used IRI, and Costello & Comrey's depression and anxiety scales. They also found a negative correlation (Ghorbani et al., 2003).

Table 1
Correlations among variables for iranians (above diagonal) and americans (below diagonal) and scale alphas, means (M) and standard deviations for each sample

Variables	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Commitment Scale	–	0.27***	0.33***	−0.23**	0.49***	0.28***	−0.51***	−0.41***	−0.61***
2. Empathic Concern	0.39***	–	0.17*	0.34***	0.02	0.23***	−0.10	0.14*	−0.17*
3. Perspective Taking	0.31***	0.50***	–	−0.23**	0.23**	0.33***	−0.30***	−0.21**	−0.31***
4. Empathic Distress	−0.26***	−0.07	−0.16*	–	−0.38***	−0.05	0.44***	0.45***	0.28***
5. Identity Scale	0.55***	0.26***	0.26***	−0.36***	–	0.06	−0.54***	−0.52***	−0.60***
6. Attributional Complexity	0.46***	0.43***	0.49***	−0.17*	0.29***	–	−0.20**	−0.07	−0.19**
7. Perceived Stress	−0.47***	−0.19**	−0.27***	0.51***	−0.57***	−0.34***	–	0.50***	0.65***
8. Anxiety Scale	−0.41***	−0.09	−0.18**	0.52***	−0.45***	−0.18**	0.52***	–	0.52***
9. Depression Scale	−0.76***	−0.43***	−0.33***	0.24***	−0.61***	−0.44***	0.54***	0.44***	–
Iran									
Alpha	0.83	0.66	0.54	0.70	0.75	0.73	0.83	0.73	0.87
M	2.02	2.79	2.42	2.07	2.06	2.33	1.78	1.85	1.54
S.D.	0.51	0.66	0.62	0.73	0.54	0.43	0.61	0.67	0.73
USA									
Alpha	0.86	0.74	0.68	0.63	0.85	0.87	0.82	0.77	0.93
M	2.15	2.86	2.53	1.68	2.61	2.45	1.72	1.50	0.89
S.D.	0.50	0.62	0.63	0.59	0.58	0.53	0.57	0.68	0.78

For American sample $N = 213$. For Iranian sample $N = 218$.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

(Ghorbani et al., 2003).

A study by Donges et al. (2005) gives further validation for the notion that perspective

taking is limited in depression. They describe a finding of depression, as measured by the BDI, to be negatively correlated with scores on a sub-scale on the Levels of Emotional Awareness Scale (LEAS) (Donges et al., 2005). LEAS is a measure of individual differences in emotional awareness (Bajgar, Ciarrochi, Lane, & Deane, 2005). They measured perspective taking by using the sub-scale from the LEAS (Donges et al., 2005), which consists of hypothetical interpersonal situations with descriptions of possible emotions of self and others which are meant to be scored (Lane, Quinlan, Schwartz, Walker, & Zeitlin, 1990). Schreiter et al. (2013) believe that this finding may indicate limited perspective taking ability in depression (Schreiter et al., 2013).

Thomas et al. (2007) also found that lower ability of perspective taking was related to higher scores of depressive symptoms in women. They say that this means that higher scores of depressive symptoms was related to lower scores on cognitive aspects of empathy. They used the Primary Care Evaluation of Mental Disorders (PRIME-MD), to measure depressive symptoms, and the IRI to measure perspective taking (Thomas et al., 2007). The PRIME-MD is a two item survey (Spitzer et al., 1994).

In an experiment it was found that those with MDD had less perspective taking ability as measured by the IRI. MDD was measured with the TEQ, and this correlation was found despite low levels of MDD in the participants. What was also found was that a higher number of past depressive episodes was linked to a worsened ability of perspective taking. A higher perspective taking dysfunction may lead to further impairments in individuals with MDD (Cusi et al., 2011).

Schreiter et al. (2013) show evidence for lower ability of ToM, a function of cognitive empathy, and higher levels of depression being associated (Schreiter et al., 2013). For example,

Inoue et al. (2004) found that patients with MDD had lower ToM ability. They measured ToM with Wechsler Adult Intelligence Scale – Revised, and depression was assessed using DSM-IV (Inoue et al., 2004). They consider this to be support of the idea that cognitive empathy is impaired in depressed individuals. The reason for the poor ToM in depressed individuals is thought to be because of a cognitive deficit. Specifically, dysfunctional frontal brain areas are thought to be the cause, and these areas are active when performing an objective measurement of ToM, called Movie for the Assessment of Social Cognition (MASC) (Schreiter et al., 2013). MASC is a movie, and the research participant answers some questions about the mental states of the actors in the movie after watching it (Dziobek et al., 2006). The more severe the symptoms of depression are, the lower the cognitive empathic performance and executive function seem to become (Schreiter et al., 2013).

A study by Lee et al. (2001) showed that volunteer caregivers with higher levels of depression, as measured by the CES-D, had lower cognitive empathic ability, and lower cognitive empathy could predict the severity of the depression. Cognitive empathy was measured with the Barrett-Lennard Empathy Scale which measures using 16 self-report questions (Lee et al., 2001).

What can be seen from these results of perspective taking, ToM, and cognitive empathy altogether is that cognitive empathy is limited in depression. The results of the relationship between perspective taking and depression were as mentioned limited, but the findings of ToM and cognitive empathy that have been presented point to a negative relationship of cognitive empathy and depression.

What we have seen so far is relationships between each of empathy, oxytocin and depression. What will follow now is a presentation of how empathy, oxytocin and depression all

affect each other. In particular, one research by Pincus et al. (2010) has tried to find the relationship of depression, oxytocin and mentalization (Pincus et al., 2010).

Correlations of empathy, oxytocin, and depression; how do they function together?

Oxytocin has been shown to improve socially reinforced learning and face recognition, to prevent or reduce anxiety, and to affect maternal care-taking in mother-infant relationships. Oxytocin release is heightened when breastfeeding, in early skin to skin contact, and later in sexual intercourse and climax. Low levels of oxytocin has been correlated with MDD, and those with lower levels of oxytocin often feel less affiliation with others. Depressive symptoms often involve experiences like insecure attachment and losses. A lower social functioning has in research often been correlated with an enhanced risk for symptom reccurance of MDD (Pincus et al., 2010).

An experiment has found that in mice with spared nerve injury (SNI), social isolation was correlated with increased depressive-like behavior following the injury (Norman et al., 2010). SNI means altering behavior by performing lesions to two or three branches of the sciatic nerve and leaving one intact (Decosterd & Woolf, 2000). They studied how social factors would affect depressive-like behavior in mice with SNI. The mice were either paired two and two, or they were socially isolated for 2 weeks before conducting SNI surgery or a sham surgery, and one week after. The socially isolated mice were treated with oxytocin, and the paired mice were treated with an oxytocin receptor antagonist. They found that social interaction is related to the physiological and behavioral responses to the injury, in that less social interaction could predict higher depressive-like behavior. They used the forced swim test and by using this, they found that depressive-like behavior developed only in the socially isolated mice with the nerve injury. The administration of oxytocin decreased the effect that SNI has on the depressive-like behaviors in the socially isolated mice. The paired mice that were treated with an oxytocin receptor antagonist, had depressive-like behavior similar to the socially isolated mice. This altogether proposes that social factors have an influence

on affective responses to SNI. In other words, social factors affect the development of depressive-like behavior following SNI and this is possibly through alterations in oxytocin. They mention that oxytocin increases positive social behavior like positive communication, and trust, and this may mean that oxytocin has a positive effect on health outcomes as well (Norman et al., 2010).

Higher plasma oxytocin has been found positively related to the receiving of trusting behavior as well as the reciprocation of trust (Zak, Kurzban, & Matzner, 2005). Plasma oxytocin levels were higher during positive communication behaviors (Gouin et al., 2010), and closeness and affectionate contact in families have also been found positively related to higher levels of plasma oxytocin (Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010). In contrast, women with higher plasma oxytocin reported insufficient social contacts with especially mothers, best friends, and social groups. In this lies support for plasma oxytocin being positively correlated with interpersonal distress (Taylor, Gonzaga, Klein, Hu, Greendale, & Seeman, 2006). Also, Taylor, Saphire-Bernstein, & Seeman (2010) found that higher plasma oxytocin may be an indicator of distressed pair-bonds in women (Taylor et al., 2010). This is seen as a bit complicated and one theory for the variation is that oxytocin levels are positively related to sensitivity to social cues and/or social motivation (Bartz, Zaki, Bolger, & Ochsner, 2011). Administration of intra-nasal oxytocin has been found to enhance the correct identification of emotions (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009), also known as emotional recognition which is a component of emotional empathy (Shamay-Tsoory et al., 2009). Hurlemann et al. (2010) did as mentioned present that administration of intra-nasal oxytocin increased emotional empathy (Hurlemann et al., 2010) but the effect that oxytocin has on emotional empathy, emotional recognition, trust perception, and trust behavior, seems to be moderated by the influences of the social environment and/or the individual to whom the oxytocin is being administered. The factors that affect the results could be task difficulty, stimuli valence, familiarity of other participants, reliability, in- and out-group status, social cognitive skills and
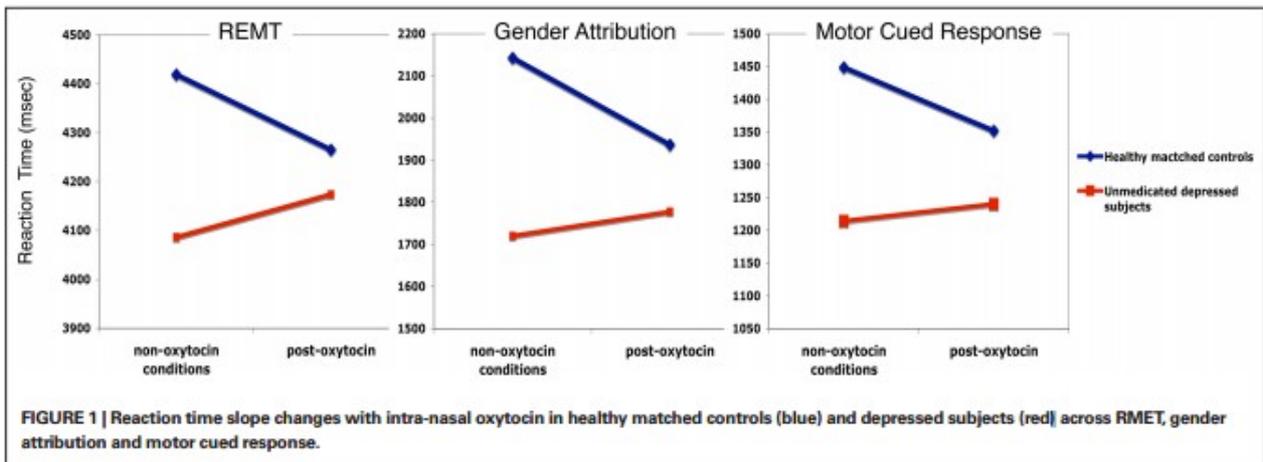
knowledge, attachment anxiety, and disorders. Oxytocin may facilitate social cognition and pro-sociality by reducing anxiety, increasing social motivation, and/or increasing salience of social cues (Bartz et al., 2011), and oxytocin does as mentioned prevent and reduce anxiety (Pincus et al., 2010).

In females, higher oxytocin has been found to be related to enhanced activity in the insula (Domes et al., 2010), and the insula is as mentioned a brain area involved in emotional empathy (Decety & Ickes, 2011). Intra-nasal administration of oxytocin in women proved to have a difference in the impact on the neural circuitry in healthy individuals as compared to in those with MDD. Oxytocin increased activity in the right amygdala, and caudate nucleus in healthy women, and in women with MDD there was an increased activation in right middle frontal gyrus, and right insula (Pincus et al., 2010).

Pincus et al. (2010) has looked at oxytocin regarding its modulation of the brain activity in people with MDD, to correlate this with attribution of emotional mental states in others, also known as mentalization (Pincus et al., 2010) which is a type of cognitive empathy (Shamay-Tsoory et al., 2009). They believe themselves to be first to investigate this. In mentalization, neural areas like amygdala, superior temporal gyrus, and medial and orbito-frontal cortex are involved. In this study, 10 majorly depressed individuals and 10 healthy individuals participated. Some were administered intra-nasal oxytocin and others were placebo controls. Each one performed the RMET where they pushed buttons to choose an attribute of a picture. This test was done before and after the oxytocin administration or placebo control. The neural activity was measured using fMRI, and they also made behavioral measures in the form of reaction time and accuracy of response during the RMET. They wanted to see if there was a change in reaction time pre and post drug administration, and they looked to see if there was a difference in the reaction time of depressed versus healthy subjects

(Pincus et al., 2010).

Depression is known to decrease the ability of mentalization, and this may be because one in depression has limited social interactions, and function in a more distant way. In the healthy subjects, oxytocin increased the activity in ventral regions like ventromedial, parahippocampal, amygdala, and semantic associative areas. In the majorly depressed subjects, oxytocin increased activation in higher order cognitive areas such as superior middle frontal gyrus, and increased activity in insula. The activation of ventral areas in the healthy subjects may indicate an affective appraisal and social appraisal in the activity. This shows that there is a difference in the effect that oxytocin has on majorly depressed and healthy individuals. Oxytocin tended to shorten the reaction time in the healthy subjects and lengthen it in individuals with MDD but overall the reaction time was faster in individuals with MDD than healthy individuals. The reason for the shorter reaction time in MDD patients may be because they could be mentalizing in a more impulsive way, and healthy individuals activate an increased number of higher order cognitive and emotional regions. Regarding the fastened reaction time in healthy subjects it may be that in healthy individuals oxytocin activates an emotionally reflexive appraisal state that involves less reflection. A finding supporting this is that at difficult tasks healthy individuals had better results when administered oxytocin (Pincus et al., 2010).

FIGURE 1 | Reaction time slope changes with intra-nasal oxytocin in healthy matched controls (blue) and depressed subjects (red) across RMET, gender attribution and motor cued response.

(Pincus et al., 2010).

They conclude that major depression is related to higher paralimbic activity during attribution of emotional mental states of others, and this neural activity in the majorly depressed individuals seems to be partly modulated by oxytocin. Studies have found that ventral limbic and paralimbic activity is abnormal in depressed individuals, and these same areas are involved in social relatedness and mentalization. The research of Pincus et al. (2010) show that majorly depressed individuals mentally attribute differently in the RMET than healthy subjects. Also, intra-nasal oxytocin affects the activity in the neural areas involved in the mental attribution and improves cognitive and affective mental attribution, dependent on the distress and capacity to empathize in an individual (Pincus et al., 2010).

Striepens, Kendrick, Maier, & Hurlemann (2011) explain that amygdala has a role in decreasing responses to negative social stimuli and increasing responses to positive. They also put forward research on how oxytocin affects the amygdala. For example, oxytocin treatment leads to decreased amygdala activity to fearful faces and increased activation to happy faces (Striepens et al., 2011). Oxytocin also decreased amygdala activation in "selfish" people who was exposed to pain (Singer et al., 2008).

Conclusion and discussion

The aim was to see how empathy, oxytocin and depression correlate with each other. Specifically, the questions were whether there exist positive relationships between oxytocin and empathy, as well as depression and empathy. Another main aim was to find out whether depression and empathy have a negative relationship. Focus has also been on what neural areas of activity they share. A key issue is whether one can alter the oxytocin levels for example by intra-nasal administration, in order to affect empathy and/or depression. Administration of oxytocin has been a recurrent focus so there should be a sufficient amount of research on this.

The connection of empathy, oxytocin, and depression

The conclusion of this research is that there exist correlations among empathy, oxytocin, and depression. Some results are contradictory with others, but the results do, as mentioned, differ due to internal and external factors. Emotional empathy seems to be positively associated with both blood oxytocin levels and intra-nasal oxytocin administration. Emotional empathy has in most studies been found to have a positive relationship with depression. Cognitive empathy does also have a positive relationship with intra-nasal oxytocin, but there seems to be a negative correlation between cognitive empathy and depression. Depression and oxytocin have a seemingly negative relationship, where blood oxytocin is negatively correlated with depression and intra-nasal administration of oxytocin has anti-depressive effects.

It is unclear in which order and direction these relationships occur, so there is a variety of possible ways. Following are some hypotheses regarding the correlations. One possibility is that administration of intra-nasal oxytocin increases both emotional and cognitive empathy, and cognitive empathy can in turn decrease depression, while emotional empathy can increase depression. It seems as if it is possible to administer intra-nasal oxytocin in order to alleviate depression or enhance empathy. I reason that oxytocin has an impact on both depression and empathy, and can affect them both internally and by administration.

Regarding the relationship of empathy and depression, the question remains whether it is depression that affects empathy or empathy that affects depression. We conclude here that it could go both ways, since the finding by Nicolas et al. (2009) of empathic family stress being related to depression (Nicolas et al., 2009) could point to troublesome situations in the family being the cause of the empathic distress leading to depressive symptoms. At the same time Pincus et al. (2010) found that abnormalities of areas involved in mentalizing exist in individuals with MDD (Pincus et al., 2010), but these impairments could be the cause of MDD as well as MDD causing the impairments .

Another hypothesis about the way in which these relationships emerge is based on what Bartz et al. (2011) found about higher plasma oxytocin being related to major depression during a social affiliation task, and administration of oxytocin heightening emotional empathy (Bartz et al., 2011). From this finding it is derived that oxytocin could be the cause of a sensitivity to social cues, resulting in emotional empathy, which in turn leads to higher levels of depression.

One hypothesis regards the finding that oxytocin shortened the reaction time for healthy

subjects, and lengthened it in individuals with MDD (Pincus et al., 2010). These individuals may be majorly depressed because of a decrease in oxytocin, and that in turn resulting in a decrease in reaction time, but lengthening the reaction time when exposed to more oxytocin.

Regarding the bond of oxytocin, contact, and depression, Gordon et al. (2010) did as mentioned say that closeness and affectionate contact was positively correlated with plasma oxytocin (Gordon et al., 2010), but in women, insufficient social contact was also positively correlated with plasma oxytocin (Taylor et al. 2006). In women, distressed pair-bond relationships were positively correlated with plasma oxytocin (Taylor et al., 2010), and depression does as mentioned seem to have a negative relationship with plasma oxytocin (Scantamburlo et al., 2007). This could all mean that individuals get distressed due to not receiving enough closeness and affection from those one experience a bond with. This could in the end lead to depression, leading to less oxytocin.

The neural areas of common involvement

The neural areas of involvement of empathy oxytocin, and depression have been presented. Found is that empathy, oxytocin and depression have some neural areas of affect in common.

Amygdala is as mentioned abnormal in those with MDD (Manji et al., 2001), and amygdala is active in mentalization (Pincus et al., 2010). This is seen as further proof of mentalization being of lesser function in those with MDD. Scantamburlo (2007) mentions that oxytocin exists in

amygdala (Scantamburlo, et al., 2007), so there may be a mediating role of oxytocin on MDD and mentalization. Rodrigues et al. (2009) also mentions that intra-nasal oxytocin decreased activity in amygdala when exposed to social stimuli as well as emotional stimuli (Rodrigues et al., 2009). Oxytocin increases emotional empathy and damage to amygdala led to impairments on emotional empathy. Therefor it is concluded that oxytocin may increase emotional empathy by affecting the amydala (Striepens et al., 2011). Both imitating and perceiving emotional expressions also shows increased activation in amygdala and insula (Decety & Ickes, 2011).

Another area of common involvement is hippocampus. According to Nestler et al. (2002), memory is often of lesser function in those with depression and hippocampus is highly involved in this function (Nestler et al., 2002). Hippocampus is involved in ToM and this means that autobiographical memories play a role in inferences of others mental states (Shamay-Tsoory, 2011). Scatamburlo et al. (2007) tell us that oxytocin has been found in hippocampus (Scantamburlo et al., 2007). In some individuals with MDD, hippocampus is decreased in volume (Bremner et al., 2000).

Last, we have the cingulate cortex. During the observation of pain but also during exposure to own pain, the anterior cingulate cortex is more active (Shamay-Tsoory, 2011). Oxytocin has been found in cingulate cortex (Barraza & Zak, 2009), and volumetric differences in this area exists in depressed individuals compared to controls (Aan het rot et al., 2009).

It is concluded that it may be possible to stimulate or injure one of these three areas in order to affect empathy, oxytocin, and/or depression. For example damage to amygdala did as mentioned result in impaired emotional empathy, so damage to the other areas could perhaps have an impact on empathy too.

Future research

Future research should look at how all three function together and why they affect each other. There is also a need to see if, how, and to what degree these could be altered in order to change each other. An example is to see if one can use intra-nasal oxytocin to increase or decrease empathy and/or depression in the therapeutic setting. There is a need to see what factors influence the results and how, and to find consistent results and clarify how it all relates. Another direction of future research should be what exactly it is that causes these relationships. Are there any mediating factors, and is it causations or correlations we are seeing. Research should also focus on if and how it is possible to stimulate amygdala, hippocampus and/or cingulate cortex in order for it to have an impact on empathy, oxytocin and/or depression.

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