Social Cognition

Alexandra Patin and René Hurlemann

Contents

A. Patin • R. Hurlemann (✉)
Department of Psychiatry, University of Bonn, 53105 Bonn, Germany

Division of Medical Psychology, University of Bonn, 53105 Bonn, Germany
e-mail: renehurlemann@icloud.com

K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_10

Abstract

Social cognition is a major problem underlying deficiencies in interpersonal relationships in several psychiatric populations. And yet there is currently no gold standard for pharmacological treatment of psychiatric illness that directly targets these social cognitive areas. This chapter serves to illustrate some of the most innovative attempts at pharmacological modulation of social cognition in psychiatric illnesses including schizophrenia, borderline personality disorder, autism spectrum disorders, antisocial personality disorder and psychopathy, social anxiety disorder, and posttraumatic stress disorder. Pharmacological modulation includes studies administering oxytocin, ecstasy (MDMA), modafinil, methylphenidate, and D-cycloserine. Furthermore, some background on social cognition research in healthy individuals, which could be helpful in developing future treatments, is provided as well as the potential for each drug as a long-term treatment option.

Keywords

Social cognition • Schizophrenia • Anxiety disorders • Autism spectrum disorder • Oxytocin

1 Introduction

1.1 What Is Social Cognition?

Although the concepts on their own are relatively well integrated into the language of everyday literature, when put together the term social cognition is suddenly more difficult to clearly define. In a review of social behavior in humans, Ralph Adolphs describes the problem as being one of inclusion: "If the social is ubiquitous, we face the problem of including all aspects of cognition as social" (Adolphs 2003, p. 165).

At the base of social cognition traditionally lies emotion recognition, which has been argued to be the key to understanding how another person feels, what they are intending to do, or how they will react to a stimulus (Elfenbein and Ambady 2002). Included in the definition of social cognition for purposes of this chapter are also, among others, empathy and theory of mind, or the ability to infer feelings and emotions in another, cooperation, trust, and social feedback-based learning.

A further important facet of social cognition is reciprocity: it is not enough to merely perceive and understand social cues, but one must be able to give appropriate signals and reactions as well (Roepke et al. 2013).

1.2 Brain Regions Involved in Social Cognition

Although related, the neural networks involved in different social cognition domains are distinct. Face processing, for instance, involves the fusiform gyrus, or fusiform face area, for processing static features, the superior temporal sulcus for processing mimicry and dynamic changes in the face, and the amygdala (Adolphs 2003; Haxby et al. 2000). The amygdala, alongside the ventromedial prefrontal cortex, is also of great interest to social cognition researchers as they share rich functional connections and have been found to play a role in psychopathy, depression, anxiety disorders, autism, and schizophrenia (Tudusciuc and Adolphs 2013). Social cognition as a broader concept appears to have its roots in a network involving the prefrontal cortex (PFC), amygdala, cingulate gyrus, fusiform gyrus, insula and further regions in the somatosensory cortex, superior temporal sulcus, and the supramarginal gyrus (Tudusciuc and Adolphs 2013).

2 Illnesses Characterized by Low Social Cognition

A lack of social cognition is a cornerstone of several illnesses characterized by the inability to interact with others at a normal, healthy level. Specifically, emotion recognition has consistently correlated with characteristics such as social anxiety and avoidance, distress, depression, antisocial behavior, and psychopathy (McClure and Nowicki Jr 2001). Both healthy and patient populations show the importance of social cognition to interpersonal interactions. For instance, healthy participants have shown a link between fear recognition ability and an increased desire toward altruistic behavior (Marsh et al. 2007), as well as report having better relationships and a lower depression rate (Carton et al. 1999). In patient populations, social cognition has been found to have a predictive value, and autism or psychosis patients with lower social cognitive abilities statistically show lower social function (Bertrand et al. 2007; Losh et al. 2009).

There are indications in the literature that therapeutic augmentation with pharmacological modulation can be used to support social cognition in healthy participants, and one common theme among these is the emerging possibility of beneficial treatments for patients with schizophrenia, antisocial disorders, and social anxiety. Moreover, there have been several approaches toward enhancing social cognition in psychiatric illness. For one, cognitive enhancement therapy (CET) involves neurocognitive and social cognitive improvements based on a computer-based training in attention, memory, and problem solving and further exercises in perspective taking, gistfulness, social context appraisal, and other areas of social cognition (Eack 2013).

2.1 Schizophrenia

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), schizophrenia is a disorder within the schizophrenia spectrum and is characterized in part by negative symptoms, which make up a large part of the clinical manifestation of schizophrenia and have a direct effect on social cognition. They include diminished emotional expression, avolition (a reduced motivation for self-initiated activity), alogia (reduction in speech output), anhedonia (a reduced ability to gain pleasure from positive stimuli), and asociality (reduced interest in social interaction). Particularly salient in schizophrenia are diminished emotional expression and avolition (American Psychiatric Association 2013).

One debilitating consequence of schizophrenia is social and occupational dysfunction, although patients may well possess the cognitive ability to complete required tasks (American Psychiatric Association 2013). Initial studies directly aiming to improve social cognitive skills in individuals with schizophrenia have shown an increase in theory of mind following training (Bechi et al. 2012; Bechi et al. 2013), as well as focusing on concrete social cognition, such as in CET (Eack 2013). Patients with schizophrenia usually experience their first symptoms early on in adult life, and a large minority of patients show an onset before they reach 19 years of age (Cullen et al. 2008), and the disease affects 0.3–0.7 % of adults overall (van Os and Kapur 2009). Other findings report a much higher prevalence of schizophrenia and related categories of illness of 2–3 % (Perälä et al. 2007). Schizophrenic individuals die 12–15 years before the average population, mostly due to unhealthy lifestyles (Saha et al. 2007).

Men are affected with the disease more often than women (Roy et al. 2001). As of yet, no single cause has been pinpointed, although there is a strong evidence for a genetic predisposition (van Os and Kapur 2009). Twin studies show that there is a heritability rate of up to 80 % (van Os and Kapur 2009). The typical pharmacological treatment involves antipsychotic drugs working antagonistically at the D2 receptor, but this is usually made in addition to psychological treatment as well as social support systems (van Os and Kapur 2009).

Cognitive impairments are a common manifestation of schizophrenia, including memory, attention, and executive function (Fioravanti et al. 2005). Indeed, schizophrenia was first known as dementia praecox at its discovery precisely because of these deficits (Kraepelin 1971; van Os and Kapur 2009). Individuals with schizophrenia show a much higher use of drugs than the general population, and alcohol or nicotine use is found in half to over half the population (Mueser et al. 1992; Šagud et al. 2009). This introduces the question of whether schizophrenic individuals use substances such as nicotine as an effort to support cognitive enhancement and are perhaps lacking this support in conventional therapeutic regimes. Structural and functional neural abnormalities have been found in several cases in schizophrenic individuals, including neuroinflammation in orbitofrontal white matter and decreased astroglial density in the subgenual cingulate white matter (Najjar and Pearlman 2015), as well as abnormal functional hub density in the frontal and limbic association areas, for example, suggesting difficulty in

information integration over different neural regions (Bassett et al. 2008; Zhang et al. 2012).

2.2 Borderline Personality Disorder

While borderline personality disorder (BPD) affects 1–3 % of adults (Trull et al. 2010), it affects a much larger rate of 10–20 % of psychiatric patient populations (Korzekwa et al. 2008), making it one of the leading disorders marked by social cognition deficits. The DSM-5 characterizes BPD individuals as making great effort to avoid abandonment, having feelings of emptiness, and being in unstable and intense interpersonal relationships, among other symptoms (American Psychiatric Association 2013). These are symptoms that directly reflect difficulties in social cognition, as they are illustrative of difficulties patients have in understanding and dealing with others.

From very early on in social cognition research, it became apparent that patients with BPD showed a negative bias toward judging the intentions of others as malevolent (Lerner and St. Peter 1984; Stuart et al. 1990). A lack in both cognitive and emotional empathy could also serve as a major underpinning for BPD individuals' difficulties in interactions (Roepke et al. 2013). Further studies have shown that BPD individuals have difficulties with perceiving, processing, and responding to social cues from others (Brodsky et al. 2006; Gunderson and Lyons-Ruth 2008; Stiglmayr et al. 2005).

The underlying mechanism for these deficits is difficult to discern, but there is growing support for the idea that emotional hypervigilance disrupts normal processing of emotional stimuli, specifically in terms of emotion recognition (Domes et al. 2009; Linehan 1995). This idea is in support of findings showing that BPD individuals have greater sensitivity when faced with social rejection (Staebler et al. 2011; Stiglmayr et al. 2005).

Structural and functional abnormalities have been found in the amygdala for one, suggesting that this is an important neural region for therapeutic approaches (Domes et al. 2009) focusing on cognitive and emotional empathy, emotion recognition, trust and rejection processing, and moral judgments, all of which show strong deficits in BPD individuals (Herpertz and Bertsch 2014; Roepke et al. 2013).

2.3 Autism Spectrum Disorders

Autism spectrum disorder (ASD) patients are strongly influenced by social cognitive deficits; in terms of diagnostics, the DSM-5 characterizes ASD individuals by verbal and nonverbal communication difficulties, difficulties when interacting with others, and repetitive movements or behaviors, among others (American Psychiatric Association 2014). All of these traits make normal social relationships close to impossible, but the first two are specifically concerned with social cognition per se, thus making ASD a leading candidate for social cognition treatment development.

Patients with autism suffer from a difficulty in judging the value of social signals and struggle with emotion recognition, making interpersonal interaction difficult (Gross 2004; Hill and Frith 2003). One underlying mechanism could involve reduced activation of the fusiform face gyrus, inferior occipital gyrus, superior temporal sulcus, and amygdala, and an increased response by the frontal cortex and primary visual cortex, during face processing in autism patients (Pierce et al. 2001). Early findings have indicated that autistic children lack a theory of mind (Baron-Cohen et al. 1985). Structural as well as functional deficits in autistic individuals during social cognitive tasks often include the amygdala (Baron-Cohen et al. 1999, 2000; Pierce et al. 2001), although there is currently no single identifiable neural region or network responsible for the disorder.

2.4 Antisocial Personality Disorder and Psychopathy

According to the DSM-5, antisocial personality disorder (ASPD) is at times manifested in social cognitive symptoms such as a lack of remorse, deceitfulness, and failure to conform to social norms (American Psychiatric Association 2013). The underlying mechanisms for social cognition deficiencies, however, are not entirely clear.

Psychopathy is associated with ASPD, though not interchangeable with it (Hare and Neumann 2006). One popular model of psychopathy is the Violence Inhibition Mechanism (VIM) model, which describes an inability to read and react to social signals of submission, such as facial expressions of fear, sadness, or shame (Blair 2001; Blair et al. 1997). This inability to react appropriately has the effect that individuals with ASPD or psychopathy do not empathize with victims, and the inhibiting force normally stopping violence or antisocial behavior is removed. Here, too, the underlying cause for this extreme lack of empathy is not clear, though it could depend on reduced neural responses following emotional stimuli (Meffert et al. 2013).

A meta-analysis of antisocial personality disorder showed that one of the strongest characteristics of patients is the inability to recognize fearful faces and emotional stimuli in general (Sterzer et al. 2005), which is able to be tracked to amygdala dysfunction (Birbaumer et al. 2005; Kiehl et al. 2001; Marsh and Blair 2008; Veit et al. 2013). An additional area of interest is the ventromedial PFC (Blair 2008), as both areas have shown abnormal activation during social cognitive tasks, such as emotional memory (Kiehl et al. 2001). In terms of intra-amygdala activity, individuals with psychopathy show increased activation in the central amygdala and reduced activation in the basolateral amygdala during emotional processing tasks (Moul et al. 2012).

As opposed to a specific site of trauma or lesion, the amygdala and ventromedial PFC, among other areas, make up a network in which the exact location or nature of the dysfunction is not easy to pin down (Blair 2008). Psychopathy is progressive in nature (Lynam et al. 2007), making treatment early on in life a worthwhile pursuit. Interestingly, one study found that while psychopathic individuals do not show pure

executive function deficits, they do show lower levels of executive functioning when an emotional component is included (Lapierre et al. 1995). This supports the argument that social cognition, rather than pure cognition, is lacking in ASPD and psychopathic patients.

2.5 Social Anxiety Disorder

With a lifetime prevalence of approx. 12 % (Kessler et al. 2005), social anxiety disorder (SAD) affects millions of people worldwide. According to the DSM-5, SAD is characterized by symptoms such as disabling anxiety in social settings in which the individual will be under observation by others, and even complete avoidance of social situations, among other symptoms (American Psychiatric Association 2013).

Studies investigating the underlying mechanisms of these symptoms have shown a cognitive bias toward interpreting social cues to be more negative as well as toward negative self-representation (Constans et al. 1999; Hirsch and Clark 2004; Mogg et al. 2004; Rapee and Abbott 2006; Stopa and Clark 2000; Voncken et al. 2003). Furthermore, socially anxious individuals show lower theory of mind ability than non-socially anxious individuals, even independently of an interpretation bias (Hezel and McNally 2014).

2.6 Posttraumatic Stress Disorder

A highly misunderstood and prevalent disease following a traumatic event is posttraumatic stress disorder, with a lifetime prevalence of 6.8–9.2 %, depending on age (Kessler et al. 2005). Among lifetime PTSD individuals, almost half of both women and men suffer from a major depressive episode following the trauma, and over 50 % of males and almost 28 % of females will meet the criteria for alcohol abuse or alcohol dependence (Kessler et al. 1995). According to the DSM-5, PTSD individuals are also characterized by social cognition deficits, for example, persistent and exaggerated negative beliefs regarding themselves or the world around them, feelings of detachment or estrangement, hypervigilance, or an exaggerated startle response (American Psychiatric Association 2013).

3 The Effect of Pharmacological Modulation of Social Cognition

As illustrated above, deficits in social cognition are a common theme throughout psychiatric illnesses, and they are arguably the underlying reason for many of the socially debilitating consequences of disease. There is unfortunately no single pharmacological gold standard currently available for the treatment of social cognitive deficits. However, there have been several innovative efforts to develop

treatments to combat these symptoms. This chapter should serve to illuminate these efforts and findings.

3.1 Oxytocin

Pharmacological properties of OT

Oxytocin (OT) research has climbed exponentially in recent years, for the most part due to the interest spawned by its effects on social cognition and social behavior as a neuromodulator. Originally named for its hormonal properties in inducing uterine contractions during birth, stemming from the Greek words ὀξύς (swift) and τόκος (birth), OT has rapidly become a drug of choice when exploring social cognition. For the most part, following synthesis in the supraoptic and paraventricular nuclei of the hypothalamus, OT proceeds via axonal transport to the neurohypophysis, where it is stored in secretory vesicles together with the OT carrier protein neurophysin I and secreted into the bloodstream (Brownstein et al. 1980).

Synthesis of OT is regulated by the OT gene located on chromosome 20 in humans. OT is mainly produced in the supraorbital (SON) and paraventricular (PVN) hypothalamic nuclei. The magnocellular cells of the PVN terminate in the neurohypophysis, amygdala, and nucleus accumbens, while the parvocellular cells of the PVN terminate in other CNS regions (Knobloch et al. 2012). OT secretion is dependent on neuronal depolarization and subsequent Ca^{2+}-dependent exocytosis of the vesicles (Brownstein et al. 1980; Gimpl and Fahrenholz 2001). OT central release also shows effects of priming (Ludwig and Leng 2006). Additionally, OT is synthesized in much smaller quantities peripherally in the uterus, placenta, amnion, corpus luteum, testis, and heart, for example (Gimpl and Fahrenholz 2001). OT was synthetically synthesized for the first time in 1953 by Vincent du Vigneaud and was thus the first polypeptide hormone to be sequenced and synthesized (Pitocin, Syntocinon; cys–tyr–ile–gln–asn–cys–pro–leu–gly–NH2) (du Vigneaud et al. 1953, 1954).

There is currently only one known OT receptor (OTR). The OTR is a G_q-protein-coupled receptor of the rhodopsin-type (class I), coded for by the OTR gene located on chromosome 3 (Gimpl and Fahrenholz 2001; Simmons Jr et al. 1995). The OTR has been found in the human brain in the central and basolateral amygdala, medial preoptic area, anterior and ventromedial hypothalamus, olfactory nucleus, vertical limb of the diagonal band, ventrolateral septum, anterior cingulate and hypoglossal and solitary nuclei, the basal nucleus of Meynert, and at times in the globus pallidus and ventral pallidum (Boccia et al. 2013; Loup et al. 1991). Social animals show high rates of OT receptor density in the nucleus accumbens and the prelimbic cortex, which

(continued)

modulate feelings of reward (Lim et al. 2004), as well as in the amygdala (Huber et al. 2005).

The exact mechanism of how or whether OT completely crosses the blood–brain barrier is unknown (Banks and Kastin 1985; Ermisch et al. 1985a, b; Meisenberg and Simmons 1983). Animal studies have shown that intravenous injection of OT results in approximately 0.01 % of OT actually crossing the blood–brain barrier (Kendrick et al. 1991). Because of this, there is most likely no correlation between endocrine OT release at the neurohypophysis and cerebrospinal fluid (CSF) levels, which are most likely influenced by neurons reaching into the third ventricle, limbic system, brain stem, and spinal cord (Altemus et al. 2004; Gimpl and Fahrenholz 2001; Kagerbauer et al. 2013; Martin et al. 2014; Striepens et al. 2013).

The exact pharmacokinetics of OT in humans are not yet completely settled. The half-life of OT ranges from roughly 2 min in plasma (Jones and Robinson 1982; Meyer et al. 1987) to 3–5 min in women in vitro (Rydén and Sjöholm 1969) and 20 min in CSF (Mens et al. 1983). OT is rapidly degraded in vitro following the addition of plasma from pregnant women, showing an 85 % reduction in OT concentration in the course of 1 h, but not in nonpregnant women or men (Leake et al. 1980). Twenty-four international units (IU) of intranasal OT has been shown to increase plasma OT levels to their highest levels 15 min following administration, whereas cerebrospinal fluid peak levels were reached 75 min later (Striepens et al. 2013).

3.1.1 OT in Healthy Individuals

Earlier studies exploring the effects of OT as a neurotransmitter focused mainly on prosocial effects of OT. However, initial groundbreaking studies soon illustrated a far more complex picture: a single dose of 24 IU of OT in healthy subjects, latency 45 min, not only enhanced prosocial behavior, but also negative emotions, such as schadenfreude and envy (Shamay-Tsoory et al. 2009). Likewise, OT has been found to enhance protective responses, evident in a potentiated acoustic startle response to negative stimuli and increased recollection of negative stimuli (Striepens et al. 2012). In this vein, the literature has strived to explore the various facets of OT in social settings, and several strides have been made in social cognitive domains. One of these domains is theory of mind, also called cognitive empathy. This ability has been suggested to increase emotional empathy, or the ability to feel what the other person is feeling, also known as putting oneself in another's shoes. Further findings show that OT increases responses to emotional faces (Shahrestani et al. 2013; Van IJzendoorn and Bakermans-Kranenburg 2012), as well as emotional empathy ratings (single dose, 24 IU, latency 45 min) (Hurlemann et al. 2010) in healthy participants.

The ability to transfer this recognition of emotion to a judgment of how the other person will likely act, a process known as "mind reading" (Siegal and Varley 2002;

Stone et al. 2003), is also increased following OT administration (single dose, 24 IU, latency 45 min) (Domes et al. 2007), suggesting a wide spectrum of areas related to emotion recognition sensitive to OT effects. At an intersection of cognitive and emotional domains, OT (single dose, 24 IU, 45 min latency) was shown to increase the effect of positive versus negative social feedback on learning during a declarative memory task in healthy males (Hurlemann et al. 2010).

In a further area of social cognition, healthy subjects given OT showed that they were more trusting during social interaction and responded less to social stress, as well as more cooperative (Bartz et al. 2011b; Heinrichs et al. 2003; Kosfeld et al. 2005). Furthermore, OT appears to increase social approach and protective behavior (Lim and Young 2006; Preckel et al. 2014; Scheele et al. 2012). The underlying mechanism for this effect could be a reduced amygdala response to vague or threatening stimuli (Baumgartner et al. 2008; Meyer-Lindenberg 2008). As such, OT appears to counteract social transmission of fear via social signals of anxiety inducing stimuli and could thus hold therapeutic potential for patients with anxiety disorders (Eckstein and Hurlemann 2013).

3.1.2 OT in Psychiatric Illness

ASD

Patient populations have shown that OT is a promising area of research in terms of treatment augmentation. For instance, ASD subjects are found to have reduced plasma OT levels (Green et al. 2001; Modahl et al. 1998; but see also Jansen et al. 2006). Furthermore, several studies have found a likely correlation between susceptibility to ASD and genetic variations in the OT receptor gene (Auranen et al. 2002; Shao et al. 2002; Wermter et al. 2010; Wu et al. 2005).

Exogenous OT administration in participants with ASD has been shown to increase comprehension and memory for the social-emotional words happy, angry, or sad (continuous infusion of 10 U/ml OT in 1.0 l of saline over 4 h per indwelling intravenous catheter; infusion rate titrated 25 ml every 15 min in the first hour, 50 ml in the second, 100 ml in the third, and infused at a constant rate of 700 ml/h in the fourth hour; testing was completed at baseline just before the infusion, 30, 60, 120, 180, and 240 min during infusion) (Hollander et al. 2007).

In an innovative study of skin conductance response (SCR) to human versus nonhuman sounds, a single dose of 24 IU OT (latency 1 h) resulted in an overall reduction in SCRs in healthy controls to all sounds, but an increase in SCRs to human sounds relative to nonhuman sounds (Lin et al. 2014). Patients under placebo showed a similar SCR pattern toward both sounds, but a similar pattern to OT-treated controls following OT administration. Thus, OT apparently worked to assimilate the patterns and levels of SCR in patients versus controls. Finally, SCR differences toward human versus nonhuman sounds following OT correlated with the patients' social function and interpersonal reactivity.

In terms of face perception, a study examining the differential neural response to emotions versus nonsocial objects found that OT enhanced neural response while processing emotions (single dose; 25 IU for participants aged 16–19 years, 18 IU

for ages 12–15, 12 IU for ages 7–11; latency 45 min) (Gordon et al. 2013). A single dose of 24 IU OT, 45 min prior to testing, increased amygdala response to emotional faces (Domes et al. 2013), and a study of high-functioning ASD and Asperger patients was found to show increased social interaction and more normal face processing following a single dose of 24 IU OT 50 min prior to task completion (Andari et al. 2010). Recognition of nonverbal, information-based judgments of emotional faces was increased in ASD patients following a single dose of 24 IU OT (latency 40 min), and authors furthermore found that abnormal medial PFC activity was improved following OT (Watanabe et al. 2014).

More specifically, emotion recognition was increased following single dose of either 24 IU (participants aged 16–19) or 18 IU (ages 12–15) OT administration, latency of 45 min, in young participants with Asperger's disorder (Guastella et al. 2010). Emotion recognition, as well as emotional well-being, was also increased following a 6-week administration in ASD adults (24 IU twice daily) (Anagnostou et al. 2012). In a more long-term study, OT showed positive effects on social cognition areas including social recognition, empathic accuracy, and theory of mind in a 12-week treatment course (dosage 0.2, 0.26, 0.33, and 0.4 IU/kg/dose, twice daily) (Anagnostou et al. 2014).

Although the above studies were not successful in showing behavioral changes, a recent meta-analysis of intranasal OT as potential treatment for ASD found a moderate effect size of OT and suggested it is thus worth pursuing for therapeutic use (Bakermans-Kranenburg and van IJzendoorn 2013).

Schizophrenia

Endogenous OT in schizophrenic individuals has been found to correlate with symptom severity (Rubin et al. 2010) as well as social cognitive bias (Walss-Bass et al. 2013), and plasma OT levels in patients positively correlate with emotion recognition (Goldman et al. 2008). Additionally, there is evidence for a strong interaction between OT and other neurotransmitters such as serotonin, for instance (Lee et al. 2003; Mottolese et al. 2014).

Several studies examining the effects of exogenous OT administration in schizophrenic patients, both following a single dose as well as more long-term use, have been completed. In an augmentation study, patients received 40 IU OT for 6 weeks 30 min prior to a twice weekly social cognitive skills training sessions (Davis et al. 2014). The authors reported significant improvements in empathic accuracy both 1 week following the final training session and 1 month later. A second study employing a 6-week regimen of 24 IU OT twice daily examined participant response to social cognitive measures as well as social skills and clinical symptoms 50 min after the final morning dose at the end of week 6 (Gibson et al. 2014). Findings included improved theory of mind and fear recognition, and increased perspective taking.

Improved emotion recognition was also found in two further studies following a single dose of 24 IU OT after 45 min (fear recognition) (Fischer-Shofty et al. 2013) and after 50 min (Averbeck et al. 2012). Following a much higher single dose of 40 IU and a latency of 30 min, schizophrenic individuals showed significantly

improved ability for controlled social cognition, or the ability to perceive and understand indirectly expressed emotions or intentions over long time periods (Woolley et al. 2014). In a further study using a single dose of 40 IU (latency 30 min), schizophrenic individuals increased performance on higher-level social cognition assessments, including detection of sarcasm and deception and empathy, but not on lower-level assessments, such as facial affect perception, social perception, and detection of lies (Davis et al. 2013). Thus, it appears that improvements in schizophrenia positively benefit from a higher dosage of OT, and it would be interesting to find out in further research under what conditions this correlation applies.

Interestingly, along the same vein, whereas a low single dose of 10 IU OT (latency 45 min) was detrimental to emotion recognition, a higher single dose of 20 IU (latency 45 min) improved emotion recognition in polydipsic patients, specifically reducing a bias toward fear perception (Goldman et al. 2011). Supporting these findings, 24 IU OT twice daily improved theory of mind following a 14-day treatment (latency 50 min) (Pedersen et al. 2011). Nonsignificant findings from the same study showed that schizophrenic volunteers additionally showed increased trust.

BPD

Endogenous OT levels have been found to be lower in women with BPD and negatively correlated with aggressiveness and symptom severity (Bertsch et al. 2013).

Exogenous OT administration in patients with BPD has shown mixed effects. For one, OT apparently obstructed trust and cooperation in a study of BPD individuals given a single dose of 40 IU OT and tested 35 min later, apparently due to an increased desire to punish the other player in a social dilemma game (Bartz et al. 2011a; Ebert et al. 2013).

On the other hand, BPD individuals showed a lowered stress response following 40 IU OT (latency 60 min) than placebo, manifested in a relative absence of both dysphoria and cortisol in response to the Trier Social Stress Test (Simeon et al. 2011). A study examining avoidance reactions showed that, while placebo-treated BPD individuals revealed an avoidance reaction to angry faces, BPD individuals treated with 24 IU OT (single dose, latency 45 min) did not, thus suggesting that OT abolished the hypervigilance for threatening stimuli in BPD individuals (Brüne et al. 2013). Similarly, female BPD patients given 26 IU OT (single dose, latency 45 min) were found to normalize their perception of angry faces, including reduced abnormal fixation changes to the eyes as well as the absence of hyperactive amygdala response to angry faces, indicating that the characteristic BPD hypersensitivity was abolished under OT (Bertsch et al. 2013).

ASPD and psychopathy

The literature concerning OT and psychopathy is limited, but shows some highly interesting findings. Studies of the OTR gene have found it to be influential to psychopathic traits: in one study, the rs1042778 genotype TT was linked to high levels of callous-unemotional traits in children diagnosed with disruptive

behavioral problems (Dadds et al. 2014b). A further study of 4- to 16-year-old males diagnosed with oppositional-defiant or conduct disorder linked increased methylation of the OTR gene as well as with lower endogenous OT levels in older male participants to high levels of callous-unemotional traits, and reported that higher methylation correlated with low endogenous OT (Dadds et al. 2014a).

Exogenous intracerebroventricular OT in rats resulted in reduced aggressive behavior and increased social exploration (5 μl OTR peptidergic antagonist {desGly-NH_2,d(CH_2)$_5$[Tyr(Me)^2,Thr^4]OVT}, latency 10 min) (Calcagnoli et al. 2013). In a recent meta-analysis of the effect of OT on emotion recognition in healthy participants, OT was found to improve overall performance on recognizing facial expressions, first and foremost for happy and fearful faces (Shahrestani et al. 2013). As the authors suggest based on previous findings in this area, this could be vital to interpersonal communication, as fear recognition is key to feeling empathy for the pain of another being, blocking antisocial impulses and thus important for illnesses characterized by these (Marsh and Blair 2008; Shahrestani et al. 2013).

As of yet, no augmentation therapy has been attempted with emotional training and OT.

SAD

Endogenous OT findings in SAD patients paint an interesting picture. In one study, plasma OT was found to be similar in patients and healthy controls, but differences emerged within the patient group (Hoge et al. 2008). For one, OT levels positively correlated with symptom severity and were furthermore linked to dissatisfaction in social relationships. The authors explained this finding by suggesting that social deficits in anxiety or autistic disorders may be associated with increased levels of OT as a compensatory mechanism following OTR dysfunction.

Exogenous, intranasal administration of 24 IU OT 45–90 min prior to exposure therapy (four sessions) resulted in patients reporting a reduced negative bias toward negative metal representations of self as well as toward their speech performance and appearance (Guastella et al. 2009).

A further study showed that generalized SAD individuals given OT showed increased functional connectivity between the amygdala and bilateral insula and middle cingulate/dorsal anterior cingulate gyrus when processing fearful faces, bringing them closer to connectivity patterns shown by healthy controls (Gorka et al. 2014). OT was also shown to normalize resting state functional connectivity of the left and right amygdala with the rostral anterior cingulate cortex/medial PFC following a single dose of 24 IU OT in another generalized SAD patient population (Dodhia et al. 2014). Additionally, the study found that the more severe the social anxiety in patients, the greater amygdala-frontal connectivity was increased.

In a further study, amygdala hyperactivity in generalized SAD patients in response to fearful faces compared to healthy controls was shown to normalize following a single dose of 24 IU OT (latency 45 min) (Labuschagne et al. 2010). Additionally, an increased medial PFC and left anterior cingulate cortex response to sad faces was also improved following 24 IU OT (single dose, 50 min latency) (Labuschagne et al. 2012).

PTSD

Two studies have found that the OT receptor variation rs53576 allele is associated with posttraumatic stress and the ability to cope (Bradley et al. 2013; Lucas-Thompson and Holman 2013). Only one study has administered exogenous OT to PTSD individuals, and showed that physiologic responses during a combat imagery task were lower following 20 IU OT than placebo (single dose, latency 1 h) (Pitman et al. 1993).

3.1.3 Conclusions: Potential for OT as a Viable Long-Term Treatment Option

Although there is great promise for the success of OT as a long-term treatment option in psychiatric illness, there is still a great deal of research needed. As the authors of a comprehensive review of OT effects on social behavior report, the majority of OT studies on social cognition report that drug effects represent an interplay with stimulus or task, and that the question thus becomes, which conditions allow for an effect of OT to shine through (Bartz et al. 2011b).

For one, the pharmacodynamics of OT have yet to be explored experimentally. The optimal dosage and latency for pharmacological experiments remain unclear. This makes setting up a proper paradigm, as well as interpreting OT's effects on studies to separate from differences in paradigm more difficult. The effects are well illustrated in the finding that a lower vs. higher doses of OT can have the complete opposite effect in social cognition (Goldman et al. 2011) and can differentially influence aggressive behavior (Calcagnoli et al. 2013).

In order to measure accurately the effects of OT on social cognition, and therefore for OT to be used as a valid therapeutic method in illnesses marked by lower social cognition, there needs to be a standardization of the literature. For instance, optimal dosage and latency should be empirically determined for healthy participants (Shahrestani et al. 2013). Furthermore, response to exogenous OT should be measured in terms of standardized markers (Shahrestani et al. 2013), and intranasal administration should be standardized (Guastella et al. 2013).

In terms of emotion recognition, paradigms need to be standardized to include all basic emotions presented in a similar format to aid comparison across studies showing an effect of OT (Shahrestani et al. 2013). Currently, the literature is strongly focused on male participants. However, if OT is to become a viable treatment option, females need to be considered equally. Initial findings have shown that emotional processing is differentially affected by OT in females compared to males (Domes et al. 2010), and this remains an area to be further explored.

Additional genetic testing would be beneficial to expanding the understanding of OT in both healthy and patient groups. CD38, for example, a protein generally associated with cancer markers, has been linked in several cases to the OT receptor and the uptake of exogenous OT (Higashida et al. 2010; Higashida et al. 2011). Another therapeutically important example is the common OT receptor single nucleotide polymorphism, rs53576, which has been associated with the ability to benefit from social support under psychosocial stress (Chen et al. 2011). These are not the only potentially game-changing genetic differences that could influence the

course of therapeutic OT administration, and more research is needed to determine how differences would affect different patients during treatment.

The possibility of OT for therapeutic use should not be ruled out due to these difficulties. OT remains an extremely powerful mediator of social bonds, and thus highly important for research in psychiatric illness characterized by a lack of these bonds (Scheele et al. 2013). For example, autistic children show normal response in the fusiform face gyrus when presented with their mother's face, but not when viewing other adults' faces (Pierce and Redcay 2008). OT has been long understood as a crucial element in maternal bonding (Kendrick 2004; Kendrick et al. 1997), and could thus present an important clue to the differential face processing in autistic children versus adults (Pierce et al. 2001; Pierce and Redcay 2008).

3.2 3,4-Methylenedioxymethamphetamine (Ecstasy)

Pharmacological properties of MDMA

It is not exactly clear how 3,4-methylenedioxymethamphetamine (MDMA) produces its effects, but there have been several studies documenting its potential mechanisms. Structurally, MDMA is a ring-substituted amphetamine similar to mescaline and methamphetamine (de la Torre et al. 2004). It works as an agonist to the trace amine-associated receptor 1 (TAAR1), thus working toward monoamine transporter reuptake inhibition (Miller 2011). The S(+) isomer of MDMA is a psychostimulant and has an effect on empathy, while the R isomer has hallucinogenic effects (de la Torre et al. 2004).

MDMA works mainly as a serotonin (5-HT), dopamine (DA), and noradrenaline (NA) reuptake inhibitor and/or releaser; the mechanism is one of membrane transport reversal and subsequent flow of 5-HT, DA, and NA into the synaptic cleft and to the postsynaptic membrane (de la Torre et al. 2004). Emotional excitation following 1.5 mg/kg MDMA was blocked by both a single oral dose of 50 mg of the 5-HT_{2A} receptor antagonist ketanserin and 1.4 mg of intravenous haloperidol, a D_2 receptor antagonist, implicating both serotonergic and dopaminergic influences in euphoric mood changes under MDMA (Liechti and Vollenweider 2001). MDMA also acts to increase cortisol, prolactin, ADH, and ACTH secretion (de la Torre et al. 2004).

The pharmacokinetics following a single dose of 75, 100, and 125 mg MDMA in humans are listed in Table 1. MDMA follows a nonlinear pattern, with lower doses being associated with higher urinary recovery and higher doses with lower recovery (de la Torre et al. 2004). Repeat doses show an exponential rate of plasma concentration of MDMA, with a C_{max} of 29 % following two successive doses of 100 mg MDMA over 24 h (Farre et al. 2004). Blood concentrations show a peak at 1–2 h following administration and a return to baseline after 4–6 h (Mas et al. 1999).

Table 1 Pharmacokinetics of different single oral doses of MDMA

Single dosage (mg)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)	k_a (h^{-1})
75 mg[a]	130.9	1.8	7.86	2.3835
100 mg[b]	225.5 ± 26.1	2.3 ± 1.1	9.0 ± 2.3	2.7 ± 1.5
125 mg[a]	236.4	2.4	8.73	2.1253

$n = 8$ for all results; C_{max}, peak plasma concentration; t_{max}, time until peak plasma concentration; $t_{1/2}$, elimination half-life; k_a, absorption constant; ng, nanograms
[a]Mas et al. (1999)
[b]de la Torre et al. (2004)

3.2.1 MDMA in Healthy Individuals

The literature regarding MDMA is far less developed than OT; however, some important observations have been documented in regard to social cognition. One study reported reduced fear recognition alongside increased self-reported loving feelings and friendliness following 1.5 mg/kg MDMA over 4 weekly sessions (latency 65 min) (Bedi et al. 2010). Similar results were reported in a study examining response to emotion recognition, which showed that 125 mg MDMA led to increased recognition of positive emotions, but decreased recognition of negative emotions (Hysek et al. 2012).

Behaviorally, 2 mg/kg MDMA (single dose, latency up to 5 h) resulted in increased friendliness, sociability, and talkativeness (Tancer and Johanson 2003). A further study found differential dose-dependent neural responses: the amygdala showed a dampened response to angry facial expressions following 1.5 mg/kg MDMA, while the ventral striatum showed an increased response to happy faces following 0.75 mg/kg MDMA (single dose, latency 45 min) (Bedi et al. 2009).

Likely mechanisms for MDMA's effects can be found in studies showing that MDMA acts as a stimulant for endogenous OT release (Dumont et al. 2009, 100 mg MDMA, single dose; Hysek et al. 2012; Kirkpatrick et al. 2014, 1.5 mg/kg MDMA, single dose, peak at 90–120 min latency; Thompson et al. 2007, injection of 5 mg/kg MDMA in rats) and could thus work as a potentiating force during prosocial behavior. Because there have been some contradictory findings (Kuypers et al. 2014), however, much more research is needed.

3.2.2 MDMA in Psychiatric Illness

Currently, there are no patient studies implementing MDMA for social cognitive improvement. However, MDMA is interesting when considering psychiatric illnesses marked by the inability to form meaningful, intimate relationships, because it increases prosocial function in healthy individuals (Bedi et al. 2009; Dumont et al. 2009). On the other hand, MDMA has been shown to significantly reduce cognitive function in many different areas in nonpsychiatric populations, as well as increase negative mood states (Parrott 2013), suggesting that it could be a difficult route of treatment development for psychiatric illness.

One area in which MDMA is surprisingly well researched relative to other illnesses is in individuals with PTSD, as an augmentation for psychotherapy. In an initial study, PTSD patients received single, initial dose of 125 mg MDMA and a

supplemental, optional dose of 62.5 mg 2–2.5 h after and relaxed while participating in therapeutic discussion with a therapist over 2 sessions interspersed among 17 sessions total (latency not applicable, onset of MDMA effects 45–75 min following initial dose, peak at 2–2.5 h, duration 4–5 h following single dose, 5–6 h following supplemental dose) (Mithoefer et al. 2011). Subjects who received MDMA showed an 83 % clinical response rate following psychotherapy compared to 25 % in the placebo group. A follow-up of the same patients showed that the vast majority still showed clinical improvements (Mithoefer et al. 2013). A further study found that a single dose of 125 mg + 62.5 mg supplemental dose MDMA over three sessions of psychotherapy (alongside 12 nondrug therapy sessions) lowered self-reported symptoms of PTSD (Oehen et al. 2013). Though these studies do not show a specific improvement in social cognition per se, they do imply an improvement in social interaction, as the therapy is necessarily led by a therapist, thus dependent on a social influence.

3.2.3 Conclusions: Potential for MDMA as a Viable Long-Term Treatment Option

More than other pharmacological interventions, MDMA as a potential treatment option for psychiatric illness is made much more difficult due to the legality of its use. In addition, studies regarding its effects are lacking, and contradictory findings have been shown. That said, MDMA does show promise in several areas of emotional processing relevant to social cognition and would thus be well worth pursuing as a possible augmentation for therapy.

3.3 Modafinil

Pharmacological properties of modafinil

Modafinil (2-[(diphenylmethyl)sulfinyl] acetamide; Vigil) is a psychostimulant which works indirectly on the glutamate and GABA receptors. Additional indirect modulation of neurotransmission includes an increase in dopamine, noradrenaline, and serotonin secretion. Pharmacokinetics are t_{max} 2–3 h, $t_{1/2}$ 10–12 h, or 15 h steady state following repeated doses. Oral bioavailability is 11–52 % and plasma protein binding 62 %. Modafinil is mainly used as a waking agent for sleeping disorders. Typical dosage ranges from 200 to 400 mg/day. (Benkert et al. 2013) Further uses for modafinil include treatment for depression (Fava et al. 2007), depressive episodes in bipolar disorder (Calabrese et al. 2010; Frye et al. 2007), cocaine addiction (Dackis et al. 2004), and attention deficit/hyperactivity disorder (ADHD) (Biederman and Pliszka 2008), among other disorders.

3.3.1 Modafinil in Healthy Individuals

Healthy participants in studies investigating cognitive enhancement benefits of modafinil have shown that it improves attention, memory, spatial planning, and executive functions, but this seems to have a dose-dependent influence (Kelley et al. 2012; Repantis et al. 2010). Cognitive enhancement has also been shown in some psychiatric illnesses, such as schizophrenia (Saavedra-Velez et al. 2009; Turner et al. 2004; Wittkampf et al. 2012).

3.3.2 Modafinil in Psychiatric Illness

Findings in psychiatric participants are mixed. In terms of emotional processing, 200 mg modafinil (single dose, latency 2 h) improved recognition of emotional faces, and significantly sad faces, but did not increase sensitivity to reward or punishment or performance in cognitive tasks with emotional components or improve mood in first episode psychosis (Scoriels et al. 2011). Unfortunately, findings are few and far between for modafinil and social cognition in psychiatric illness. Potential for the drug in the future is dependent on more research and is made more difficult by contraindications such as addiction disorders (absolute contraindication) or anxiety and psychosis (relative contraindications) (Benkert et al. 2013), which plague a large portion of psychiatric patients.

3.3.3 Conclusions: Potential for Modafinil as a Viable Long-Term Treatment Option

Modafinil acts in several areas of the brain including the amygdala, lending support to the drug as a worthwhile treatment for illnesses characterized by amygdala dysfunction. However, because a single dose of 100 mg modafinil (latency 3 h) has been shown to cause increased anxiety in healthy volunteers depending on dosage (Randall et al. 2003), this would need to be closely observed in psychiatric populations characterized by hypervigilance or anxiety, for example. Furthermore, there is evidence that modafinil can create a tolerance in the user as well as have addictive properties (Volkow et al. 2009), thus creating problems as a long-term treatment option.

3.4 Methylphenidate (Ritalin)

Pharmacological properties of MPH

Methylphenidate (MPH) (methyl phenyl(piperidin-2-yl)acetate; Ritalin, Concerta, Methylin, Equasym XL, among others) is a psychostimulant used for treating ADHD in children over 6 years of age and adolescents and narcolepsy. Pharmacokinetics are as follows: t_{max} 2 h, $t_{1/2}$ 2.4 h in children, 2.1 h in adults. Oral bioavailability is 30 % and plasma protein binding approx. 20 %. Its effects are felt quickly, within 15–30 min. Following

(continued)

decay, patients sometimes report feeling the symptoms in stronger intensity (rebound phenomenon), but this disappears after further administration. Administration of MPH must be started gradually. Initial dosage is 5–10 mg/day, building up to max 60 mg/day for ADHD in children as well as narcolepsy. MPH has the potential to become addictive (Benkert et al. 2013).

3.4.1 MPH in Psychiatric Illness

MPH has been for the most part restricted to use in ADHD, and the effects of MPH in social cognition are limited to early studies showing benefits of MPH in classroom and social settings in hyperactive youth. Unfortunately, pharmacological data are not available in detail for all studies; methodological data are reported here where available. Findings include fewer negative interactions with peers in a social setting (Hinshaw et al. 1984a), greater self-control following a MPH + self-control training when confronted with a stressful and socially threatening situation (Hinshaw et al. 1984b), as well as reduced intensity of negative behaviors (both studies occurred over a 3-week period of adjunct treatment in addition to daily medication; dosages for morning administration were 5–40 mg and 0.15–1.16 mg/kg for the first study and midday administration range 5–20 mg and 0.44–0.55 mg/kg for the second) (Hinshaw et al. 1984b). Further findings supported these results and showed less disruptive behavior and improved social behavior following 10 mg MPH twice daily (Pelham et al. 1987). All studies above included adolescent boys diagnosed with ADHD, hyperactive disorder, or a similar diagnosis; unfortunately, it is not possible to provide a standard diagnosis because some studies were completed prior to current standards.

In a recent study of school children diagnosed with ADHD and comorbid social phobia, a daily dose of 0.5–1.0 mg/kg MPH per day (dose did not exceed 60 mg/day) for 12 weeks resulted in significant reductions in school-related anxiety (Golubchik et al. 2014).

In terms of aggressive behavior, MPH reduces verbal and nonverbal aggression in groups of adolescent males diagnosed with both high and low aggression levels, and, to a lesser extent, reduces aggressive response following provocation following 0.3 mg/kg MPH twice daily between 5 and 9 days over the course of 5 weeks (Murphy et al. 1992). Furthermore, MPH has been attributed to an increase in positive social interactions in ADHD patients (Hinshaw et al. 1984a). One recent study showed that MPH increased both theory of mind and empathy ratings in children with ADHD (regularly prescribed medication, latency 1–5 h) (Maoz et al. 2014). A study examining emotion recognition in ADHD children following 4-week treatment with mean 24.1 mg/day MPH (range 10–60 mg/day) 60 min prior to testing showed improved anger and fear recognition skills (Williams et al. 2008).

3.4.2 Conclusions: Potential for MPH as a Viable Long-Term Treatment Option

Unfortunately, the effects on social cognition following MPH have been researched only in a very small pool of studies and therefore are lacking in generalizability. Furthermore, a large portion of the research was completed prior to modern diagnoses, thus limiting the ability to understand results in a more modern context. Lastly, the effects of MPH on social cognition in healthy individuals could shed valuable light on the mechanisms by which this drug could help patient populations.

3.5 D-Cycloserine

Pharmacological properties of DCS

D-cycloserine (DCS) (D-4-amino-3-isoxazolidone) is a partial *N*-methyl-D-aspartate (NMDA) receptor agonist, thus expressing a glutamatergic (excitatory) influence. The NMDA receptor also holds a glycine-binding site, and which must also be co-activated to allow for NMDA receptor signaling. (Johnson and Ascher 1987; Kleckner and Dingledine 1988) Plasma concentrations are detectable within 1 h of ingestion. Peak plasma levels are 10 mg/l, reached after 3–4 h. Elimination half-life of DCS is 8–12 h. Bioavailability is excellent, and CSF levels are roughly 80–100 % of peak plasma concentrations (Holdiness 1985; Nair et al. 1956).

3.5.1 DCS in Psychiatric Illness

Traditionally an antibiotic to fight *Mycobacterium tuberculosis*, DCS has emerged as a powerful tool used in fear extinction and thus anxiety disorders, as well as cognitive functions such as memory (Onur et al. 2010). Social cognition findings, however, are limited to psychiatric populations. In individually housed mice, DCS was shown to increase social investigation and sexual behavior and decrease aggression following the introduction on an intruder (McAllister 1994). In balb/c mice reflecting behaviors mirroring those of individuals with autism, DCS led to improved sociability at a young age (Deutsch et al. 2011, 2012). Both findings suggest wide-reaching benefits of DCS in psychiatric illness in humans.

ASD

In humans, DCS has been shown to reduce withdrawal in autistic individuals, as well as generally improve clinical symptoms (Posey et al. 2004).

Schizophrenia

DCS was shown to augment cognitive remediation training (50 mg DCS administration 60 min prior to training over 8 weekly sessions) (Cain et al. 2014).

SAD

DCS has been tested as an augmentation for psychotherapy to treat SAD in initial studies. Two studies showed a greater reduction of symptoms in patients administered with 50 mg DCS 1 h prior to 4 weekly sessions employing exposure therapy than following placebo (Guastella et al. 2008; Hofmann et al. 2006). Another study, however, examining cognitive behavioral therapy (CBT) response found no benefit to 50 mg DCS 1 h prior to five exposure sessions as a part of a 12-week CBT program in terms of completion, response, or remission rate (Hofmann et al. 2013).

These findings could be explained by effects due to patient differences, as shown by two further studies. In the first, successful DCS augmentation of a 12-week CBT program, in which patients received 50 mg DCS 1 h prior to five exposure sessions, was found only for patients showing low conscientiousness and high agreeableness ratings, but not for all patients (Smits et al. 2013a). The second also used 50 mg DCS 1 h prior to five exposure sessions and found that the success of each exposure session was critical to the effect of DCS: patients who reported low fear following a session were more likely to show a greater clinical improvement at the next session if they had received DCS as opposed to placebo (Smits et al. 2013b). Likewise, the authors found that patients who received DCS and reported high fear levels following a session showed less improvement at the next session than compared to those in the placebo group. At posttreatment evaluations (week 13), patients who received DCS showed improved clinical symptoms only when they had reported low to moderate average fear levels throughout the course of treatment.

PTSD

Because of its influence on fear extinction learning, DCS has been pursued in PTSD treatment research as an augmentation to therapy. In one study, 50 mg DCS was given 30 min prior to four exposure therapy sessions, and resulted in a lower symptom reduction than patients experienced following placebo (Litz et al. 2012).

In another study, PTSD patients were given 50 mg DCS 30 min prior to a virtual reality exposure therapy over five sessions (Rothbaum et al. 2014). Primary analysis showed no difference in clinical symptoms following DCS, but when more in-depth analysis was completed, DCS was shown to increase symptom outcomes in those patients who had increased between-session learning. In a study using 50 mg DCS over 8–10 weekly exposure sessions (latency 1 h), participants showed no overall effect of having received DCS; however, DCS did show a greater reduction of symptoms in more severely affected patients (de Kleine et al. 2012). In a study examining personality differences in response to DCS, highly conscientious participants showed a better outcome following exposure therapy, as did patients with low extraversion (50 mg DCS, single dose prior to each session over ten sessions, latency n/a) (de Kleine et al. 2014).

3.5.2 Conclusions: Potential for DCS as a Viable Long-Term Treatment Option

In terms of psychiatric and psychological findings, the NMDA receptor has been implicated as having a crucial role in synaptic plasticity (Fan et al. 2014; Lee and Silva 2009; Li and Tsien 2009), and also in long-term potentiation (LTP) (Bear and Malenka 1994; Bliss and Collingridge 1993). Fear learning and fear extinction are directly dependent on LTP and thus the NMDA receptor (Blair et al. 2001; Fanselow and LeDoux 1999; Lee et al. 2001; Li et al. 1995; Walker and Davis 2002). Fear extinction is often used in therapeutic situations, and while not purely within the realm of social cognition, the social element of the therapist as a key part of treatment is supported by pharmacological modulation. A recent meta-analysis supports this and showed positive effects of DCS on exposure therapy in anxiety disorders (Rodrigues et al. 2014).

References

Adolphs R (2003) Cognitive neuroscience of human social behaviour. Nat Rev Neurosci 4(3):165–178

Altemus M, Fong J, Yang R, Damast S, Luine V, Ferguson D (2004) Changes in cerebrospinal fluid neurochemistry during pregnancy. Biol Psychiatry 56(6):386–392

American Psychiatric Association (2013) The diagnostic and statistical manual of mental disorders: DSM 5. American Psychiatric Association, Washington, DC

American Psychiatric Association (2014) Autism spectrum disorders. Retrieved 24 June 2014, from http://www.psychiatry.org/autism

Anagnostou E, Soorya L, Chaplin W, Bartz J, Halpern D, Wasserman S et al (2012) Intranasal oxytocin versus placebo in the treatment of adults with autism spectrum disorders: a randomized controlled trial. Mol Autism 3(1):16. doi:10.1186/2040-2392-3-16

Anagnostou E, Soorya L, Brian J, Dupuis A, Mankad D, Smile S, Jacob S (2014) Intranasal oxytocin in the treatment of autism spectrum disorders: a review of literature and early safety and efficacy data in youth. Brain Res 1580:188–198, http://dx.doi.org/10.1016/j.brainres.2014.01.049

Andari E, Duhamel JR, Zalla T, Herbrecht E, Leboyer M, Sirigu A (2010) Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. Proc Natl Acad Sci U S A 107(9):4389–4394. doi:10.1073/pnas.0910249107

Auranen M, Vanhala R, Varilo T, Ayers K, Kempas E, Ylisaukko-Oja T et al (2002) A genomewide screen for autism-spectrum disorders: evidence for a major susceptibility locus on chromosome 3q25-27. Am J Hum Genet 71(4):777–790. doi:10.1086/342720

Averbeck BB, Bobin T, Evans S, Shergill SS (2012) Emotion recognition and oxytocin in patients with schizophrenia. Psychol Med 42(2):259–266. doi:10.1017/s0033291711001413

Bakermans-Kranenburg MJ, van IJzendoorn MH (2013) Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. Transl Psychiatry 3:e258. doi:10.1038/tp.2013.34

Banks WA, Kastin AJ (1985) Permeability of the blood-brain barrier to neuropeptides: the case for penetration. Psychoneuroendocrinology 10(4):385–399, http://dx.doi.org/10.1016/0306-4530(85)90079-4

Baron-Cohen S, Leslie AM, Frith U (1985) Does the autistic child have a "theory of mind"? Cognition 21(1):37–46, http://dx.doi.org/10.1016/0010-0277(85)90022-8

Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, Simmons A, Williams SCR (1999) Social intelligence in the normal and autistic brain: an fMRI study. Eur J Neurosci 11(6):1891–1898. doi:10.1046/j.1460-9568.1999.00621.x

Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SCR (2000) The amygdala theory of autism. Neurosci Biobehav Rev 24(3):355–364, http://dx.doi.org/10.1016/S0149-7634(00)00011-7

Bartz JA, Simeon D, Hamilton H, Kim S, Crystal S, Braun A et al (2011a) Oxytocin can hinder trust and cooperation in borderline personality disorder. Soc Cogn Affect Neurosci 6(5):556–563. doi:10.1093/scan/nsq085

Bartz JA, Zaki J, Bolger N, Ochsner KN (2011b) Social effects of oxytocin in humans: context and person matter. Trends Cogn Sci 15(7):301–309. doi:10.1016/j.tics.2011.05.002

Bassett DS, Bullmore E, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A (2008) Hierarchical organization of human cortical networks in health and schizophrenia. J Neurosci 28(37):9239–9248

Baumgartner T, Heinrichs M, Vonlanthen A, Fischbacher U, Fehr E (2008) Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron 58(4):639–650

Bear MF, Malenka RC (1994) Synaptic plasticity: LTP and LTD. Curr Opin Neurobiol 4(3):389–399

Bechi M, Riccaboni R, Ali S, Fresi F, Buonocore M, Bosia M et al (2012) Theory of mind and emotion processing training for patients with schizophrenia: preliminary findings. Psychiatry Res 198(3):371–377. doi:10.1016/j.psychres.2012.02.004

Bechi M, Spangaro M, Bosia M, Zanoletti A, Fresi F, Buonocore M et al (2013) Theory of Mind intervention for outpatients with schizophrenia. Neuropsychol Rehabil 23(3):383–400. doi:10.1080/09602011.2012.762751

Bedi G, Phan KL, Angstadt M, de Wit H (2009) Effects of MDMA on sociability and neural response to social threat and social reward. Psychopharmacology (Berl) 207(1):73–83. doi:10.1007/s00213-009-1635-z

Bedi G, Hyman D, de Wit H (2010) Is ecstasy an "empathogen"? Effects of +/-3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. Biol Psychiatry 68(12):1134–1140. doi:10.1016/j.biopsych.2010.08.003

Benkert O, Hippius H, Gründer G, Heiser P, Hiemke C, Himmerich H et al (2013) Kompendium der psychiatrischen Pharmakotherapie. Springer, Berlin

Bertrand MC, Sutton H, Achim AM, Malla AK, Lepage M (2007) Social cognitive impairments in first episode psychosis. Schizophr Res 95(1–3):124–133. doi:10.1016/j.schres.2007.05.033

Bertsch K, Gamer M, Schmidt B, Schmidinger I, Walther S, Kästel T et al (2013) Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. Am J Psychiatry 170(10):1169–1177

Biederman J, Pliszka SR (2008) Modafinil improves symptoms of attention-deficit/hyperactivity disorder across subtypes in children and adolescents. J Pediatr 152(3):394–399.e392, http://dx.doi.org/10.1016/j.jpeds.2007.07.052

Birbaumer N, Veit R, Lotze M, Erb M, Hermann C, Grodd W, Flor H (2005) Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. Arch Gen Psychiatry 62(7):799–805. doi:10.1001/archpsyc.62.7.799

Blair RJ (2001) Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. J Neurol Neurosurg Psychiatry 71(6):727–731

Blair RJ (2008) The amygdala and ventromedial prefrontal cortex: functional contributions and dysfunction in psychopathy. Philos Trans R Soc Lond B Biol Sci 363(1503):2557–2565. doi:10.1098/rstb.2008.0027

Blair RJ, Jones L, Clark F, Smith M (1997) The psychopathic individual: a lack of responsiveness to distress cues? Psychophysiology 34(2):192–198

Blair HT, Schafe GE, Bauer EP, Rodrigues SM, LeDoux JE (2001) Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. Learn Mem 8(5):229–242

Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361(6407):31–39

Boccia M, Petrusz P, Suzuki K, Marson L, Pedersen C (2013) Immunohistochemical localization of oxytocin receptors in human brain. Neuroscience 253:155–164

Bradley B, Davis TA, Wingo AP, Mercer KB, Ressler KJ (2013) Family environment and adult resilience: contributions of positive parenting and the oxytocin receptor gene. Eur J Psychotraumatol 4, http://www.ejpt.net/index.php/ejpt/rt/captureCite/21659/0/ApaCitationPlugin, http://www.ncbi.nlm.nih.gov/pubmed/?term=bradley+wingo+mercer+family

Brodsky BS, Groves SA, Oquendo MA, Mann JJ, Stanley B (2006) Interpersonal precipitants and suicide attempts in borderline personality disorder. Suicide Life Threat Behav 36(3):313–322

Brownstein MJ, Russell JT, Gainer H (1980) Synthesis, transport, and release of posterior pituitary hormones. Science 207(4429):373–378. doi:10.1126/science.6153132

Brüne M, Ebert A, Kolb M, Tas C, Edel MA, Roser P (2013) Oxytocin influences avoidant reactions to social threat in adults with borderline personality disorder. Hum Psychopharmacol 28(6):552–561

Cain CK, McCue M, Bello I, Creedon T, Tang D, Laska E, Goff DC (2014) d-Cycloserine augmentation of cognitive remediation in schizophrenia. Schizophr Res 153(1–3):177–183, http://dx.doi.org/10.1016/j.schres.2014.01.016

Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA (2010) Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. J Clin Psychiatry 71 (10):1363–1370

Calcagnoli F, de Boer SF, Althaus M, den Boer JA, Koolhaas JM (2013) Antiaggressive activity of central oxytocin in male rats. Psychopharmacology (Berl) 229(4):639–651. doi:10.1007/s00213-013-3124-7

Carton JS, Kessler EA, Pape CL (1999) Nonverbal decoding skills and relationship well-being in adults. J Nonverbal Behav 23(1):91–100

Chen FS, Kumsta R, von Dawans B, Monakhov M, Ebstein RP, Heinrichs M (2011) Common oxytocin receptor gene (OXTR) polymorphism and social support interact to reduce stress in humans. Proc Natl Acad Sci U S A 108(50):19937–19942. doi:10.1073/pnas.1113079108

Constans JI, Penn DL, Ihen GH, Hope DA (1999) Interpretive biases for ambiguous stimuli in social anxiety. Behav Res Ther 37(7):643–651

Cullen KR, Kumra S, Westerman M, Schulz SC (2008) Atypical antipsychotics for treatment of schizophrenia spectrum disorders. Psychiatric Times: Schizophrenia. Retrieved 25 June 2014

Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP (2004) A double-blind, placebo-controlled trial of modafinil for cocaine dependence. Neuropsychopharmacology 30 (1):205–211

Dadds MR, Moul C, Cauchi A, Dobson-Stone C, Hawes DJ, Brennan J, Ebstein RE (2014a) Methylation of the oxytocin receptor gene and oxytocin blood levels in the development of psychopathy. Dev Psychopathol 26(01):33–40. doi:10.1017/S0954579413000497

Dadds MR, Moul C, Cauchi A, Dobson-Stone C, Hawes DJ, Brennan J et al (2014b) Polymorphisms in the oxytocin receptor gene are associated with the development of psychopathy. Dev Psychopathol 26(01):21–31. doi:10.1017/S0954579413000485

Davis MC, Lee J, Horan WP, Clarke AD, McGee MR, Green MF, Marder SR (2013) Effects of single dose intranasal oxytocin on social cognition in schizophrenia. Schizophr Res 147 (2):393–397

Davis MC, Green MF, Lee J, Horan WP, Senturk D, Clarke AD, Marder SR (2014) Oxytocin-augmented social cognitive skills training in schizophrenia [original article]. Neuropsychopharmacology. doi:10.1038/npp.2014.68

de Kleine RA, Hendriks G-J, Kusters WJ, Broekman TG, van Minnen A (2012) A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. Biol Psychiatry 71(11):962–968

de Kleine RA, Hendriks G-J, Smits JA, Broekman TG, van Minnen A (2014) Prescriptive variables for D-cycloserine augmentation of exposure therapy for posttraumatic stress disorder. J Psychiatr Res 48(1):40–46

de la Torre R, Farré M, Roset PN, Pizarro N, Abanades S, Segura M et al (2004) Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. Ther Drug Monit 26(2):137–144

Deutsch SI, Burket JA, Jacome LF, Cannon WR, Herndon AL (2011) d-Cycloserine improves the impaired sociability of the Balb/c mouse. Brain Res Bull 84(1):8–11

Deutsch SI, Pepe GJ, Burket JA, Winebarger EE, Herndon AL, Benson AD (2012) d-cycloserine improves sociability and spontaneous stereotypic behaviors in 4-week old mice. Brain Res 1439:96–107, http://dx.doi.org/10.1016/j.brainres.2011.12.040

Dodhia S, Hosanagar A, Fitzgerald DA, Labuschagne I, Wood AG, Nathan PJ, Phan KL (2014) Modulation of resting-state amygdala-frontal functional connectivity by oxytocin in generalized social anxiety disorder [original article]. Neuropsychopharmacology. doi:10.1038/npp.2014.53

Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC (2007) Oxytocin improves "mind-reading" in humans. Biol Psychiatry 61(6):731–733. doi:10.1016/j.biopsych.2006.07.015

Domes G, Schulze L, Herpertz SC (2009) Emotion recognition in borderline personality disorder—a review of the literature. J Pers Disord 23(1):6–19. doi:10.1521/pedi.2009.23.1.6

Domes G, Lischke A, Berger C, Grossmann A, Hauenstein K, Heinrichs M (2010) Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology 35 (1):83–93. doi:10.1016/j.psyneuen.2009.06.016

Domes G, Heinrichs M, Kumbier E, Grossmann A, Hauenstein K, Herpertz SC (2013) Effects of intranasal oxytocin on the neural basis of face processing in autism spectrum disorder. Biol Psychiatry 74(3):164–171. doi:10.1016/j.biopsych.2013.02.007

du Vigneaud V, Ressler C, Swan CJM, Roberts CW, Katsoyannis PG, Gordon S (1953) The synthesis of an octapeptide amide with the hormonal activity of oxytocin. J Am Chem Soc 75 (19):4879–4880. doi:10.1021/ja01115a553

du Vigneaud V, Ressler C, Swan JM, Roberts CW, Katsoyannis PG (1954) The synthesis of oxytocin1. J Am Chem Soc 76(12):3115–3121. doi:10.1021/ja01641a004

Dumont GJ, Sweep FC, van der Steen R, Hermsen R, Donders AR, Touw DJ et al (2009) Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. Soc Neurosci 4(4):359–366. doi:10.1080/17470910802649470

Eack SM (2013) Cognitive enhancement therapy. In: Roberts DL, Penn DL (eds) Social cognition in schizophrenia. Oxford University Press, New York

Ebert A, Kolb M, Heller J, Edel M-A, Roser P, Brüne M (2013) Modulation of interpersonal trust in borderline personality disorder by intranasal oxytocin and childhood trauma. Soc Neurosci 8 (4):305–313

Eckstein M, Hurlemann R (2013) Oxytocin: evidence for a therapeutic potential of the social neuromodulator. Nervenarzt 84(11):1321–1328. doi:10.1007/s00115-013-3832-6

Elfenbein HA, Ambady N (2002) On the universality and cultural specificity of emotion recognition: a meta-analysis. Psychol Bull 128(2):203

Ermisch A, Barth T, Rühle H, Skopkova J, Hrbas P, Landgraf R (1985a) On the blood-brain barrier to peptides: accumulation of labelled vasopressin, DesGlyNH2-vasopressin and oxytocin by brain regions. Endocrinologia Experimentalis 19(1):29–37

Ermisch A, Ruhle HJ, Landgraf R, Hess J (1985b) Blood-brain barrier and peptides. J Cereb Blood Flow Metab 5(3):350–357

Fan X, Jin WY, Wang YT (2014) The NMDA receptor complex: a multifunctional machine at the glutamatergic synapse [Review]. Front Cell Neurosci 8:160. doi:10.3389/fncel.2014.00160

Fanselow MS, LeDoux JE (1999) Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. Neuron 23(2):229–232

Farre M, De La Torre R, Mathúna BÓ, Roset P, Peiro A, Torrens M et al (2004) Repeated doses administration of MDMA in humans: pharmacological effects and pharmacokinetics. Psychopharmacology (Berl) 173(3–4):364–375

Fava M, Thase ME, DeBattista C, Doghramji K, Arora S, Hughes RJ (2007) Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. Ann Clin Psychiatry 19(3):153–159

Fioravanti M, Carlone O, Vitale B, Cinti ME, Clare L (2005) A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. Neuropsychol Rev 15(2):73–95

Fischer-Shofty M, Shamay-Tsoory SG, Levkovitz Y (2013) Characterization of the effects of oxytocin on fear recognition in patients with schizophrenia and in healthy controls. Front Neurosci 7:127

Frye M, Grunze H, Suppes T, McElroy S, Keck P, Walden J et al (2007) A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry 164 (8):1242–1249

Gibson CM, Penn DL, Smedley KL, Leserman J, Elliott T, Pedersen CA (2014) A pilot six-week randomized controlled trial of oxytocin on social cognition and social skills in schizophrenia. Schizophr Res 156(2–3):261–265, http://dx.doi.org/10.1016/j.schres.2014.04.009

Gimpl G, Fahrenholz F (2001) The oxytocin receptor system: structure, function, and regulation. Physiol Rev 81(2):629–683

Goldman M, Marlow-O'Connor M, Torres I, Carter CS (2008) Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. Schizophr Res 98(1–3):247–255. doi:10.1016/j.schres.2007.09.019

Goldman MB, Gomes AM, Carter CS, Lee R (2011) Divergent effects of two different doses of intranasal oxytocin on facial affect discrimination in schizophrenic patients with and without polydipsia. Psychopharmacology (Berl) 216(1):101–110. doi:10.1007/s00213-011-2193-8

Golubchik P, Sever J, Weizman A (2014) Methylphenidate treatment in children with attention deficit hyperactivity disorder and comorbid social phobia. Int Clin Psychopharmacol 29 (4):212–215. doi:10.1097/YIC.0000000000000029

Gordon I, Vander Wyk BC, Bennett RH, Cordeaux C, Lucas MV, Eilbott JA et al (2013) Oxytocin enhances brain function in children with autism. Proc Natl Acad Sci U S A 110 (52):20953–20958. doi:10.1073/pnas.1312857110

Gorka SM, Fitzgerald DA, Labuschagne I, Hosanagar A, Wood AG, Nathan PJ, Phan KL (2014) Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. Neuropsychopharmacology. doi:10.1038/npp.2014.168

Green L, Fein D, Modahl C, Feinstein C, Waterhouse L, Morris M (2001) Oxytocin and autistic disorder: alterations in peptide forms. Biol Psychiatry 50(8):609–613

Gross TF (2004) The perception of four basic emotions in human and nonhuman faces by children with autism and other developmental disabilities. J Abnorm Child Psychol 32(5):469–480

Guastella AJ, Richardson R, Lovibond PF, Rapee RM, Gaston JE, Mitchell P, Dadds MR (2008) A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. Biol Psychiatry 63(6):544–549, http://dx.doi.org/10.1016/j.biopsych.2007.11.011

Guastella AJ, Howard AL, Dadds MR, Mitchell P, Carson DS (2009) A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. Psychoneuroendocrinology 34(6):917–923, http://dx.doi.org/10.1016/j.psyneuen.2009.01.005

Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, Hickie IB (2010) Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. Biol Psychiatry 67(7):692–694. doi:10.1016/j.biopsych.2009.09.020

Guastella AJ, Hickie IB, McGuinness MM, Otis M, Woods EA, Disinger HM et al (2013) Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research. Psychoneuroendocrinology 38(5):612–625

Gunderson JG, Lyons-Ruth K (2008) BPD's interpersonal hypersensitivity phenotype: a gene-environment-developmental model. J Pers Disord 22(1):22

Hare RD, Neumann CS (2006) The PCL-R assessment of psychopathy. In: Patrick CJ (ed) Handbook of psychopathy. Guilford, New York, pp 58–88
Haxby JV, Hoffman EA, Gobbini MI (2000) The distributed human neural system for face perception. Trends Cogn Sci 4(6):223–233
Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U (2003) Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol Psychiatry 54 (12):1389–1398
Herpertz SC, Bertsch K (2014) The social-cognitive basis of personality disorders. Curr Opin Psychiatry 27(1):73–77
Hezel DM, McNally RJ (2014) Theory of mind impairments in social anxiety disorder. Behav Ther 45(4):530–540, http://dx.doi.org/10.1016/j.beth.2014.02.010c
Higashida H, Lopatina O, Yoshihara T, Pichugina YA, Soumarokov AA, Munesue T et al (2010) Oxytocin signal and social behaviour: comparison among adult and infant oxytocin, oxytocin receptor and CD38 gene knockout mice. J Neuroendocrinol 22(5):373–379. doi:10.1111/j.1365-2826.2010.01976.x
Higashida H, Yokoyama S, Munesue T, Kikuchi M, Minabe Y, Lopatina O (2011) CD38 gene knockout juvenile mice: a model of oxytocin signal defects in autism. Biol Pharm Bull 34 (9):1369–1372
Hill EL, Frith U (2003) Understanding autism: insights from mind and brain. Philos Trans R Soc Lond B Biol Sci 358(1430):281–289. doi:10.1098/rstb.2002.1209
Hinshaw SP, Henker B, Whalen CK (1984a) Cognitive-behavioral and pharmacologic interventions for hyperactive boys: comparative and combined effects. J Consult Clin Psychol 52(5):739
Hinshaw SP, Henker B, Whalen CK (1984b) Self-control in hyperactive boys in anger-inducing situations: effects of cognitive-behavioral training and of methylphenidate. J Abnorm Child Psychol 12(1):55–77
Hirsch CR, Clark DM (2004) Information-processing bias in social phobia. Clin Psychol Rev 24 (7):799–825
Hofmann SG, Pollack MH, Otto MW (2006) Augmentation treatment of psychotherapy for anxiety disorders with D-cycloserine. CNS Drug Rev 12(3–4):208–217. doi:10.1111/j.1527-3458.2006.00208.x
Hofmann SG, Smits JA, Rosenfield D, Simon N, Otto MW, Meuret AE et al (2013) D-Cycloserine as an augmentation strategy with cognitive-behavioral therapy for social anxiety disorder. Am J Psychiatry 170(7):751–758. doi:10.1176/appi.ajp.2013.12070974
Hoge EA, Pollack MH, Kaufman RE, Zak PJ, Simon NM (2008) Oxytocin levels in social anxiety disorder. CNS Neurosci Ther 14(3):165–170
Holdiness MR (1985) Cerebrospinal fluid pharmacokinetics of the antituberculosis drugs. Clin Pharmacokinet 10:532–534
Hollander E, Bartz J, Chaplin W, Phillips A, Sumner J, Soorya L et al (2007) Oxytocin increases retention of social cognition in autism. Biol Psychiatry 61(4):498–503. doi:10.1016/j.biopsych.2006.05.030
Huber D, Veinante P, Stoop R (2005) Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. Science 308(5719):245–248
Hurlemann R, Patin A, Onur OA, Cohen MX, Baumgartner T, Metzler S et al (2010) Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. J Neurosci 30(14):4999–5007. doi:10.1523/jneurosci.5538-09.2010
Hysek CM, Domes G, Liechti ME (2012) MDMA enhances “mind reading” of positive emotions and impairs “mind reading” of negative emotions. Psychopharmacology (Berl) 222 (2):293–302. doi:10.1007/s00213-012-2645-9
Jansen LM, Gispen-de Wied CC, Wiegant VM, Westenberg HG, Lahuis BE, Van Engeland H (2006) Autonomic and neuroendocrine responses to a psychosocial stressor in adults with autistic spectrum disorder. J Autism Dev Disord 36(7):891–899

Johnson J, Ascher P (1987) Glycine potentiates the NMDA response in cultured mouse brain neurons. Nature 325(6104):529–531

Jones P, Robinson I (1982) Differential clearance of neurophysin and neurohypophysial peptides from the cerebrospinal fluid in conscious guinea pigs. Neuroendocrinology 34(4):297–302

Kagerbauer S, Martin J, Schuster T, Blobner M, Kochs E, Landgraf R (2013) Plasma oxytocin and vasopressin do not predict neuropeptide concentrations in human cerebrospinal fluid. J Neuroendocrinol 25(7):668–673

Kelley AM, Webb CM, Athy JR, Ley S, Gaydos S (2012) Cognition enhancement by modafinil: a meta-analysis. Aviat Space Environ Med 83(7):685–690

Kendrick KM (2004) The neurobiology of social bonds. J Neuroendocrinol 16(12):1007–1008

Kendrick K, Keverne E, Hinton M, Goode J (1991) Cerebrospinal fluid and plasma concentrations of oxytocin and vasopressin during parturition and vaginocervical stimulation in the sheep. Brain Res Bull 26(5):803–807

Kendrick KM, Da Costa AP, Broad KD, Ohkura S, Guevara R, Lévy F, Keverne EB (1997) Neural control of maternal behaviour and olfactory recognition of offspring. Brain Res Bull 44(4):383–395

Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (1995) Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52(12):1048–1060

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62(6):593–602

Kiehl KA, Smith AM, Hare RD, Mendrek A, Forster BB, Brink J, Liddle PF (2001) Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. Biol Psychiatry 50(9):677–684

Kirkpatrick MG, Francis SM, Lee R, de Wit H, Jacob S (2014) Plasma oxytocin concentrations following MDMA or intranasal oxytocin in humans. Psychoneuroendocrinology 46:23–31, http://dx.doi.org/10.1016/j.psyneuen.2014.04.006

Kleckner NW, Dingledine R (1988) Requirement for glycine in activation of NMDA-receptors expressed in Xenopus oocytes. Science 241(4867):835–837

Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH et al (2012) Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73 (3):553–566, http://dx.doi.org/10.1016/j.neuron.2011.11.030

Korzekwa MI, Dell PF, Links PS, Thabane L, Webb SP (2008) Estimating the prevalence of borderline personality disorder in psychiatric outpatients using a two-phase procedure. Compr Psychiatry 49(4):380–386

Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E (2005) Oxytocin increases trust in humans. Nature 435(7042):673–676. doi:10.1038/nature03701

Kraepelin E (1971) Dementia praecox and paraphrenia. Krieger, Huntington, NY

Kuypers KP, de la Torre R, Farre M, Yubero-Lahoz S, Dziobek I, Van den Bos W, Ramaekers JG (2014) No evidence that MDMA-induced enhancement of emotional empathy is related to peripheral oxytocin levels or 5-HT1a receptor activation. PLoS One 9(6):e100719

Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M et al (2010) Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. Neuropsychopharmacology 35(12):2403–2413

Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M et al (2012) Medial frontal hyperactivity to sad faces in generalized social anxiety disorder and modulation by oxytocin. Int J Neuropsychopharmacol 15(07):883–896. doi:10.1017/S1461145711001489

Lapierre D, Braun CM, Hodgins S (1995) Ventral frontal deficits in psychopathy: neuropsychological test findings. Neuropsychologia 33(2):139–151

Leake RD, Weitzman RE, Fisher DA (1980) Pharmacokinetics of oxytocin in the human subject. Obstet Gynecol 56(6):701–704

Lee Y-S, Silva AJ (2009) The molecular and cellular biology of enhanced cognition. Nat Rev Neurosci 10(2):126–140

Lee HJ, Choi J-S, Brown TH, Kim JJ (2001) Amygdalar NMDA receptors are critical for the expression of multiple conditioned fear responses. J Neurosci 21(11):4116–4124
Lee R, Garcia F, van de Kar LD, Hauger RD, Coccaro EF (2003) Plasma oxytocin in response to pharmaco-challenge to D-fenfluramine and placebo in healthy men. Psychiatry Res 118 (2):129–136
Lerner H, St. Peter S (1984) The Roschach H response and object relations. J Pers Assess 48 (4):345–350
Li F, Tsien JZ (2009) Memory and the NMDA receptors. N Engl J Med 361(3):302
Li XF, Phillips R, LeDoux JE (1995) NMDA and non-NMDA receptors contribute to synaptic transmission between the medial geniculate body and the lateral nucleus of the amygdala. Exp Brain Res 105(1):87–100
Liechti ME, Vollenweider FX (2001) Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. Hum Psychopharmacol 16(8):589–598. doi:10.1002/hup.348
Lim MM, Young LJ (2006) Neuropeptidergic regulation of affiliative behavior and social bonding in animals. Horm Behav 50(4):506–517
Lim MM, Murphy AZ, Young LJ (2004) Ventral striatopallidal oxytocin and vasopressin V1a receptors in the monogamous prairie vole (Microtus ochrogaster). J Comp Neurol 468 (4):555–570
Lin I-F, Kashino M, Ohta H, Yamada T, Tani M, Watanabe H et al (2014) The effect of intranasal oxytocin versus placebo treatment on the autonomic responses to human sounds in autism: a single-blind, randomized, placebo-controlled, crossover design study. Mol Autism 5(1):20
Linehan M (1995) Understanding borderline personality disorder. Guildford, New York
Litz BT, Salters-Pedneault K, Steenkamp MM, Hermos JA, Bryant RA, Otto MW, Hofmann SG (2012) A randomized placebo-controlled trial of D-cycloserine and exposure therapy for posttraumatic stress disorder. J Psychiatr Res 46(9):1184–1190
Losh M, Adolphs R, Poe MD, Couture S, Penn D, Baranek GT, Piven J (2009) Neuropsychological profile of autism and the broad autism phenotype. Arch Gen Psychiatry 66(5):518–526
Loup F, Tribollet E, Dubois-Dauphin M, Dreifuss J (1991) Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. Brain Res 555(2):220–232
Lucas-Thompson RG, Holman EA (2013) Environmental stress, oxytocin receptor gene (OXTR) polymorphism, and mental health following collective stress. Horm Behav 63(4):615–624, http://dx.doi.org/10.1016/j.yhbeh.2013.02.015
Ludwig M, Leng G (2006) Dendritic peptide release and peptide-dependent behaviours. Nat Rev Neurosci 7(2):126–136
Lynam DR, Caspi A, Moffitt TE, Loeber R, Stouthamer-Loeber M (2007) Longitudinal evidence that psychopathy scores in early adolescence predict adult psychopathy. J Abnorm Psychol 116 (1):155–165. doi:10.1037/0021-843x.116.1.155
Maoz H, Tsviban L, Gvirts HZ, Shamay-Tsoory SG, Levkovitz Y, Watemberg N, Bloch Y (2014) Stimulants improve theory of mind in children with attention deficit/hyperactivity disorder. J Psychopharmacol 28(3):212–219. doi:10.1177/0269881113492030
Marsh AA, Blair RJ (2008) Deficits in facial affect recognition among antisocial populations: a meta-analysis. Neurosci Biobehav Rev 32(3):454–465. doi:10.1016/j.neubiorev.2007.08.003
Marsh AA, Kozak MN, Ambady N (2007) Accurate identification of fear facial expressions predicts prosocial behavior. Emotion 7(2):239
Martin J, Kagerbauer SM, Schuster T, Blobner M, Kochs EF, Landgraf R (2014) Vasopressin and oxytocin in CSF and plasma of patients with aneurysmal subarachnoid haemorrhage. Neuropeptides 48(2):91–96
Mas M, Farré M, de la Torre R, Roset PN, Ortuño J, Segura J, Camí J (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. J Pharmacol Exp Ther 290(1):136–145

McAllister K (1994) D-cycloserine enhances social behaviour in individually-housed mice in the resident-intruder test. Psychopharmacology (Berl) 116(3):317–325
McClure EB, Nowicki S Jr (2001) Associations between social anxiety and nonverbal processing skill in preadolescent boys and girls. J Nonverbal Behav 25(1):3–19
Meffert H, Gazzola V, den Boer JA, Bartels AAJ, Keysers C (2013) Reduced spontaneous but relatively normal deliberate vicarious representations in psychopathy. Brain 136 (8):2550–2562. doi:10.1093/brain/awt190
Meisenberg G, Simmons WH (1983) Peptides and the blood-brain barrier. Life Sci 32 (23):2611–2623, http://dx.doi.org/10.1016/0024-3205(83)90352-1
Mens WB, Witter A, Van Wimersma Greidanus TB (1983) Penetration of neurohypophyseal hormones from plasma into cerebrospinal fluid (CSF): half-times of disappearance of these neuropeptides from CSF. Brain Res 262(1):143–149
Meyer C, Freund-Mercier M, Guerne Y, Richard P (1987) Relationship between oxytocin release and amplitude of oxytocin cell neurosecretory bursts during suckling in the rat. J Endocrinol 114(2):263–270
Meyer-Lindenberg A (2008) Impact of prosocial neuropeptides on human brain function. In: Inga DN, Rainer L (eds) Progress in brain research, vol 170. Elsevier, New York, pp 463–470
Miller GM (2011) The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. J Neurochem 116 (2):164–176
Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R (2011) The safety and efficacy of ±3, 4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. J Psychopharmacol 25(4):439–452
Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B et al (2013) Durability of improvement in posttraumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3, 4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. J Psychopharmacol 27(1):28–39. doi:10.1177/0269881112456611
Modahl C, Green LA, Fein D, Morris M, Waterhouse L, Feinstein C, Levin H (1998) Plasma oxytocin levels in autistic children. Biol Psychiatry 43(4):270–277
Mogg K, Philippot P, Bradley BP (2004) Selective attention to angry faces in clinical social phobia. J Abnorm Psychol 113(1):160
Mottolese R, Redouté J, Costes N, Le Bars D, Sirigu A (2014) Switching brain serotonin with oxytocin. Proc Natl Acad Sci U S A 111(23):8637–8642. doi:10.1073/pnas.1319810111
Moul C, Killcross S, Dadds MR (2012) A model of differential amygdala activation in psychopathy. Psychol Rev 119(4):789–806. doi:10.1037/a0029342
Mueser KT, Yarnold P, Bellack A (1992) Diagnostic and demographic correlates of substance abuse in schizophrenia and major affective disorder. Acta Psychiatrica Scandinavica 85 (1):48–55
Murphy DA, Pelham WE, Lang AR (1992) Aggression in boys with attention deficit-hyperactivity disorder: methylphenidate effects on naturalistically observed aggression, response to provocation, and social information processing. J Abnorm Child Psychol 20(5):451–466
Nair KGS, Epstein IG, Baron H, Mulinos MG (1956) Absorption, distribution and excretion of cycloserine in man. Antibiot Annu 3:136–140
Najjar S, Pearlman DM (2015) Neuroinflammation and white matter pathology in schizophrenia: systematic review. Schizophr Res 161(1):102–112
Oehen P, Traber R, Widmer V, Schnyder U (2013) A randomized, controlled pilot study of MDMA (±3, 4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). J Psychopharmacol 27(1):40–52
Onur OA, Schlaepfer TE, Kukolja J, Bauer A, Jeung H, Patin A et al (2010) The N-methyl-D-aspartate receptor co-agonist D-cycloserine facilitates declarative learning and hippocampal

activity in humans. Biol Psychiatry 67(12):1205–1211, http://dx.doi.org/10.1016/j.biopsych.2010.01.022
Parrott AC (2013) Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research. Hum Psychopharmacol 28(4):289–307. doi:10.1002/hup.2318
Pedersen CA, Gibson CM, Rau SW, Salimi K, Smedley KL, Casey RL et al (2011) Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. Schizophr Res 132(1):50–53
Pelham WE, Sturges J, Hoza J, Schmidt C, Bijlsma JJ, Milich R, Moorer S (1987) Sustained release and standard methylphenidate effects on cognitive and social behavior in children with attention deficit disorder. Pediatrics 80(4):491–501
Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S et al (2007) Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry 64(1):19–28
Pierce K, Redcay E (2008) Fusiform function in children with an autism spectrum disorder is a matter of "who". Biol Psychiatry 64(7):552–560
Pierce K, Müller R-A, Ambrose J, Allen G, Courchesne E (2001) Face processing occurs outside the fusiform 'face area' in autism: evidence from functional MRI. Brain 124(10):2059–2073
Pitman RK, Orr SP, Lasko NB (1993) Effects of intranasal vasopressin and oxytocin on physiologic responding during personal combat imagery in Vietnam veterans with posttraumatic stress disorder. Psychiatry Res 48(2):107–117, http://dx.doi.org/10.1016/0165-1781(93)90035-F
Posey DJ, Kem DL, Swiezy NB, Sweeten TL, Wiegand RE, McDougle CJ (2004) A pilot study of D-cycloserine in subjects with autistic disorder. Am J Psychiatry 161(11):2115–2117
Preckel K, Scheele D, Kendrick KM, Maier W, Hurlemann R (2014) Oxytocin facilitates social approach behavior in women. Front Behav Neurosci 8:191. doi:10.3389/fnbeh.2014.00191
Randall DC, Shneerson JM, Plaha KK, File SE (2003) Modafinil affects mood, but not cognitive function, in healthy young volunteers. Hum Psychopharmacol 18(3):163–173
Rapee RM, Abbott MJ (2006) Mental representation of observable attributes in people with social phobia. J Behav Ther Exp Psychiatry 37(2):113–126
Repantis D, Schlattmann P, Laisney O, Heuser I (2010) Modafinil and methylphenidate for neuroenhancement in healthy individuals: a systematic review. Pharmacol Res 62(3):187–206
Rodrigues H, Figueira I, Lopes A, Gonçalves R, Mendlowicz MV, Coutinho ESF, Ventura P (2014) Does D-cycloserine enhance exposure therapy for anxiety disorders in humans? A meta-analysis. PLoS One 9(7):e93519
Roepke S, Vater A, Preißler S, Heekeren HR, Dziobek I (2013) Social cognition in borderline personality disorder. Front Neurosci 6:195. doi:10.3389/fnins.2012.00195
Rothbaum BO, Price M, Jovanovic T, Norrholm SD, Gerardi M, Dunlop B et al (2014) A Randomized, double-blind evaluation of d-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan war veterans. Am J Psychiatry 171(6):640–648
Roy M-A, Maziade M, Labbé A, Mérette C (2001) Male gender is associated with deficit schizophrenia: a meta-analysis. Schizophr Res 47(2):141–147
Rubin LH, Carter CS, Drogos L, Pournajafi-Nazarloo H, Sweeney JA, Maki PM (2010) Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophr Res 124(1–3):13–21. doi:10.1016/j.schres.2010.09.014
Rydén G, Sjöholm I (1969) Half-life of oxytocin in blood of pregnant and non-pregnant women. Acta Endocrinologica 61(3):425–431. doi:10.1530/acta.0.0610425
Saavedra-Velez C, Yusim A, Anbarasan D, Lindenmayer J-P (2009) Modafinil as an adjunctive treatment of sedation, negative symptoms, and cognition in schizophrenia: a critical review. J Clin Psychiatry 70(1):104–112
Šagud M, Mihaljević-Peleš A, Mück-Šeler D, Pivac N, Vuksan-Ćusa B, Brataljenović T, Jakovljević M (2009) Smoking and schizophrenia. Psychiatria Danubina 21(3):371–375
Saha S, Chant D, McGrath J (2007) A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry 64(10):1123–1131

Scheele D, Striepens N, Gunturkun O, Deutschlander S, Maier W, Kendrick KM, Hurlemann R (2012) Oxytocin modulates social distance between males and females. J Neurosci 32 (46):16074–16079. doi:10.1523/jneurosci. 2755-12.2012

Scheele D, Wille A, Kendrick KM, Stoffel-Wagner B, Becker B, Güntürkün O et al (2013) Oxytocin enhances brain reward system responses in men viewing the face of their female partner. Proc Natl Acad Sci U S A 110(50):20308–20313

Scoriels L, Barnett JH, Murray GK, Cherukuru S, Fielding M, Cheng F et al (2011) Effects of modafinil on emotional processing in first episode psychosis. Biol Psychiatry 69(5):457–464

Shahrestani S, Kemp AH, Guastella AJ (2013) The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. Neuropsychopharmacology 38(10):1929–1936. doi:10.1038/npp.2013.86

Shamay-Tsoory SG, Fischer M, Dvash J, Harari H, Perach-Bloom N, Levkovitz Y (2009) Intranasal administration of oxytocin increases envy and schadenfreude (gloating). Biol Psychiatry 66(9):864–870. doi:10.1016/j.biopsych.2009.06.009

Shao Y, Wolpert CM, Raiford KL, Menold MM, Donnelly SL, Ravan SA et al (2002) Genomic screen and follow-up analysis for autistic disorder. Am J Med Genet 114(1):99–105

Siegal M, Varley R (2002) Neural systems involved in 'theory of mind'. Nat Rev Neurosci 3(6):463–471

Simeon D, Bartz J, Hamilton H, Crystal S, Braun A, Ketay S, Hollander E (2011) Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study. Psychoneuroendocrinology 36(9):1418–1421. doi:10.1016/j.psyneuen.2011.03.013

Simmons CF Jr, Clancy TE, Quan R, Knoll JH (1995) The oxytocin receptor gene (OXTR) localizes to human chromosome 3p25 by fluorescence *in situ* hybridization and PCR analysis of somatic cell hybrids. Genomics 26(3):623–625

Smits JA, Hofmann SG, Rosenfield D, DeBoer LB, Costa PT, Simon NM et al (2013a) D-cycloserine augmentation of cognitive behavioral group therapy of social anxiety disorder: prognostic and prescriptive variables. J Consult Clin Psychol 81(6):1100–1112. doi:10.1037/a0034120

Smits JA, Rosenfield D, Otto MW, Marques L, Davis ML, Meuret AE et al (2013b) d-cycloserine enhancement of exposure therapy for social anxiety disorder depends on the success of exposure sessions. J Psychiatr Res 47(10):1455–1461, http://dx.doi.org/10.1016/j.jpsychires.2013.06.020

Staebler K, Renneberg B, Stopsack M, Fiedler P, Weiler M, Roepke S (2011) Facial emotional expression in reaction to social exclusion in borderline personality disorder. Psychol Med 41 (09):1929–1938

Sterzer P, Stadler C, Krebs A, Kleinschmidt A, Poustka F (2005) Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. Biol Psychiatry 57(1):7–15. doi:10.1016/j.biopsych.2004.10.008

Stiglmayr C, Grathwol T, Linehan M, Ihorst G, Fahrenberg J, Bohus M (2005) Aversive tension in patients with borderline personality disorder: a computer-based controlled field study. Acta Psychiatr Scand 111(5):372–379

Stone VE, Baron-Cohen S, Calder A, Keane J, Young A (2003) Acquired theory of mind impairments in individuals with bilateral amygdala lesions. Neuropsychologia 41(2):209–220

Stopa L, Clark DM (2000) Social phobia and interpretation of social events. Behav Res Ther 38(3):273–283

Striepens D, Scheele D, Kendrick KM, Becker B, Schäfer L, Schwalba K et al. (2012) Oxytocin facilitates protective responses to aversive social stimuli in males. Proc Natl Acad Sci U S A 109(44):18144–18149.

Striepens N, Kendrick KM, Hanking V, Landgraf R, Wüllner U, Maier W, Hurlemann R (2013) Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. Sci Rep 3:3440

Stuart J, Western D, Lohr N, Benjamin J, Becker S, Vorus N, Silk K (1990) Object relations in borderlines, depressives, and normals: an examination of human responses on the Rorschach. J Pers Assess 55(1–2):296–318

Tancer M, Johanson C-E (2003) Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP. Drug Alcohol Depend 72(1):33–44, http://dx.doi.org/10.1016/S0376-8716(03)00172-8

Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS (2007) A role for oxytocin and 5-HT(1A) receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine ("ecstasy"). Neuroscience 146(2):509–514. doi:10.1016/j.neuroscience.2007.02.032

Trull TJ, Jahng S, Tomko RL, Wood PK, Sher KJ (2010) Revised NESARC personality disorder diagnoses: gender, prevalence, and comorbidity with substance dependence disorders. J Pers Disord 24(4):412

Tudusciuc O, Adolphs R (2013) Social cognitive neuroscience: clinical foundations. In: Roberts DL, Penn DL (eds) Social cognition in schizophrenia. Oxford University Press, New York

Turner DC, Clark L, Pomarol-Clotet E, McKenna P, Robbins TW, Sahakian BJ (2004) Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. Neuropsychopharmacology 29(7):1363–1373

Van IJzendoorn MH, Bakermans-Kranenburg MJ (2012) A sniff of trust: meta-analysis of the effects of intranasal oxytocin administration on face recognition, trust to in-group, and trust to out-group. Psychoneuroendocrinology 37(3):438–443. doi:10.1016/j.psyneuen.2011.07.008

van Os J, Kapur S (2009) Schizophrenia. Lancet 374(9690):635–645, http://dx.doi.org/10.1016/S0140-6736(09)60995-8

Veit R, Konicar L, Klinzing JG, Barth B, Yilmaz O, Birbaumer N (2013) Deficient fear conditioning in psychopathy as a function of interpersonal and affective disturbances. Front Hum Neurosci 7:706. doi:10.3389/fnhum.2013.00706

Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F et al (2009) Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA 301(11):1148–1154

Voncken MJ, Bögels SM, de Vries K (2003) Interpretation and judgmental biases in social phobia. Behav Res Ther 41(12):1481–1488

Walker DL, Davis M (2002) The role of amygdala glutamate receptors in fear learning, fear-potentiated startle, and extinction. Pharmacol Biochem Behav 71(3):379–392

Walss-Bass C, Fernandes JM, Roberts DL, Service H, Velligan D (2013) Differential correlations between plasma oxytocin and social cognitive capacity and bias in schizophrenia. Schizophr Res 147(2-3):387–392. doi:10.1016/j.schres.2013.04.003

Watanabe T, Abe O, Kuwabara H et al (2014) Mitigation of sociocommunicational deficits of autism through oxytocin-induced recovery of medial prefrontal activity: a randomized trial. JAMA Psychiatry 71(2):166–175. doi:10.1001/jamapsychiatry.2013.3181

Wermter A-K, Kamp-Becker I, Hesse P, Schulte-Körne G, Strauch K, Remschmidt H (2010) Evidence for the involvement of genetic variation in the oxytocin receptor gene (OXTR) in the etiology of autistic disorders on high-functioning level. Am J Med Genet B Neuropsychiatr Genet 153B(2):629–639. doi:10.1002/ajmg.b.31032

Williams LM, Hermens DF, Palmer D, Kohn M, Clarke S, Keage H et al (2008) Misinterpreting emotional expressions in attention-deficit/hyperactivity disorder: evidence for a neural marker and stimulant effects. Biol Psychiatry 63(10):917–926, http://dx.doi.org/10.1016/j.biopsych.2007.11.022

Wittkampf LC, Arends J, Timmerman L, Lancel M (2012) A review of modafinil and armodafinil as add-on therapy in antipsychotic-treated patients with schizophrenia. Ther Adv Psychopharmacol 2(3):115–125

Woolley J, Chuang B, Lam O, Lai W, O'Donovan A, Rankin K, Mathalon D (2014) Oxytocin administration enhances controlled social cognition in patients with schizophrenia. Psychoneuroendocrinology 47:116–125

Wu S, Jia M, Ruan Y, Liu J, Guo Y, Shuang M et al (2005) Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population. Biol Psychiatry 58(1):74–77. doi:10.1016/j.biopsych.2005.03.013

Zhang Y, Lin L, Lin C-P, Zhou Y, Chou K-H, Lo C-Y et al (2012) Abnormal topological organization of structural brain networks in schizophrenia. Schizophr Res 141(2):109–118