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Title: Similar effects of intranasal oxytocin administration and acute alcohol consumption on socio-cognitions, emotions and behaviour: Implications for the mechanisms of action

Running title: Oxytocin and alcohol

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Similar effects of intranasal oxytocin administration and acute alcohol consumption on socio-cognitions, emotions and behaviour: Implications for the mechanisms of action

1. Introduction

Oxytocin (OT), a neuropeptide hormone released from the posterior pituitary gland, plays well established roles in childbirth and lactation. More recently, studies of monogamous voles have led to an understanding of the role that oxytocin plays in the formation of long lasting social attachments (Carter 1998; Ross et al., 2009; Young & Wang, 2004). Such work has emphasised how oxytocin released from terminals and dendrites of neurons within the brain (Ludwig & Leng, 2006) can act on oxytocin receptors expressed by structures such as the medial nuclei of the amygdala to drive the formation of partner preference (Ferguson et al., 2001; Young & Wang, 2004; Insel & Young, 2001).

The effects of raising intracerebral oxytocin levels, by intranasal (*in*OT) administration, on human social functioning have been extensively researched. Much of this work has involved studying the effects of *in*OT on socio-cognitions and emotions. The findings have led to the general conclusion that raising oxytocin levels is associated with increases in prosocial behaviours including increased tendencies to behave altruistically, generously and empathically, and to trust others more (Zak et al., 2007; Barraza & Zak, 2009; Baumgarter et al., 2008; Kosfeld et al., 2005). This has led to excitement with respect to the possibility of treating some psychological/psychiatric conditions with the compound (Meyer-Lindenberg et al., 2011). It should, however, be noted that intranasal oxytocin administration is also associated with amplifying some aspects of antisocial behaviour, including gloating and envious responses in relation to competitors (Shamay-Tsoory et al., 2009), and exaggerating ethnocentric biases (De Dreu et al., 2010, 2011).

One complication relating to interpreting the actions of *in*OT relates to the degree to which the peptide can penetrate the blood brain barrier. Systemically administered neuropeptides in general do not enter the brain with ease. However, the use of *in*OT procedures may be more effective than intravenously and other systemic routes. Studies in both animals and humans have shown that inhalation administered neuropeptides do enter the CSF and can affect neural activity in structures such as the amygdala without inducing significant peripheral and hormonal effects (Born, Lange, Kern, McGregor, Bickel, & Fehm, 2002; Striepens et al. 2013).

Much of the detail of the mechanisms by which oxytocin exerts its effects on human social behaviour is still to be determined. There is currently debate as to whether these changes are mediated by the neuropeptide exerting specific actions in a selective manner on particular aspects of social behavior, or whether they result secondarily as a product of more low level general effects (Churchland & Winkielman, 2012). In this paper we highlight the strong similarities in the effects elicited by *in*OT and by acute consumption of modest doses of alcohol on an array of social-cognitions and emotions, ranging from fear, anxiety and stress, to aggression and in-group favouritism. We hypothesise that, although the two compounds work on very different receptors, they nonetheless will induce common effects on GABA transmission in the prefrontal cortex and limbic structures. Having explored this potentially common neural mechanism behind the similar socio-affective responses we then explore the possibility that both drugs act by unmasking modes of acting and thinking that are acquired earlier in development.

2. Effects of oxytocin and acute alcohol consumption on social-cognitions and behavior

2.1. Fear, anxiety and stress

The potential anxiolytic effects of oxytocin have been inferred from the observation of reduced anxiety and stress responses in breast feeding/suckling mammals which is accompanied by increased release of the peptide (UvnasMoberg, 1998). Work with experimental animals has confirmed this postulated relationship. For example, OT reduces anxiety when administered directly in to the cerebral ventricles (Windle et al., 1997, Carter et al., 1998), paraventricular nucleus of the hypothalamus (Blume et al., 2008) and prelimbic area of the medial prefrontal cortex (Sabihi et al., 2014) of experimental rodents. Sub-cutaneous injections of OT have also been shown to reduce startle responses in rodents in a fear-potentiated startle paradigm (Missig et al., 2010), and cause reductions in stress responses as indicated by attenuated corticosterone (Windle et al., 1997; Mantella et al., 2004) and ACTH release in rodents and primates (Parker et al., 2005) respectively. It has also been shown in humans that both plasma and CSF levels of OT significantly negatively predict trait anxiety scores (Carson et al., 2014).

A series of studies have shown that *in*OT can similarly reduce fear responses, exert anxiolytic effects and reduce the release of corticosteroid stress hormones in humans. One of the most persuasive studies is that by Kirsch et al. (2005), which looked at the acute effects of *in*OT on amygdala responses to fear-inducing visual images as shown by fMRI. This work demonstrated that boosting OT levels in healthy participants reduces both fear responses in the amygdala itself and the coupling of amygdala activity with that of midbrain structures involved in autonomic and behavioural aspects of fear responses (see Table 1).

Table 1 about here

Other studies have focused on individuals who suffer from anxiety disorders. In this regard, Guastella et al. (2009) showed that *in*OT improves mental representations of the self in individuals with social anxiety disorder when taken in addition to exposure therapy.

Similarly, Labuschagne et al. (2012) showed in a fMRI study that *in*OT tempered medial prefrontal and anterior cingulate responses to negative social cues, including fearful faces, in patients with generalized social anxiety disorder.

Moreover, *in*OT reduces cortisol levels in response to acute psychological stressors, including experimentally induced social rejection (Linnen et al., 2012) and social stress tests, where an interaction with social support is seen (Heinrichs et al., 2003). These effects, however, may be attenuated in men who experienced early parental separation (Meinlschmidt & Heim, 2007). *in*OT is also reported to reduce the magnitude of cortisol release induced by physiological stressors such as intense exercise (Cardosa et al., 2013).

The capacity for acute alcohol consumption to reduce anxiety has been known for centuries. This relationship has been subject to experimental scrutiny in recent years. For example, Sayette et al. (1992) demonstrated that acute alcohol consumption reduced negative emotional reactions in social drinkers on a social stressor test. Alcohol can also moderate fear reactions, and has been shown to reduce amygdala responses in social drinkers to threatening stimuli (Gilman et al., 2008; Sripada et al., 2011). Similarly, it is thought that individuals who suffer from social phobia may self-medicate with alcohol (Carrigan & Randall, 2003). These anxiolytic and fear reducing responses are most likely mediated via an effect of alcohol on the central and medial nuclei of the amygdala (Pandey, 2006). Alcohol may also be able to reduce stress effects via an action on the central amygdala (CeA) nuclei. For example, Nie et al. (2004) showed that alcohol interacts with CRF1 receptors to enhance GABAergic synaptic transmission in the CeA.

Although acute *in*OT administration elicits anxiolytic effects, elevated levels of oxytocin may be associated with prolonged exposure to stressors, especially in early life. For example, maltreated children show raised urinary OT levels (a marker of cerebral OT levels) as do

adult offenders who experienced early childhood maltreatment (Seltzer et al., 2014; Mitchell et al., 2013). Similarly, Hoge et al. (2008) showed that plasma oxytocin levels correlated with higher social anxiety symptoms in patients with Generalized Social Anxiety Disorder (GSAD). A parallel relationship may occur with alcohol whereby acute consumption decreases anxiety but chronic consumption and dependence is associated with anxiety disorders (Schuckit & Hesselbroc, 1994).

2.2. Trust, Generosity and Altruism

A succession of papers has reported that elevated OT levels are associated with increases in trust, generosity and altruism as measured in social decision making games. For example, *in*OT has been associated with the maintenance of trust even after betrayal (Baumgartner et al., 2008) and irrespective of the tendency to take risks (Kosfeld et al., 2005). Similarly, Theodoridou et al. (2009) demonstrated that *in*OT increased the ratings of trustworthiness and attractiveness of others. Furthermore, *in*OT can enhance generosity and to a lesser extent, altruism in one-shot decision making games (Zak et al., 2007).

Similar effects have been reported following acute alcohol consumption. Lynn et al. (1988) demonstrated that there is a relationship between alcohol consumed and size of tip in restaurant diners. More formally, Steele et al. (1985) showed that alcohol can dose dependently make individuals more generous on tasks which involve helping another complete an unpleasant task. The data suggest that the effect is mediated by alcohol helping to override inhibiting pressures which act to prevent the expression of generosity.

2.3. Social decision making games

In these games, which include the ultimatum game and the dictator game, participants are required to carve up either real or imaginary monetary rewards between themselves and in-

groups and out-groups. Both *in*OT and acute alcohol consumption have been shown to affect responding behavior on these games by affecting the generosity of responses to out-group members (Radke & De Bruijn, 2012), and by increasing rejection rates of apparently unfair offers (Morewedge et al., 2014).

2.4. Morality

Although *in*OT may increase prosocial behaviours such as trust and generosity, its actions may be more circumspect than first appears. *in*OT caused individuals to be more dishonest in a coin-tossing prediction game in order to benefit fellow group members (Shalvi & De Dreu, 2014). Similarly, acute alcohol consumption can also induce changes in moral behaviour. For example, Denton and Krebs (1990) demonstrated that alcohol consumption is associated with transient decreases in moral maturity.

2.5. Facial emotional expression recognition

Several studies have examined the role of OT in the recognition of facial emotional expressions. Much of this work has contrasted the effects of the neuropeptide on the recognition of positive versus negative emotions. Several studies have reported that OT improves the perception of happy faces (Marsh et al., 2010; Schulze et al., 2011). These findings are supported by the results of a meta-analysis, which concluded that *in*OT significantly improves recognition accuracy for happy faces (Shahrestani et al., 2013). In equivalent experiments involving experimental primates, Parr et al. (2013) showed that *in*OT reduced the monkey's attention to negative facial expressions. However Shahrestani et al., (2013) also concluded that fearful faces are also recognised more accurately following *in*OT, suggesting that the beneficial effects on recognition may also apply to this negative emotional expression.

Alcohol, like *in*OT, affects emotional facial expression recognition. For example, Kano et al. (2003) showed that a low dose of alcohol significantly improved the recognition of happy faces but not negative facial emotional expressions. Moreover, others have shown that alcohol makes sad faces harder to recognise accurately. For example, Kamboj et al. (2013) showed that alcohol causes sad faces to be classified as neutral, while Craig et al. (2009) reported that alcohol raised the threshold for the accurate identification of sad faces. Similarly, Stevens et al. (2006) showed that both social phobic and control participants rated angry faces as less rejecting following alcohol consumption.

2.6. Risk taking

Although the literature on OT and risk taking in humans is relatively small (for example, see Kosfeld et al., 2005), there is some impressive literature on this in rodents. This work has demonstrated that sexual activity and mating induces the release of OT within the hypothalamic paraventricular nucleus, reduces the level of anxiety and increases risk-taking behavior in male rats (Waldherr & Neumann, 2007; Kavaliers et al., 2008). Similarly, alcohol has long been associated with increased risk taking in humans, with recent interests focusing on the effects of alcohol in increasing the likelihood of risky sexual practices (Cooper, 2002; Halpern-Felsher et al., 1996).

2.7. Analgesia

The potential analgesic effects of OT are reviewed by Uvnas Moberg (1998). Daily injections of OT for 5 days increased the withdrawal latency to a hot noxious stimulus in a tail flick test (Agren et al., 1995). Furthermore, Kavaliers et al. (2006) showed that OT knockout mice show an attenuation of the analgesic response, as shown by decreased latency in foot withdrawal in a hot-plate test, which is normally elicited by exposure to an infected conspecific.

The analgesic effects of alcohol have been known since ancient Greek times (Rosso, 2012). Experiments have shown that acute alcohol administration results in a transient lowering of the sensitivity to painful electric shocks (Stewart, 1995) and a significant increase in pain tolerance but not pain threshold (Perrino et al., 2008).

2.8. Aggression

Although OT is associated with prosocial behaviours, there are nonetheless positive relationships between OT and aggressiveness under particular circumstances. This may reflect the role of OT in parenting and maternal aggression (Debiec, 2005). However, *in*OT also increases the probability of aggression towards an intimate partner as self-disclosed by participants following a provocation task (De Wall et al., 2014). This effect, however, was limited to participants with high trait physical aggressiveness.

An association between the expression of aggressive behaviours and alcohol is well established (e.g., Giancola & Parrott, 2008; Hoaken & Pihl, 2000). However, Giancola (2002) demonstrated that, like *in*OT, the effect of alcohol on increasing aggressive responses in the Taylor Aggression Paradigm, where electric shocks are administered to a fictitious opponent during a competitive task, is limited to individuals with high dispositional aggressivity.

Related observations of how the effects of *in*OT are dependent on both personality traits and context have been reviewed by others (Bartz, Zaki, Bolger, & Ochsner, 2011; Quintana, Alvares, Hickie, & Guastella, 2015). These reports emphasize how personality and individual differences along with situational factors can markedly influence the cognitive, affective and behavioural responses to *in*OT.

2.9. Reward

The role that OT plays in driving the formation of attachments between conspecifics has led to the hypothesis that OT can act on the brain's reward circuits by encouraging the release of dopamine by ventral tegmental area (VTA) neurons into the nucleus accumbens. This hypothesis has been supported by Liu and Wang (2003) who showed that interactions of dopamine and oxytocin systems in the striatum are needed for forming and maintaining attachment bonds. Further support is provided by the observation that OT dose-dependently excites dopamine neurons in the VTA (Tang et al., 2014), and acts as a reinforcer, like other drugs and natural rewards, under both solitary and social conditions (Kent et al., 2013).

Similar observations have also been made with respect to alcohol. For example, Xiao and Ye (2008) showed that alcohol boosts activity in VTA dopamine neurons by an action on local GABAergic mechanisms. Furthermore, Gilman et al. (2008) showed in an fMRI study that alcohol strongly activated striatal reward circuits, with the level of activation correlating with the levels of self-rated intoxication.

2.10. Empathy/Theory of Mind (ToM)/Eye gaze

Understanding the role of OT in mediating empathic responses is made difficult by the complexity of the empathy concept in itself. There is general agreement that empathy can be subdivided into affective empathy, or emotional contagion, and cognitive empathy, which includes perspective taking and ToM (Bernhardt & Singer, 2012; Decety, 2011; Shamay-Tsoory, 2011). Shamay-Tsoory et al. (2009) have elegantly demonstrated that these two different components of empathy are mediated by dissociable neuronal networks. Furthermore, it appears that affective empathy appears earlier in development than cognitive empathy (Shamay-Tsoory et al. 2009).

There are reports of *in*OT increasing empathic sensitivity. For example, Krueger et al. (2013) reported that *in*OT increased the perception of harm for victims. Moreover, Shamay-Tsoory et al. (2013) showed that *in*OT increased estimates of how much pain a member of an ethnic out-group was experiencing as a product of an accident. Hurlemann et al. (2010) similarly reported that *in*OT potentiated emotional empathic responses to both positive and negative valence stimuli. However, no equivalent effects were seen for cognitive empathy.

By contrast, Domes et al. (2007) showed that *in*OT improved performance on the Reading the Mind in the Eyes Test, a test of ToM which necessitates inferring an individual's emotions on the basis of images of the eye region of their face. *in*OT may also exert an influence over emotion recognition by affecting eye scan paths. Both Domes et al. (2013) and Guastella et al. (2008) have shown that *in*OT increases the number of fixations and total gaze time toward the eye region of faces, that is, the facial region that is particularly rich in emotional cues.

There are surprisingly few articles reporting the effects of acute alcohol consumption on empathy. However, one study has reported that alcohol increases affective empathy, whereby acute alcohol consumption increases the contagion of true smiles (Duchenne smiles), especially in males interacting with females (Fairbairn & Sayette, 2014).

2.11. In-group favouritism/out-group derogation and in-group conformity

Despite the predominance of articles on the pro-social effects of OT, there are nonetheless some reports of it generating negative social cognitions. For example, Shamay-Tsoory et al. (2009) reported that *in*OT increases envy and gloating in competitive game situations. In a similar vein, De Dreu and colleagues (2010, 2011) have reported that *in*OT promotes parochial altruism, that is, a tendency to support an in-group at the expense of an out-group. De Dreu et al. (2011) showed that *in*OT was associated with a tendency to promote in-group trust and cooperation, alongside defensive aggression toward competing out-groups.

Moreover, Sheng et al. (2013) reported that *in*OT enhances an EEG correlate of empathic responding to images of ethnic in-group faces, but not out-group faces, feeling pain. Stallen et al. (2012) also showed that *in*OT enhanced the tendency for individuals to express the same opinions and judgments as members of their in-group.

Equivalent effects have been reported following acute alcohol consumption. For example, Mitchell et al. (2015) showed that drinking modest doses of alcohol resulted in Caucasian participants judging White faces to be more attractive than when sober. However, this effect was not seen when the participants judged black faces and is thus indicative of alcohol promoting in-group favouritism. Moreover, Kirchner et al. (2006) showed that acute alcohol consumption increases the co-ordination of verbal and non-verbal behaviours and self-reported bonding between in-group members. Furthermore, Sayette et al. (2012) showed in a large scale study with over 700 participants, that alcohol facilitated bonding in social groups, promoted smiling and reduced individual level behaviours associated with negative affect.

2.12. Subjective effects of inOT and acute alcohol consumption

Although a myriad of socioaffective effects have been described following *in*OT, the procedure is not generally associated with marked subjective changes in mood (Kirkpartrick et al., 2014; MacDonald et al. 2011). With the typically used single dose of OT, in the range of 20-40 IU, effects of euphoria, light headedness and drowsiness have only occasionally been reported and participants are only rarely able to reliably determine whether they received *in*OT or placebo (MacDonald et al. 2011). By contrast, alcohol clearly has the capacity to induce marked changes in mood. It should be noted, however, that low to moderate doses of alcohol do not necessarily induce subjective changes in mood. Indeed, double blind laboratory based experiments with low to moderate doses of alcohol are frequently conducted where the participants are unaware of whether they consumed the

alcoholic drink or placebo (Kirchner et al., 2006; Sayette et al., 2012; Sripada et al., 2011; Steele et al., 1985).

3. Potential common neurobiological mechanisms underlying the effects of *in*OT and acute alcohol consumption and therapeutic implications

This extensive list of similar socio-cognitive responses resulting from the administration of *in*OT and acute alcohol consumption implies that the two drugs are ultimately acting on common neural circuits. Thus, although the two ligands act at different receptors they may nonetheless exert equivalent actions on prefrontal and limbic circuits.

Alcohol exerts its primary pharmacological action by acting synergistically with GABA, primarily at variants of the GABA-A receptor complex which contain a delta subunit (Roberto et al., 2003; Akk & Steinbach, 2003). Most of the effects of alcohol on social behaviour are thus thought to reflect the ligand modifying GABA transmission in: the amygdala to reduce anxiety, the VTA/nucleus accumbens to elicit a sense of reward, and parts of the prefrontal cortex. Many of the socio-affective actions of oxytocin may likewise reflect modifications of GABAergic transmission. Indeed, Viviani et al. (2010) have shown using in vitro techniques that oxytocin acts presynaptically to induce a massive release of GABA from neurons in the central amygdala nuclei while benzodiazepines induce similar effects at a circuit level by acting synergistically with GABA post-synaptically (see Figure 1). Consequently, both *in*OT and acute alcohol consumption would result in an equivalent increase in GABAergic mediated inhibition of the circuit. Similarly, Bulbul et al. (2011) demonstrated that some of the anxiolytic effects of OT are mediated via its actions on GABA-A receptors in the hypothalamus and Owen et al. (2013) has argued that analogous OT/GABA interactions operate in the hippocampus to inhibit pyramidal neurons.

Figure 1 about here

If this model of oxytocin functioning is correct, it follows that the potential therapeutic actions of OT could be mimicked by alcohol, or by any manipulation that boosts GABA-A receptor mediated function, including administration of benzodiazepines. Tentative support for this claim can be found. Preliminary evidence suggests that *in*OT can ameliorate the symptoms of autism and increase socio-cognitive functioning in affected individuals (Andari et al., 2010; Hollander et al., 2007, 2003; Guastella et al., 2010). Equally Han and colleagues have shown that low, non-sedative and non-anxiolytic, doses of benzodiazepines improve deficits in social interaction in a mouse model of idiopathic autism (Han et al., 2014). The hyper-connectiveness model of autism (see Courchesne et al., 2007) speculates that aberrant functioning in autism results from early brain overgrowth. This overgrowth is thought to result in an excess of local cortical interactions which impede the functional interactions between more distant brain sites. Pharmacological manipulations which increase GABA transmission and so reduce the activity of these local cortical systems would consequently be expected to have a therapeutic effect.

4. Effects of acute alcohol consumption and *in*OT on prepotent responses and socio-affective responses seen in children

Although alcohol exerts its primary pharmacological action by boosting GABA-mediated inhibition, its effects on socio-affective behaviours are typically attributed to a process of disinhibition. For instance, alcohol can be seen as impeding the activity of high level prefrontal cortical regions and the resultant compromised executive function allows the expression of an otherwise suppressed behavioural response. Alcohol induced release of prepotent responses can, for example, be seen in Stroop tasks (Marinkovic et al., 2012; Rose

& Duka 2008), n-back working memory tasks (Casbon et al., 2003) and go/no-go tasks (Rose & Duka, 2008).

The release of prepotent responses following alcohol consumption may lead to socio-cognitive behaviours that are similar to those observed among young children at early stages of prefrontal development. Executive functioning is known to be limited in infants, with children around the age of 4-5 showing difficulties in inhibiting prepotent responses (Livesey & Morgan,1991; Kerr & Zelazo, 2004). However, adolescents still perform more poorly than young adults on Stroop tests (Vijayakumar et al., 2014, Veroude et al., 2013). This gradual and protracted development of executive functioning is assumed to reflect the prolonged maturation of the prefrontal cortex which continues into adulthood. This slow process is characterised by a shift in reliance on ventromedial areas of the prefrontal cortex for resolving cognitive interference to structures which lie more dorsolaterally. This mirrors the shift from the ready expression of emotional and instinctual behaviors to more controlled and abstract responses (Fuster, 2002).

Following on from this it can be argued that acute alcohol consumption, and by analogy *in*OT, will encourage the release of prepotent responses, that is, responses that would be more typical of those made at an earlier developmental stage. A considerable array of evidence supports this position as follows.

4.1. Trust

There is some evidence to suggest that young children intrinsically trust others prior to developing a sense of mistrust (See Table 2). Vanderbilt et al. (2011), for example, showed that three year old children accept advice from reliable and unreliable helpers in an experimental game, whereas 5 year olds showed selective trust and would only take advice from reliable helpers. Similarly, Heyman et al. (2013) showed that 3 year old children have

trouble ignoring misleading advice if it appears to have been intentionally offered by others. Thus, *in*OT could be seen as enabling the release of the default condition of trusting.

Table 2 about here

4.2. Altruism

Warneken and Tomasello (2008, 2009) argue that although altruism is rare in non-humans it is present in very young children. For example, it has been shown that 18 month old children readily help others to achieve their goals. This altruistic behaviour appears to be intrinsically driven and can be disrupted if extrinsic rewards are given in an attempt to reinforce the pro-social behaviour. Similarly, Harbaugh et al. (2000) showed that children around the age of 6 years respond differently to 12 year old children and adults in a public goods game. Participants of all ages show initial altruistic behaviour but this is only maintained in younger children. This parallels the *in*OT maintenance of trust following betrayal as shown by Baumgartner et al. (2008).

4.3. Gloating/spite

Fehr et al. (2013) reported that spitefulness decreases with increasing age amongst children aged from 8-17 years. This effect matches the increase in envy and gloating that can be elicited by *in*OT (Shamay-Tsoory et al., 2009).

4.4. In-group favoritism

In-group love can be seen in preschool children (Buttelmann & Boehm, 2014) and can drive in-group biases. However, out-group hate only appears in children over the age of six years. Similarly, Inguglia and Musso (2013) studied reactions to national out-groups in Italian children. In-group favouritism was seen in children from the age of six, whereas derogation

of a national out-group was only seen in older children. These observations are equivalent to those of De Dreu and colleagues who showed that *in*OT promotes in-group favouritism without necessarily inducing large out-group derogation effects (De Dreu et al., 2010). (See table 1)

4.5. Empathy and sympathy

Roth-Hanania et al. (2011) showed that children as young as 24 months old can show empathy for the distress of another. Furthermore, Decety and Michalska (2010) imaged the brain mechanisms that respond to seeing pain intentionally inflicted on another individual. Neural activity shifted from medial prefrontal structures, which predominated in the brains of 7 year olds, to lateral prefrontal areas in adults. This may underlie a move from visceral responses to the affective stimuli to more abstract cognitive responses and so parallel the effect of *in*OT in potentiating emotional but not cognitive empathy (Hurlemann et al., 2010).

4.6. Happy facial expressions

Gao and Maurer (2010) demonstrated that children are as sensitive as adults to facial expressions of happiness from the age of 5 years. However, sensitivity to other facial emotional expressions develops gradually up to the age of 10 years with sensitivity to anger and sadness developing last. This would correspond to the observed effects of *in*OT on preferentially boosting the recognition of happy facial expressions relative to negative ones (Marsh et al., 2010; Schulze et al., 2011; Shahrestani et al., 2013).

5. Conclusion

The similarity in behavioural/cognitive/emotional effects induced by *in*OT and alcohol, taken together with their common effects on GABAergic transmission in identified neural circuits, implies that the two compounds act in similar ways. A plausible model to account for their

social effects would be the removal of inhibitory brakes which normally act to suppress the expression of response tendencies that are characteristic of earlier developmental stages. From this it would be predicted that both *in*OT and alcohol would exert greater effects on inhibiting circuits in the dorsolateral prefrontal cortex than the more primitive ventromedial cortex.

This analysis also implies that any therapeutic effects induced by *in*OT could potentially be elicited by other pharmacological manipulations which boost GABAergic transmission in specific neural circuits. Such manipulations would include the administration of benzodiazepines. Indeed, as noted above, low doses of benzodiazepines have recently been shown to be beneficial in an animal model of autism (Han et al., 2014). However, given the addictive and dependency issues surrounding both alcohol and benzodiazepines, their long term use in treating chronic neuropsychiatric conditions would have to be pursued with extreme caution. Against this background it is chastening to note how little is known about the chronic effects of *in*OT.

The conclusion that oxytocin is exerting many of its socio-cognitive effects by suppressing the action of prefrontal and limbic cortical circuits may at first sight seem surprising. However, few psychoactive drugs exert their actions by boosting neuronal activity in the sophisticated ways needed to encode for trust, generosity, empathy etc. Psychoactive drugs are far more likely to elicit effects by reducing unwanted neural activity. Exceptions would include drugs that boost monoamine transmission such as dopaminergic agents used to treat the symptoms of Parkinson's disease. But even here, the drugs are most likely enabling normal cortical functioning to resume by reducing the interference from abnormally discharging basal ganglia structures (Mitchell et al., 1989). If this conjecture is correct, then it would appear that *in*OT may act by unmasking your inner child.

6. References

Agren, G., Lundeberg, T., Uvna¨s-Moberg, K., & Sato, A. (1995) The oxytocin antagonist 1-deamino-2-D-Tyr (Oet)-4-Thr-8-Orn oxytocin reverses the increase in the withdrawal response latency to thermal, but not mechanical nociceptive stimuli following oxytocin administration or massage-like stroking in rats. *Neuroscience Letters, 187*, 49–52.

Akk, G., & Steinbach, J. H. (2003). Low doses of ethanol and a neuroactive steroid positively interact to modulate rat GABAA receptor function. *The Journal of Physiology*, *546*, 641-646.

Andari, E., Duhamel, J. R., Zalla, T., Herbrecht, E., Leboyer, M., & Sirigu, A. (2010). Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proceedings of the National Academy of Sciences*, *107*, 4389-4394.

Barraza, J. A., & Zak, P. J. (2009). Empathy toward strangers triggers oxytocin release and subsequent generosity. *Annals of the New York Academy of Sciences*, *1167*, 182-189.

Bartz, J. A., Zaki, J., Bolger, N., & Ochsner, K. N. (2011). Social effects of oxytocin in humans: Context and person matter. *Trends in Cognitive Sciences, 15,* 301-309.

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*, 639-650.

Bernhardt B. C. & Singer, T. (2012). The neural basis of empathy. *Annual Review of Neuroscience, 35*, 1-23.

Blume, A., Bosch, O. J., Miklos, S., Torner, L., Wales, L., Waldherr, M., & Neumann, I. D. (2008). Oxytocin reduces anxiety via ERK1/2 activation: local effect within the rat

hypothalamic paraventricular nucleus. *European Journal of Neuroscience*, *27*, 1947-1956.

Born, J., Lange, T., Kern, W., McGregor, G. P., Bickel, U., & Fehm, H. L. (2002). Sniffing neuropeptides: A transnasal approach to the human brain. *Nature Neuroscience, 5,* 514-516.

Bülbül, M., Babygirija, R., Cerjak, D., Yoshimoto, S., Ludwig, K., & Takahashi, T. (2011). Hypothalamic oxytocin attenuates CRF expression via GABA A receptors in rats. *Brain Research*, *1387*, 39-45.

Buttelmann, D., & Böhm, R. (2014). The ontogeny of the motivation that underlies in-group bias. *Psychological Science*. doi: 10.1177/0956797613516802

Cardoso, C., Ellenbogen, M. A., Orlando, M. A., Bacon, S. L., & Joober, R. (2013). Intranasal oxytocin attenuates the cortisol response to physical stress: a dose–response study. *Psychoneuroendocrinology*, *38*, 399-407.

Carrigan, M. H., & Randall, C. L. (2003). Self-medication in social phobia: a review of the alcohol literature. *Addictive Behaviors*, *28*, 269-284.

Carson, D. S., Berquist, S. W., Trujillo, T. H., Garner, J. P., Hannah, S. L., Hyde, S. A., ... & Parker, K. J. (2014). Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children. *Molecular Psychiatry.* doi: 10.1038/mp.2014.132

Carter, C. S. (1998). Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology*, *23*, 779-818.

Casbon, T. S., Curtin, J. J., Lang, A. R., & Patrick, C. J. (2003). Deleterious effects of alcohol intoxication: diminished cognitive control and its behavioral consequences. *Journal of Abnormal Psychology, 112*, 476-.

Churchland, P. S., & Winkielman, P. (2012). Modulating social behavior with oxytocin: how does it work? What does it mean? *Hormones and Behavior*, *61*, 392-399

Cooper, M. L. (2002). Alcohol use and risky sexual behavior among college students and youth: Evaluating the evidence. *Journal of Studies on Alcohol and Drugs*, 14, 101-117.

Courchesne, E., Pierce, K., Schumann, C. M., Redcay, E., Buckwalter, J. A., Kennedy, D. P., & Morgan, J. (2007). Mapping early brain development in autism. *Neuron*, *56*, 399-413.

Craig, L. C., Attwood, A. S., Benton, C. P., Penton-Voak, I. S., & Munafo, M. R. (2009). Effects of acute alcohol consumption and alcohol expectancy on processing of perceptual cues of emotional expression. *Journal of Psychopharmacology,* 23, 258-265.

Dębiec, J. (2005). Peptides of love and fear: vasopressin and oxytocin modulate the integration of information in the amygdala. *Bioessays*, 27, 869-873.

Decety, J. (2011). Dissecting the neural mechanisms mediating empathy. *Emotion Review 3,* 92–108.

Decety, J., & Michalska, K. J. (2010). Neurodevelopmental changes in the circuits underlying empathy and sympathy from childhood to adulthood. *Developmental Science*, *13*, 886-899.

De Dreu, C. K., Greer, L. L., Handgraaf, M. J., Shalvi, S., Van Kleef, G. A., Baas, M., ... & Feith, S. W. (2010). The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans. *Science*, *328*, 1408-1411.

De Dreu, C. K., Greer, L. L., Van Kleef, G. A., Shalvi, S., & Handgraaf, M. J. (2011). Oxytocin promotes human ethnocentrism. *Proceedings of the National Academy of Sciences*, *108*, 1262-1266.

Denton, K., & Krebs, D. (1990). From the scene to the crime: The effect of alcohol and social context on moral judgment. *Journal of Personality and Social Psychology*, *59*, 242-248.

DeWall, C. N., Gillath, O., Pressman, S. D., Black, L. L., Bartz, J. A., Moskovitz, J., & Stetler, D. A. (2014). When the love hormone leads to violence oxytocin increases intimate partner violence inclinations among high trait aggressive people. *Social Psychological and Personality Science*. doi: 10.1177/1948550613516876.

Domes, G., Heinrichs, M., Michel, A., Berger, C., & Herpertz, S. C. (2007). Oxytocin improves "mind-reading" in humans. *Biological Psychiatry*, *61*, 731-733.

Domes, G., Steiner, A., Porges, S. W., & Heinrichs, M. (2013). Oxytocin differentially modulates eye gaze to naturalistic social signals of happiness and anger. *Psychoneuroendocrinology*, *38*, 1198-1202.

Fairbairn, C. E., & Sayette, M. A. (2014). A social-attributional analysis of alcohol response. *Psychological Bulletin*, *140*, 1361-1382.

Fehr, E., Glätzle-Rützler, D., & Sutter, M. (2013). The development of egalitarianism, altruism, spite and parochialism in childhood and adolescence. *European Economic Review*, *64*, 369-383.

Ferguson, J. N., Aldag, J. M., Insel, T. R., & Young, L. J. (2001). Oxytocin in the medial amygdala is essential for social recognition in the mouse. *The Journal of Neuroscience*, *21*, 8278-8285.

Fuster, J. M. (2002). Frontal lobe and cognitive development. *Journal of Neurocytology*, *31*(3-5), 373-385.

Gao, X., & Maurer, D. (2010). A happy story: Developmental changes in children's sensitivity to facial expressions of varying intensities. *Journal of Experimental Child Psychology*, *107*, 67-86.

Giancola, P. R. (2002). Alcohol-related aggression in men and women: The influence of dispositional aggressivity. *Journal of Studies on Alcohol and Drugs*, *63*, 696-.

Giancola, P. R., & Parrott, D. J. (2008). Further evidence for the validity of the Taylor aggression paradigm. *Aggressive Behavior*, *34*, 214-229.

Gilman, J. M., Ramchandani, V. A., Davis, M. B., Bjork, J. M., & Hommer, D. W. (2008). Why we like to drink: a functional magnetic resonance imaging study of the rewarding and anxiolytic effects of alcohol. *The Journal of Neuroscience*, *28*, 4583-4591.

Guastella, A. J., Carson, D. S., Dadds, M. R., Mitchell, P. B., & Cox, R. E. (2009). Does oxytocin influence the early detection of angry and happy faces? *Psychoneuroendocrinology*, *34*, 220-225.

Guastella, A. J., Einfeld, S. L., Gray, K. M., Rinehart, N. J., Tonge, B. J., Lambert, T. J., & Hickie, I. B. (2010). Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biological Psychiatry*, *67*, 692-694.

Guastella, A. J., Howard, A. L., Dadds, M. R., Mitchell, P., & Carson, D. S. (2009). A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. *Psychoneuroendocrinology*, *34*, 917-923.

Guastella, A. J., Mitchell, P. B., & Dadds, M. R. (2008). Oxytocin increases gaze to the eye region of human faces. *Biological Psychiatry*, *63*, 3-5.

Halpern-Felsher, B. L., Millstein, S. G., & Ellen, J. M. (1996). Relationship of alcohol use and risky sexual behavior: a review and analysis of findings. *Journal of Adolescent Health*, *19*, 331-336.

Han, S., Tai, C., Jones, C. J., Scheuer, T., & Catterall, W. A. (2014). Enhancement of inhibitory neurotransmission by $GABA_A$ receptors having $\alpha_{2,3}$-subunits ameliorates behavioral deficits in a mouse model of autism. *Neuron*, *81*, 1282-1289.

Harbaugh, W. T., & Krause, K. (2000). Children's altruism in public good and dictator experiments. *Economic Inquiry*, *38*, 95-109.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry*, *54*, 1389-1398.

Heyman, G. D., Sritanyaratana, L., & Vanderbilt, K. E. (2013). Young children's trust in overtly misleading advice. *Cognitive Science*, *37*, 646-667.

Hoaken, P. N.S., & Pihl, R. O. (2000). The effects of alcohol intoxication on aggressive responses in men and women. *Alcohol and Alcoholism*, *35*, 471-477.

Hoge, E. A., Pollack, M. H., Kaufman, R. E., Zak, P. J., & Simon, N. M. (2008). Oxytocin levels in social anxiety disorder. *CNS Neuroscience & Therapeutics*, *14*, 165-170.

Hollander, E., Bartz, J., Chaplin, W., Phillips, A., Sumner, J., Soorya, L., ... & Wasserman, S. (2007). Oxytocin increases retention of social cognition in autism. *Biological Psychiatry*, *61*, 498-503.

Hollander, E., Novotny, S., Hanratty, M., Yaffe, R., DeCaria, C. M., Aronowitz, B. R., & Mosovich, S. (2003). Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders. *Neuropsychopharmacology*, *28*, 193-198.

Hurlemann, R., Patin, A., Onur, O. A., Cohen, M. X., Baumgartner, T., Metzler, S., ... & Kendrick, K. M. (2010). Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *The Journal of Neuroscience*, *30*, 4999-5007.

Inguglia, C., & Musso, P. (2013). In-group favouritism and out-group derogation towards national groups: Age-related differences among Italian school children. *International Journal of Intercultural Relations*, *37*, 385-390.

Insel, T. R., & Young, L. J. (2001). The neurobiology of attachment. *Nature Reviews Neuroscience*, *2*, 129-136.

Kano, M., Gyoba, J., Kamachi, M., Mochizuki, H., Hongo, M., & Yanai, K. (2003). Low doses of alcohol have a selective effect on the recognition of happy facial expressions. *Human Psychopharmacology: Clinical and Experimental*, *18*, 131-139.

Kamboj, S. K., Joye, A., Bisby, J. A., Das, R. K., Platt, B., & Curran, H. V. (2013). Processing of facial affect in social drinkers: a dose–response study of alcohol using dynamic emotion expressions. *Psychopharmacology*, *227*, 31-39.

Kavaliers, M., Choleris, E., Ågmo, A., Braun, W. J., Colwell, D. D., Muglia, L. J., ... & Pfaff, D. W. (2006). Inadvertent social information and the avoidance of parasitized male mice: a role for oxytocin. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 4293-4298.

Kavaliers, M., Devidze, N., Choleris, E., Fudge, M., Gustafsson, J. Å., Korach, K. S., ... & Ogawa, S. (2008). Estrogen receptors α and β mediate different aspects of the facilitatory effects of female cues on male risk taking. *Psychoneuroendocrinology*, *33*, 634-642.

Kent, K., Arientyl, V., Khachatryan, M. M., & Wood, R. I. (2013). Oxytocin induces a conditioned social preference in female mice. *Journal of Neuroendocrinology*, *25*, 803-810.

Kerr, A., & Zelazo, P. D. (2004). Development of "hot" executive function: The children's gambling task. *Brain and Cognition*, *55*, 148-157.

Kirchner, T. R., Sayette, M. A., Cohn, J. F., Moreland, R. L., & Levine, J. M. (2006). Effects of alcohol on group formation among male social drinkers. *Journal of Studies on Alcohol and Drugs*, *67*, 785.

Kirkpatrick, M. G., Lee, R., Wardle, M. C., Jacob, S., & de Wit, H. (2014). Effects of MDMA and intranasal oxytocin on social and emotional processing. *Neuropsychopharmacology, 39,* 1654-1663.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., ... & Meyer-Lindenberg, A. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of Neuroscience*, *25*, 11489-11493.

Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, *435*, 673-676.

Krueger, F., Parasuraman, R., Moody, L., Twieg, P., de Visser, E., McCabe, K., ... & Lee, M. R. (2013). Oxytocin selectively increases perceptions of harm for victims but not the

desire to punish offenders of criminal offenses. *Social Cognitive and Affective Neuroscience*, *8*, 494-498.

Labuschagne, I., Phan, K. L., Wood, A., Angstadt, M., Chua, P., Heinrichs, M., ... & Nathan, P. J. (2012). Medial frontal hyperactivity to sad faces in generalized social anxiety disorder and modulation by oxytocin. *The International Journal of Neuropsychopharmacology*, *15*, 883-896.

Linnen, A. M., Ellenbogen, M. A., Cardoso, C., & Joober, R. (2012). Intranasal oxytocin and salivary cortisol concentrations during social rejection in university students. *Stress*, *15*, 393-402.

Liu, Y., & Wang, Z. X. (2003). Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. *Neuroscience*, *121*(3), 537-544.

Livesey, D. J., & Morgan, G. A. (1991). The development of response inhibition in 4-and 5-year-old children. *Australian Journal of Psychology*, *43*, 133-137.

Ludwig, M., & Leng, G. (2006). Dendritic peptide release and peptide-dependent behaviours. *Nature Reviews Neuroscience*, *7*, 126-136.

Lynn, M. (1988). The effects of alcohol consumption on restaurant tipping. *Personality and Social Psychology Bulletin*, 14, 87-91.

MacDonald, E., Dadds, M. R., Brennan, J. L., Williams, K., Levy, F., & Cauchi, A. J. (2011). A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. *Psychoneuroendocrinology, 36,* 1114-1126.

Mantella, R. C., Vollmer, R. R., Rinaman, L., Li, X., & Amico, J. A. (2004). Enhanced corticosterone concentrations and attenuated Fos expression in the medial amygdala of

female oxytocin knockout mice exposed to psychogenic stress. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *287*, R1494-R1504.

Marinkovic, K., Rickenbacher, E., Azma, S., & Artsy, E. (2012). Acute alcohol intoxication impairs top–down regulation of stroop incongruity as revealed by blood oxygen level-dependent functional magnetic resonance imaging. *Human Brain Mapping*, *33*, 319-333.

Marsh, A. A., Henry, H. Y., Pine, D. S., & Blair, R. J. R. (2010). Oxytocin improves specific recognition of positive facial expressions. *Psychopharmacology*, *209*, 225-232.

Meinlschmidt, G., & Heim, C. (2007). Sensitivity to intranasal oxytocin in adult men with early parental separation. *Biological Psychiatry*, *61*, 1109-1111.

Meyer-Lindenberg, A., Domes, G., Kirsch, P., & Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature Reviews Neuroscience*, *12*, 524-538.

Missig, G., Ayers, L. W., Schulkin, J., & Rosen, J. B. (2010). Oxytocin reduces background anxiety in a fear-potentiated startle paradigm. *Neuropsychopharmacology*, *35*, 2607-2616.

Mitchell, I. J., Clarke, C. E., Boyce, S., Robertson, R. G., Peggs, D., Sambrook, M. A., & Crossman, A. R. (1989). Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine.*Neuroscience*, *32*, 213-226.

Mitchell, I. J., Gillespie, S. M., Leverton, M., Llewellyn, V., Neale, E., & Stevenson, I. (2015). Acute alcohol consumption and secondary psychopathic traits increase ratings of

the attractiveness and health of ethnic ingroup faces but not outgroup faces. Frontiers in Psychiatry, 6. doi: 10.3389/fpsyt.2015.00025

Mitchell, I. J., Rutherford, V., Wrinch, K. A. J., & Egan, V. (2008). Paradoxical effects of alcohol intake in a convivial social setting on attitudes to violence. *Addiction Research & Theory*, *16*, 503-513.

Mitchell, I. J., Smid, W., Troelstra, J., Wever, E., Ziegler, T. E., & Beech, A. R. (2013). Psychopathic characteristics are related to high basal urinary oxytocin levels in male forensic patients. *Journal of Forensic Psychiatry & Psychology*, *24*, 309-318.

Morewedge, C. K., Krishnamurti, T., & Ariely, D. (2014). Focused on fairness: Alcohol intoxication increases the costly rejection of inequitable rewards. *Journal of Experimental Social Psychology*, *50*, 15-20.

Nie, Z., Schweitzer, P., Roberts, A. J., Madamba, S. G., Moore, S. D., & Siggins, G. R. (2004). Ethanol augments GABAergic transmission in the central amygdala via CRF1 receptors. *Science*, *303*, 1512-1514.

Owen, S. F., Tuncdemir, S. N., Bader, P. L., Tirko, N. N., Fishell, G., & Tsien, R. W. (2013). Oxytocin enhances hippocampal spike transmission by modulating fast-spiking interneurons. *Nature*, 500, 458-462.

Pandey, S. C., Zhang, H., Roy, A., & Misra, K. (2006). Central and medial amygdaloid brain-derived neurotrophic factor signaling plays a critical role in alcohol-drinking and anxiety-like behaviors. *The Journal of Neuroscience*, *26*, 8320-8331.

Parker, K. J., Buckmaster, C. L., Schatzberg, A. F., & Lyons, D. M. (2005). Intranasal oxytocin administration attenuates the ACTH stress response in monkeys. *Psychoneuroendocrinology*, *30*, 924-929.

Parr, L. A., Modi, M., Siebert, E., & Young, L. J. (2013). Intranasal oxytocin selectively attenuates rhesus monkeys' attention to negative facial expressions. *Psychoneuroendocrinology*, *38*, 1748-1756.

Perrino, A. C., Ralevski, E., Acampora, G., Edgecombe, J., Limoncelli, D., & Petrakis, I. L. (2008). Ethanol and pain sensitivity: effects in healthy subjects using an acute pain paradigm. *Alcoholism: Clinical and Experimental Research*, *32*, 952-958.

Petersson, M., Hulting, A. L., & Uvnäs-Moberg, K. (1999). Oxytocin causes a sustained decrease in plasma levels of corticosterone in rats. *Neuroscience letters*, *264*, 41-44.

Quintana, D. S., Alvares, G. A., Hickie, I. B., & Guastella, A. J. (2014). Do delivery routes of intranasally administered oxytocin account for observed effects on social cognition and behavior? A two-level model. *Neuroscience & Biobehavioral Reviews*, *49,* 182-192.

Radke, S., & De Bruijn, E. R. (2012). The other side of the coin: oxytocin decreases the adherence to fairness norms. *Frontiers in Human Neuroscience*, 6, 193, 1-7.

Roberto, M., Madamba, S. G., Moore, S. D., Tallent, M. K., & Siggins, G. R. (2003). Ethanol increases GABAergic transmission at both pre-and postsynaptic sites in rat central amygdala neurons. *Proceedings of the National Academy of Sciences*, *100*, 2053-2058.

Rose, A. K., & Duka, T. (2008). Effects of alcohol on inhibitory processes. *Behavioural Pharmacology, 19*, 284-291.

Ross, H. E., Cole, C. D., Smith, Y., Neumann, I. D., Landgraf, R., Murphy, A. Z., & Young, L. J. (2009). Characterization of the oxytocin system regulating affiliative behavior in female prairie voles. *Neuroscience*, *162*, 892-903.

Rosso, A. M. (2012). Beer and wine in antiquity: beneficial Remedy or punishment imposed by the Gods? *Acta Medico-Historica Adriatica*, *10*, 237-262.

Roth-Hanania, R., Davidov, M., & Zahn-Waxler, C. (2011). Empathy development from 8 to 16 months: Early signs of concern for others. *Infant Behavior and Development*, *34*, 447-458.

Sabihi, S., Durosko, N. E., Dong, S. M., & Leuner, B. (2014). Oxytocin in the prelimbic medial prefrontal cortex reduces anxiety-like behavior in female and male rats. *Psychoneuroendocrinology*, *45*, 31-42.

Sayette, M. A., Creswell, K. G., Dimoff, J. D., Fairbairn, C. E., Cohn, J. F., Heckman, B. W., ... & Moreland, R. L. (2012). Alcohol and group formation a multimodal investigation of the effects of alcohol on emotion and social bonding. *Psychological Science*. doi: 10.1177/0956797611435134.

Sayette, M. A., Smith, D. W., Breiner, M. J., & Wilson, G. T. (1992). The effect of alcohol on emotional response to a social stressor. *Journal of Studies on Alcohol and Drugs*, *53*, 541-545.

Schuckit, M. A., & Hesselbrock, V. (1994). Alcohol dependence and anxiety disorders: what is the relationship? *The American Journal of Psychiatry, 151,* 1723-1734.

Schulze, L., Lischke, A., Greif, J., Herpertz, S. C., Heinrichs, M., & Domes, G. (2011). Oxytocin increases recognition of masked emotional faces. *Psychoneuroendocrinology*, *36*, 1378-1382.

Seltzer, L. J., Ziegler, T., Connolly, M. J., Prososki, A. R., & Pollak, S. D. (2014). Stress-induced elevation of oxytocin in maltreated children: Evolution, neurodevelopment, and social behavior. *Child Development*, *85*, 501-512.

Shahrestani, S., Kemp, A. H., & Guastella, A. J. (2013). The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. *Neuropsychopharmacology*, *38*, 1929-1936.

Shalvi, S., & De Dreu, C. K. (2014). Oxytocin promotes group-serving dishonesty. *Proceedings of the National Academy of Sciences*, *111*, 5503-5507.

Shamay-Tsoory, S. G. (2011). The neural bases for empathy. *Neuroscientist 17,* 18–24.

Shamay-Tsoory, S. G., Abu-Akel, A., Palgi, S., Sulieman, R., Fischer-Shofty, M., Levkovitz, Y., & Decety, J. (2013). Giving peace a chance: oxytocin increases empathy to pain in the context of the Israeli–Palestinian conflict. *Psychoneuroendocrinology*, *38*, 3139-3144.

Shamay-Tsoory, S. G., Aharon-Peretz, J., & Perry, D. (2009). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain*, *132*, 617-627.

Shamay-Tsoory, S. G., Fischer, M., Dvash, J., Harari, H., Perach-Bloom, N., & Levkovitz, Y. (2009). Intranasal administration of oxytocin increases envy and schadenfreude (gloating). *Biological Psychiatry*, *66*, 864-870.

Sheng, F., Liu, Y., Zhou, B., Zhou, W., & Han, S. (2013). Oxytocin modulates the racial bias in neural responses to others' suffering. *Biological Psychology*, *92*, 380-386.

Striepens, N., Kendrick, K. M., 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. *Scientific Reports, 3.* doi:10.1038/srep03440

Sripada, C. S., Angstadt, M., McNamara, P., King, A. C., & Phan, K. L. (2011). Effects of alcohol on brain responses to social signals of threat in humans. *Neuroimage*, *55*, 371-380.

Stallen, M., De Dreu, C. K., Shalvi, S., Smidts, A., & Sanfey, A. G. (2012). The herding hormone oxytocin stimulates in-group conformity. *Psychological Science*, *23,* 1288-1292.

Steele, C. M., Critchlow, B., & Liu, T. J. (1985). Alcohol and social behavior: II. The helpful drunkard. *Journal of Personality and Social Psychology*, *48*, 35-46.

Stevens, S., Gerlach, A. L., & Rist, F. (2008). Effects of alcohol on ratings of emotional facial expressions in social phobics. *Journal of Anxiety Disorders*, *22*, 940-948.

Stewart, S. H., Finn, P. R., & Pihl, R. O. (1995). A dose-response study of the effects of alcohol on the perceptions of pain and discomfort due to electric shock in men at high familial-genetic risk for alcoholism. *Psychopharmacology*, *119*, 261-267.

Tang, Y., Chen, Z., Tao, H., Li, C., Zhang, X., Tang, A., & Liu, Y. (2014). Oxytocin activation of neurons in ventral tegmental area and interfascicular nucleus of mouse midbrain. *Neuropharmacology*, *77*, 277-284.

Theodoridou, A., Rowe, A. C., Penton-Voak, I. S., & Rogers, P. J. (2009). Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. *Hormones and Behavior*, *56*, 128-132.

Uvnäs-Moberg, K. (1998). Oxytocin may mediate the benefits of positive social interaction and emotions. *Psychoneuroendocrinology*, *23*, 819-835.

Vanderbilt, K. E., Liu, D., & Heyman, G. D. (2011). The development of distrust. *Child Development*, *82*, 1372-1380.

Veroude, K., Jolles, J., Croiset, G., & Krabbendam, L. (2013). Changes in neural mechanisms of cognitive control during the transition from late adolescence to young adulthood. *Developmental Cognitive Neuroscience*, *5*, 63-70.

Vijayakumar, N., Whittle, S., Yücel, M., Dennison, M., Simmons, J., & Allen, N. B. (2013). Prefrontal Structural Correlates of Cognitive Control during Adolescent Development: A 4-Year Longitudinal Study. *Journal of Cognitive Neuroscience, 26,* 1118-1130

Viviani, D., Terrettaz, T., Magara, F., & Stoop, R. (2010). Oxytocin enhances the inhibitory effects of diazepam in the rat central medial amygdala. *Neuropharmacology*, *58*, 62-68.

Waldherr, M., & Neumann, I. D. (2007). Centrally released oxytocin mediates mating-induced anxiolysis in male rats. *Proceedings of the National Academy of Sciences*, *104*, 16681-16684.

Warneken, F., & Tomasello, M. (2008). Extrinsic rewards undermine altruistic tendencies in 20-month-olds. *Developmental Psychology*, *44*, 1785.

Warneken, F., & Tomasello, M. (2009). Varieties of altruism in children and chimpanzees. *Trends in Cognitive Sciences*, *13*, 397-402.

Windle, R. J., Shanks, N., Lightman, S. L., & Ingram, C. D. (1997). Central Oxytocin Administration Reduces Stress-Induced Corticosterone Release and Anxiety Behavior in Rats 1. *Endocrinology*, 138, 2829-2834.

Xiao, C., & Ye, J. H. (2008). Ethanol dually modulates GABAergic synaptic transmission onto dopaminergic neurons in ventral tegmental area: role of μ-opioid receptors. *Neuroscience*, *153*, 240-248.

Young, L. J., & Wang, Z. (2004). The neurobiology of pair bonding. *Nature Neuroscience*, *7*, 1048-1054.

Zak, P. J., Stanton, A. A., & Ahmadi, S. (2007). Oxytocin increases generosity in humans. *PLoS One*, *2*, e1128.

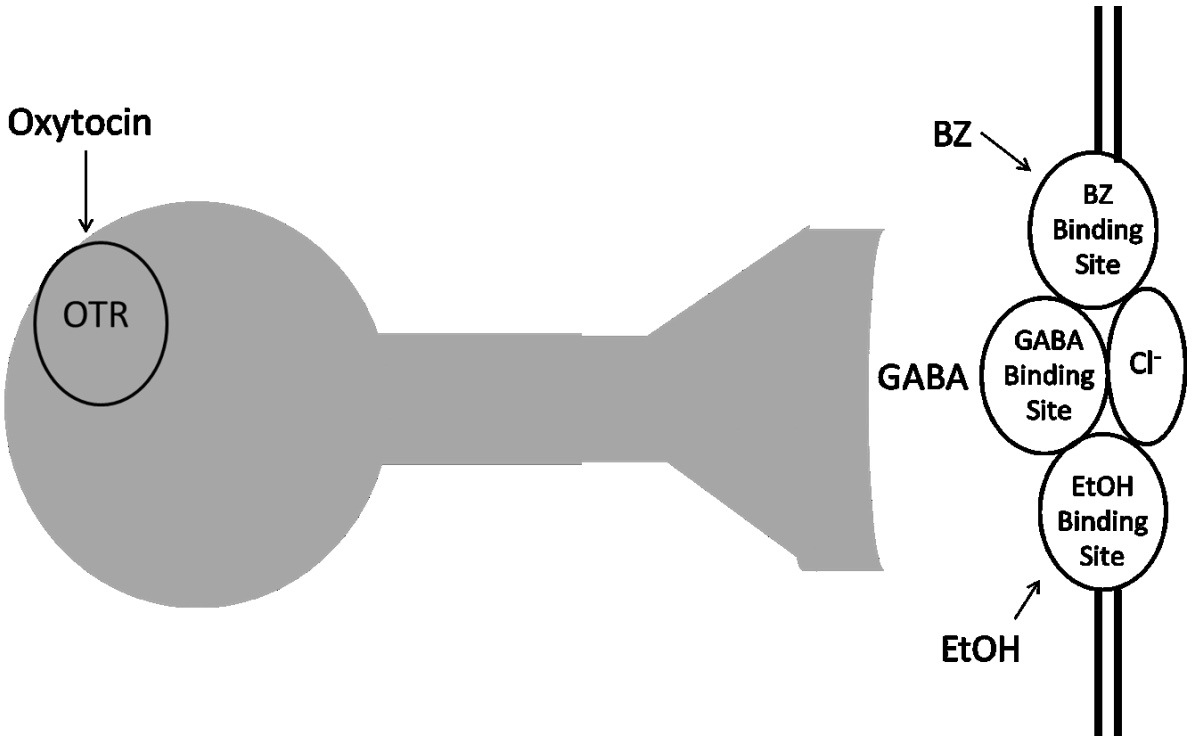

Figure 1
Cartoon to illustrate the amygdala circuitry underlying OT and GABA mediated neurotransmission.

Oxytocin acts at presynaptic oxytocin receptors to induce a massive release of GABA from neurons in the central amygdala nuclei, while both benzodiazepines and alcohol act synergistically with GABA post-synaptically (Viviani et al., 2010). Both mechanisms will result in opening of the GABA-A receptor associated chloride ion channel and so lead to inhibition of the postsynaptic neuron. Equivalent circuits can be found in the prefrontal cortex.