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# Oxytocin, testosterone, and human social cognition

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ABSTRACT

I describe an integrative social-evolutionary model for the adaptive significance of the human oxytocinergic system. The model is based on a role for this hormone in the generation and maintenance of social familiarity and affiliation across five homologous, functionally similar, and sequentially co-opted contexts: mothers with offspring, female and male mates, kin groups, individuals with reciprocity partners, and individuals within cooperating and competing social groups defined by culture. In each situation, oxytocin motivates, mediates and rewards the cognitive and behavioural processes that underlie the formation and dynamics of a more or less stable social group, and promotes a relationship between two or more individuals. Such relationships may be positive (eliciting neurological reward, reducing anxiety and thus indicating fitness-enhancing effects), or negative (increasing anxiety and distress, and thus motivating attempts to alleviate a problematic, fitness-reducing social situation). I also present evidence that testosterone exhibits opposite effects from oxytocin on diverse aspects of cognition and behaviour, most generally by favouring self-oriented, asocial and antisocial behaviours. I apply this model for effects of oxytocin and testosterone to understanding human psychological disorders centrally involving social behaviour. Reduced oxytocin and higher testosterone levels have been associated with under-developed social cognition, especially in autism. By contrast, some combination of oxytocin increased above normal levels, and lower testosterone, has been reported in a notable number of studies of schizophrenia, bipolar disorder and depression, and, in some cases, higher oxytocin involves maladaptively 'hyper-developed' social cognition in these conditions. This pattern of findings suggests that human social cognition and behaviour are structured, in part, by joint and opposing effects of oxytocin and testosterone, and that extremes of such joint effects partially mediate risks and phenotypes of autism and psychotic-affective conditions. These considerations have direct implications for the development of therapies for alleviating disorders of social cognition, and for understanding how such disorders are associated with the evolution of human cognitive-affective architecture.

*Key words*: oxytocin, testosterone, social cognition, autism, schizophrenia, depression.

CONTENTS



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## I. INTRODUCTION

Hormones with effects in the brain modulate physiology, emotions, cognition, and behaviour, without the necessity for conscious input or control (e.g. Vitzthum, 2009; Putnam & Roelofs, 2011). As such, hormone systems modify the allocation of attentional, cognitive, behavioural and energetic resources in relation to different externally directed and internal functions, in ways that are expected to be adaptive in the contexts of changing organismal condition as well as environmental contexts. Any given hormone can thus be said to have some set of coherent functions, both physiological and evolutionary (fitness-related), across particular ecological and behavioural situations.

The neuropeptide hormone oxytocin has recently been the subject of intense and increasing interest, especially in the fields of endocrinology, neuroscience, psychology, and psychiatry, since its remarkable effects on social behaviour were first described (Bethlehem *et al.*, 2014; Carter, 2014). A considerable proportion of this work has been focused on discerning what are considered to be the primary cognitive, emotional, social and behavioural functions of this hormone, especially in humans, with an eye to uncovering the roles of oxytocin in psychiatric disorders and human well-being more generally (e.g. Bartz *et al.*, 2011). Most of this research centres on proximate mechanisms and psychologically-based behavioural experiments, while relatively little takes an evolutionary perspective beyond the proposition of specific arenas for its effects, such as maternal care, pair-bonding, or affiliative behaviours, that are presumed to have adaptive significance in particular situations (e.g. Ebitz, Watson & Platt, 2013; Ebitz & Platt, 2014). The study of oxytocin thus provides excellent opportunities for furthering integration of proximate with ultimate evolutionary approaches in endocrinology, with clear implications for human health as well as for understanding the selective pressures that underlie the evolution of complex human sociality.

The purpose of this review is to propose and evaluate a synthetic, integrative model for the adaptive significance of the oxytocinergic system in humans, that synthesizes social-evolutionary with psychological approaches, and helps to reconcile the diverse and sometimes paradoxical research findings that typify the study of this hormone. Understanding of the adaptive functions of oxytocin, in the contexts of other hormonal systems, also represents a prerequisite to discerning the roles of oxytocin in the evolution of human social behaviour, and in psychiatric disorders that centrally involve social cognition. The model is based squarely on previous work, but seeks to extend it through further application of social-evolution theory, and theory for understanding disorders of human social cognition, in this context.

I first briefly describe how the oxytocin system works, physiologically. Next, I explain the evolutionary origins and dynamics of the oxytocinergic system in mammals, because this evolutionary history has important implications for how oxytocin levels, and reactivity, affect the processing and deployment of fitness-salient information across diverse social situations. Third, I provide a brief overview of current hypotheses for the primary functions of oxytocin, from psychological, neurological, and endocrinological perspectives, and explain which empirical findings do, and do not, support these hypotheses. I then present and explicate a model that can help to integrate and extend this previous work by describing a social-evolutionary framework for how oxytocin modulates social behaviour, and how testosterone exhibits a large suite of cognitive and behavioural functions that are opposite to those of oxytocin. The model helps to clarify the general role of oxytocin in mediating the formation, and forms, of fitness-salient social relationships. Next, in the context of this model, I discuss relevant literature on the roles of oxytocin and testosterone in disorders of human social cognition, mainly autism spectrum disorders and psychotic-affective disorders (primarily schizophrenia, bipolar disorder, and depression), based on the hypothesis that autism involves under-developed social cognition, while psychotic-affective conditions involve, in part, dysfunctionally increased aspects of social cognition. I conclude with discussion of applied implications, and suggestions for continued integration of proximate with ultimate approaches in the study of human neuroendocrine systems.

## II. THE PHYSIOLOGY AND NEUROBIOLOGY OF OXYTOCIN

Oxytocin is produced primarily in the hypothalamus. It is released into both the brain, where it influences neurotransmission in affiliative, reward-related and other pathways (Knobloch & Grinevich, 2014), and into the peripheral circulation, where it regulates aspects of parturition and lactation (Gimpl & Fahrenholz, 2001). In both the brain and the body, oxytocin exerts its influences through binding to oxytocin receptors and stimulation of intracellular signalling cascades.

Behavioural, brain-based effects of oxytocin include modulation of maternal behaviour, infant behaviour, social bonding, sexual and agonistic behaviour, group membership, feeding, stress, and anxiety (De Dreu, 2012; Bethlehem *et al.,* 2014; Carter, 2014). These effects are organized mainly through the brain distributions and densities of oxytocin receptors, which vary both among species that differ in their social behaviour, and within species, across developmental stages and different social and reproductive contexts, and between the sexes (Ophir *et al.,* 2012); variation in such receptors, and their tissue-specific regulation, modulates the highly pleiotropic effects of oxytocin. The oxytocinergic system also exhibits strong functional linkages with the dopaminergic and opioid systems in the brain (whereby it affects reward circuitry), with the closely related neuropeptide hormone arginine vasopressin and with the steroid hormones testosterone and oestrogen (van Anders, Goldey & Kuo, 2011), as discussed in more detail in Section V.

Oxytocin has been considered, most generally, as a hormonal mediator of prosocial behaviour, through its effects in increasing social salience (the degree to which a stimulus is chosen for attention), social motivation, social bonding, and social reward (MacDonald & MacDonald, 2010; Gordon *et al.,* 2011; Bethlehem *et al.,* 2014). However, more precise specification of how it modulates, and responds to, changes in social contexts, behaviour and cognition is required to understand the adaptive significance of its dynamics, and how they become dysregulated in human psychiatric conditions.

## III. THE EVOLUTIONARY BIOLOGY OF OXYTOCIN

### (1) Origin and evolution of oxytocin

The neuropeptide precursors and homologues of oxytocin and vasopressin evolved over 700 million years ago, but the origin of oxytocin itself traces to the evolution of placental mammals. Some marsupials, such as opossums and bandicoots, thus secrete both oxytocin and its evolutionary precursor mesotocin, while in eutherian mammals only oxytocin is produced (Acher & Chauvet, 1995). This phylogenetic trajectory illustrates a key feature of evolutionary change in phenotypes, including hormonal systems: descent with modification, such that 'new' phenotypes must, despite their novel features, always show step by step functional and structural continuity with phenotypes previously extant.

The evolutionary origin of oxytocin production in mammals thus coincides, broadly, with the origins of placentation, viviparity, lactation, and behavioural maternal care after parturition. In turn, extended mother–offspring social interaction has been viewed as a primary driver of brain expansion and reorganization, especially involving the neocortex, with the origin of placental mammals (Rowe, Macrini & Luo, 2011). The continuity of oxytocin's role in this process stems from its ancestral functions in smooth muscle contraction, which were co-opted to serve in uterine contraction for parturition, and contraction of breast tissue to expel milk for lactation (Gimpl & Fahrenholz, 2001). Viviparity, lactation, and other aspects of maternal care also involve expansion of brain functions, coordinated in part by oxytocin (and other hormones) that jointly orchestrate birth, maternal care, lactation, and offspring behaviour with regard to the mother (Anacker & Beery, 2013). As such, oxytocin production in the context of peripheral reproductive functions evolved, *via* co-option of function, to also serve as a coordinator of novel neurobehavioural functions intimately tied to newly evolved and elaborated mammalian maternal care. This co-option may have initially evolved simply *via* release of oxytocin into cerebrospinal fluid and expression of oxytocin receptors on neurons, leading to a role in neurotransmission (Knobloch & Grinevich, 2014); indeed, mesotocinergic neuronal projections to the forebrain are found in some reptiles, and such neurons appear to regulate behaviours related to nesting (Carr, Messinger & Patton, 2008; Knobloch & Grinevich, 2014).

### (2) Early and co-opted functions of oxytocin

The neurological and behavioural functions of oxytocin among early mammals would presumably have been restricted to mother–offspring relationships (Fig. 1), centring on (*i*) social recognition of one's own pups, and the subsequent formation of a social bond and basic psychological attachment, which in behavioural-ecological terms represents kin recognition, and (*ii*) pup grooming, huddling, retrieval, and defence, as well as behaviours associated directly with birth and lactation (Ferguson, Young & Insel, 2002). This suite of behaviours is coordinated, in large part, through pup–mother behavioural interactions, which serve as cues and are mediated by effects of oxytocin in the pups, who ingest this hormone in breast milk, as well as synthesizing it in response to maternal contact

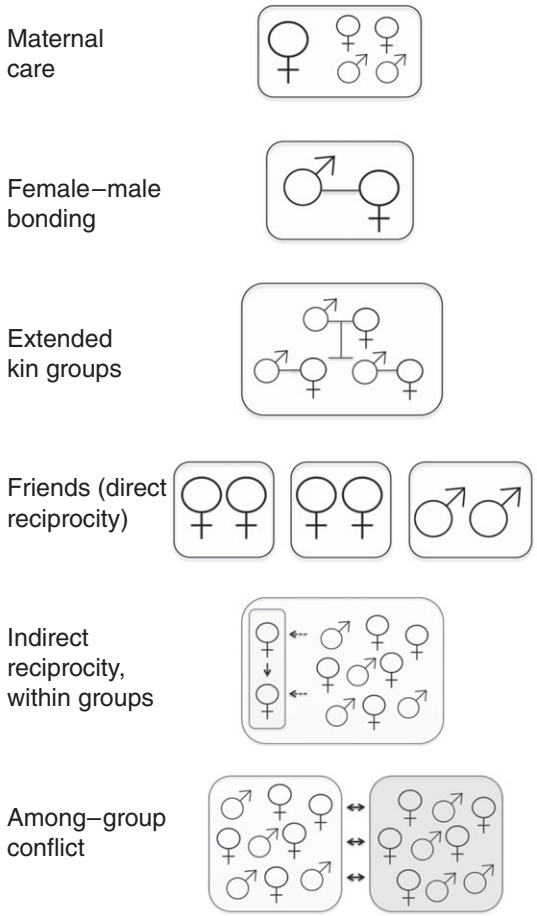


**Fig. 1.** Social-evolutionary contexts for the adaptive significance of oxytocin in its mediation of social cognition and bonding. The original function of oxytocin in maternal care among early mammals has been co-opted and elaborated to serve in female–male bonding, bonding within extended kin groups (such as cooperatively-breeding and communal forms), and bonding among friends (unrelated allies engaging in social reciprocity). Among humans, oxytocin also modulates social aspects of indirect reciprocity (morality), and bonding among ingroup members in the context of conflict with outgroups. In all of these circumstances, oxytocin regulates social attention, recognition, information processing, and relationship dynamics.

and sucking (Gordon *et al.*, 2011). In turn, milk production rates are regulated by the frequency and intensity of sucking, which is mediated by levels of maternal oxytocin. Maternal supply (of food as well as care) can thus be more or less 'automatically' coordinated with offspring demand, at least within some homeostatic bounds. Such mother–offspring dynamics, and their endocrine bases, appear to be highly conserved across all mammals, including humans (Rilling, 2013).

Motivation for maternal care, and offspring solicitation of care, derives from oxytocin in part *via* its links with brain reward systems, especially the midbrain dopaminergic pathway that activates the nucleus accumbens (Dölen *et al.*, 2013; Love, 2014). Natural selection is expected to have favoured such reward systems as quantitative indicators of behaviour that is associated with increases in correlates and components of survival and reproduction. Most generally, such systems are activated when behaviour is expected to lead, or has led historically, to higher inclusive fitness, considered as own reproduction plus effects on reproduction of kin, discounted by the degree of genetic relatedness (Hamilton, 1964; Nesse, 2004; Costa, 2013). Oxytocin indeed also functions as a satiety signal in the context of infant sucking, as well as regulating the ingestion of hedonically-activating foods such as fructose (Ott *et al.*, 2013; Sabatier, Leng & Menzies, 2013). In humans as well as other socially-interacting mammals, feeding thus represents, in part, a social behaviour mediated by oxytocin: for example, levels of plasma oxytocin in dairy calves are significantly higher when they suckle from their mother than when they drink the same milk from a bucket (Lupoli *et al.*, 2001), and in chimpanzees, elevated levels of oxytocin are associated with the sharing of food (Wittig *et al.*, 2014).

A second context for the functions of oxytocin, female–male pair-bonding (Fig. 1), comes from a social context that differs considerably from maternal care, but shares with it a large suite of core features including social recognition, familiarity, formation of a cooperating social group, defence, and reproduction. Whereas female to male bonding appears to be mediated predominantly by oxytocin, male to female bonding more strongly involves the closely related peptide hormone arginine vasopressin (Keverne & Curley, 2004). The mediation of male bonding and care (in part) by a different, but related neuropeptide apparently reflects sexually-selected differences between the sexes, in that male behaviour involves sharp trade-offs between fitness through parental care and fitness through promiscuity. This hypothesis is supported primarily by studies that link genetic variation in the arginine vasopressin receptor gene AVPR1A with both social bonding and correlates of male promiscuity, in humans and voles (Hammock & Young, 2006; Walum *et al.*, 2008).

Among females, the oxytocinergic system has thus, by neurological as well as endocrinological evidence, been co-opted to serve in a social context that is novel (pair bonding) but involves the same set of behavioural features as the mother–offspring relationship. In such circumstances, females must successfully navigate two sets of social relationships: with offspring and with their mate, imposing additional selection for sophistication of oxytocin-mediated social cognition and behaviour. In this regard, the best comparative correlate of neocortical social-brain enlargement in most mammals is the presence of pair-bonding and some degree of monogamy, rather than social group size itself (Dunbar, 2009). By contrast, among primates, sociality appears to be based predominantly on bonded relationships

comparable in sophistication to those in non-primate pair-bonded taxa, that have been extended to include many members of one's social group (Dunbar & Shultz, 2007; Dunbar, 2009).

The mammalian radiation led in diverse lineages to even more complex, cooperating social groups, including (*i*) so-called communal or cooperatively-breeding groups structured primarily by kinship, (*ii*) small groups, often dyads, of unrelated individuals who serve as reciprocating allies ('friends') to one another, and (*iii*) larger groups, of kin and non-kin, whose identities are defined by group-specific properties such as a territory and, in humans, aspects of culture and direct as well as indirect reciprocity (i.e. morality) (Alexander, 1987; Clutton-Brock, 2009; Anacker & Beery, 2013; Chapais, 2013) (Fig. 1). Each of these contexts, like maternal care, centrally involves explicit or implicit social recognition, attachment, social cooperation (as well as competition), defence of social resources against non-group members, social reward systems that drive fitness-salient social behaviours, and the creation and navigation of a social group of some kind, of two or more individuals. As such, the oxytocinergic system has apparently been co-opted strongly to modulate all of these social situations, in each case mediating not just the formation and maintenance of a social group, but also the social dynamics within groups that impact upon relationships, and the social-cognitive and emotional processes within each group member (Fig. 1). Most generally, in mammals oxytocin thus orchestrates the formation, maintenance and dynamics of either actual families, or 'psychological kinship' (Bailey & Wood, 1998) systems of direct and indirect reciprocity (Alexander, 1987; Zak & Barraza, 2013), in each case generating 'us and them' dynamics (De Dreu, 2012). These arenas of evolutionary co-option matter because they show how similar humans are to other mammals in fundamental endocrinological ways, and how some key, elaborated human phenotypes, such as systems of indirect reciprocity (morality), extensive ingroup–outgroup relationships in fission–fusion cultural and social contexts, and extensive cooperation to compete (in group *versus* group play, and in forms of social antagonism including warfare), show both continuity and divergence with regard to other mammals, in their endocrine bases. Among humans, oxytocin is also apparently represented culturally by specific words (e.g. 'hygge' in Danish and 'gemütlichkeit' in German) whose meanings correspond closely to its documented endocrine effects (e.g. Linnet, 2011).

### (3) Oxytocin, cooperation, and competition

Across all of the arenas described above, oxytocin, and arginine vasopressin are each involved in mediating both prosocial, cooperative behaviour within a dyad, family or ingroup, and agonistic behaviour directed towards non-group members, because cooperation always generates a valuable social resource for which other individuals are selected to compete (Crespi & Choe, 1997). Under basic social-evolutionary theory, cooperation only evolves in contexts of such behaviour being favoured in competition with other individuals, dyads, or groups. As such, oxytocin and arginine vasopressin are each expected to modulate both cooperative and competitive behaviours, depending on the nature of interaction partners with regard to sex, dyad, family or group membership, and dominance (van Anders *et al.,* 2011; Bartz *et al.,* 2011); such patterns are indeed observed (e.g. Bosch & Neumann, 2012), but have yet to be considered in social-evolutionary contexts. Males and females in particular are expected, under social-evolution theory and considerations from sexual selection, to differ profoundly in the dynamics of their oxytocinergic and arginine-vasopressin-mediated systems, given their divergent social and non-social avenues for maximizing inclusive fitness in socially selected contexts. Such sex differences, including many effects that are opposite between males and females, are commonly observed (e.g. Rilling *et al.,* 2014), although they have yet to be systematically addressed from perspectives based on adaptive significance.

I present this social-evolutionary perspective on the oxytocinergic system to help to understand its roles better in the most complex of all social animals, humans. The primary usefulness of this evolutionary exposition comes from comparing it with current viewpoints on oxytocin functions from psychological, endocrinological, neurological and psychiatric perspectives, to help in reconciling the diverse findings and theories that characterize this area of research.

## IV. THE PSYCHOLOGY AND SOCIAL NEUROENDOCRINOLOGY OF OXYTOCIN

### (1) Models for the adaptive social significance of oxytocin

Initial views of oxytocin as an exclusively prosocial hormone (e.g. MacDonald & MacDonald, 2010) were soon supplanted by findings that intranasal oxytocin administration can produce 'antisocial' effects in some contexts, such as elicitation of ethnocentrism (De Dreu *et al.,* 2011; Sheng *et al.,* 2013), or increased dishonesty towards outgroup members (Shalvi & De Dreu, 2014). These divergent results have motivated attempts to determine a primary, unitary cognitive-affective role of oxytocin, mainly by integrating information from experimental psychological studies of humans with endocrinological and neurological analyses of rodents, especially mice, rats, and vole species that differ in their social systems (e.g. Kemp & Guastella, 2011; Bethlehem *et al.,* 2014; Ebitz & Platt, 2014).

Three major, non-exclusive psychologically-based hypotheses have been proposed to characterize the

social functions of the oxytocinergic system (Bethlehem *et al.,* 2014). First, oxytocin is considered to increase the salience (attentional importance) of social stimuli, by increasing sensitivity to, and attention towards, socially relevant environmental cues (e.g. Bartz *et al.,* 2011; Striepens *et al.,* 2012; Wittfoth-Schardt *et al.,* 2012). This hypothesis is supported by a broad swath of evidence, such as increased attention to the eye region of faces (Guastella, Mitchell & Dadds, 2008), and increased empathy (Domes *et al.,* 2007; Palgi, Klein & Shamay-Tsoory, 2014) after oxytocin administration, the tendency for oxytocin administration to magnify and intensify existing prosocial tendencies (Bartz *et al.,* 2011; Olff *et al.,* 2013), oxytocin effects in facilitating memory of faces (Savaskan *et al.,* 2008), and associations of single nucleotide polymorphism variation in the oxytocin receptor gene OXTR with measures of social recognition, cooperation and empathy (Skuse *et al.,* 2014). In contrast to such effects, however, oxytocin may also lead to reduced attention to social cues, at least under conditions where high social vigilance may no longer be as productive as other activities (Ebitz & Platt, 2014).

Second, oxytocin is proposed to have a predominant anxiolytic (anxiety-reducing) function, such that it promotes reduced attention and reactivity to social threats, apparently by indicating socially safe or favourable circumstances (Bethlehem *et al.,* 2014). This hypothesis is supported by a large body of literature showing that experimental oxytocin administration is associated with reduced anxiety (e.g. Neumann & Landgraf, 2012), and by the inference that oxytocin may buffer stress responses and thus facilitate social amelioration of adverse and challenging situations (e.g. Heinrichs & Domes, 2008). These results, however, remain subject to the caveat that a large set of literature indicates that higher plasma oxytocin levels can be associated with increased anxiety, at least in some circumstances (e.g. Pierrehumbert *et al.,* 2010; Seltzer *et al.,* 2014). For example, replicated studies have demonstrated higher plasma oxytocin, and higher anxiety, among humans subject to social distress (Table 1), and among rodents in some stressful conditions (e.g. Pierrehumbert *et al.,* 2010). The associations of stress and anxiety with oxytocin, and their joint roles in modulating social behaviour, thus remain unclear.

Third, studies of humans and rodents have demonstrated that, as discussed briefly above, oxytocin mediates social reward sensitivity (Bethlehem *et al.,* 2014), by increasing the reward value of social stimuli. Such increases in reward sensitivity lead to positive fitness-enhancing social interactions, including, for example, preference, mutualism and altruism towards offspring, social mates, allies and one's ingroup as well as one's self in socially competitive contexts (De Dreu, 2012; Ten Velden *et al.,* 2014). This hypothesis is strongly supported by neurological evidence (Groppe *et al.,* 2013), but it does not address the potential roles of oxytocin in the converse of social reward, negative social experiences (other than anxiety) that impact within pairs or groups, which should be at least of comparable importance in modulating the fitness-related behaviour of humans and other mammals.

As noted by Bethlehem *et al.* (2014), these three hypotheses, social salience, anxiety reduction, and social reward sensitivity, are not mutually exclusive, and can indeed be integrated into an explanatory framework, whereby oxytocin increases social reward sensitivity, decreases stress and anxiety, and thereby

Table 1. Evidence that higher plasma oxytocin levels are associated with higher anxiety or higher levels of interpersonal distress

| Findings | References |
|---|---|
| Higher plasma oxytocin associated with higher interpersonal distress, among non-clinical females | Turner *et al.* (1999) |
| Higher plasma oxytocin associated with higher anxiety regarding romantic attachments, among non-clinical females and males | Marazziti *et al.* (2006) |
| Higher plasma oxytocin associated with higher relationship stress, among non-clinical post-menopausal women | Taylor *et al.* (2006) |
| Higher plasma oxytocin associated with higher social anxiety, and higher relationship distress, among individuals with Generalized Anxiety Disorder | Hoge *et al.* (2008) |
| Higher plasma oxytocin associated with higher pair-bond distress, among non-clinical females | Taylor, Saphire-Bernstein & Seeman (2010) |
| Higher plasma oxytocin reactivity associated with higher relationship distress, higher anxiety, and less forgiveness, among non-clinical females | Tabak *et al.* (2011) |
| Oxytocin administration associated with increased anxiety when subject to unpredictable experimental threat, among non-clinical individuals | Grillon *et al.* (2013) |
| Oxytocin associated with active social coping in novel, stressful social situations, among non-clinical females | Tops *et al.* (2013) |
| Higher plasma oxytocin associated with higher attachment anxiety, among non-clinical females | Weisman *et al.* (2013) |

enhances social cognition. Can the components of this framework be unified, though, in the context of the social-evolutionary perspectives described above?

### (2) A unified model of oxytocin social functions

I describe a simple model for the role of oxytocin in motivating and modulating social behaviour, which is based on social-evolution theory, the functional, phylogenetically-based commonalities of social contexts among mammals, and the findings from psychology, endocrinology and neuroscience as described above. The goal of the model is to explain, in principle, the diversity of oxytocin effects, to understand better the variation among neurotypical humans in social cognition and behaviour, and to guide analyses of health-related situations where the oxytocin system appears to have become dysregulated in some manner.

By this model, the main cognitive-affective function of oxytocin is hormonally to indicate and quantify, to relevant regions of the brain, that some socially important event may happen, is happening, or has happened, and that one should focus on it, plan regarding it, and remember it because it is expected to influence one's social relationships and socially-mediated inclusive fitness, positively or negatively (Fig. 2). Increased oxytocin is thus expected to be associated, transiently or in the longer term, with stronger emphasis on social recognition, social relationships, and intensification of social emotion and cognition, including not just affiliative emotion, but also complex social emotions (that may also influence affiliative ties) such as pride, guilt, envy, embarrassment, contempt, shame and remorse – oxytocin's own 'seven deadly sins'. Contexts include offspring, potential and actual mates, friends, social groups at any scale, and introspective social cognition regarding significant others. The valence of oxytocin-increased social cognition and emotion may be positive or negative, depending upon the fitness benefits and costs of affiliation-related behaviour in any particular situation (Bartz *et al.,* 2011). Indeed, with regard to relative fitness in socially interacting pairs, groups and larger populations, not being 'with me' often means, potentially or actually, being 'against me'.

### (3) Oxytocin and mentalizing

Under the model depicted in Fig. 2, the mechanism of oxytocin functions centrally involves activation of the neural systems that subserve mentalizing, broadly construed as engaging in social, compared to non-social, cognition, and making sense of each other, and ourselves, in terms of subjective empathic and cognitive states (Fonagy, Gergely & Jurist, 2002; Bateman & Fonagy, 2012). In neurological terms, the model thus involves oxytocin-induced lowering of thresholds for activation of social-brain regions of the cortex, including regions involved in affiliative emotion (Bethlehem *et al.,* 2013; Rocchetti *et al.,* 2014). Such oxytocin-administration effects on activation of human social brain regions (brain areas that subserve the acquisition, processing and use of social information) have been best studied in the context of autism; thus, three recent studies have demonstrated strong oxytocin-induced increases in activation of specific cortical social-brain areas (Gordon *et al.,* 2013; Domes *et al.,* 2014; Watanabe *et al.,* 2014), especially in regions of the medial prefrontal cortex that regulate processes related to theory of mind (Amodio & Frith, 2006). In contrast to this increased activation of brain regions that underpin social cognition, oxytocin administration tends to dampen activation of the amygdala for negative emotions, thus reducing perception and processing of fear, stress and anger (e.g. Gamer, Zurowski & Büchel, 2010). Oxytocin administration also leads to increased functional connectivity between the amygdala and some social-brain regions such as the orbitofrontal cortex (Riem *et al.,* 2012; Sripada *et al.,* 2013), which may serve to foster the controlled mentalization that leads to enhanced, more-deliberative social decision-making; by direct contrast, testosterone reduces functional connectivity between these regions (Volman *et al.,* 2011; Spielberg *et al.,* 2014) and is thereby expected to reduce controlled mentalization, in contexts where aggressive behaviour is favoured over affiliation or cooperation. Such opposite, 'anticorrelated' activation patterns have also been reported for the ventromedial prefrontal cortex (a key social-brain region that regulates social emotionality) in relation to the amygdala (e.g. Stanton *et al.,* 2009), and more broadly for the 'default network' of the brain that subserves many social, mentalistic, and introspective cognitive systems, compared to the 'task-positive' network that is dedicated to mechanistic, non-social cognitive processing (Jack *et al.,* 2012; Kubit & Jack, 2013). By this model, oxytocin thus represents, most simply, a hormone that promotes social cognition and mentalizing, in contexts that are both simple (such as positive affiliation, emotion recognition, affective empathizing, or individual recognition) and more complex (such as theory of mind, complex social emotionality, or ingroup–outgroup balances of cooperation and competition), and may be transient or longer lasting. Dependency of prosocial oxytocin effects on social information is clearly exemplified in a study by Declerck, Boone & Kiyonari (2010), who found that in two cooperative games, oxytocin administration led to increased cooperation when social information was present, but reduced cooperation when it was not.

### (4) Positive *versus* negative valence to oxytocin modulation of social behaviour

Social interactions and relationships mediated by oxytocin can, of course, be either positive, negative or uncertain with regard to effects on one's inclusive fitness. They may also be simple and predictable, or

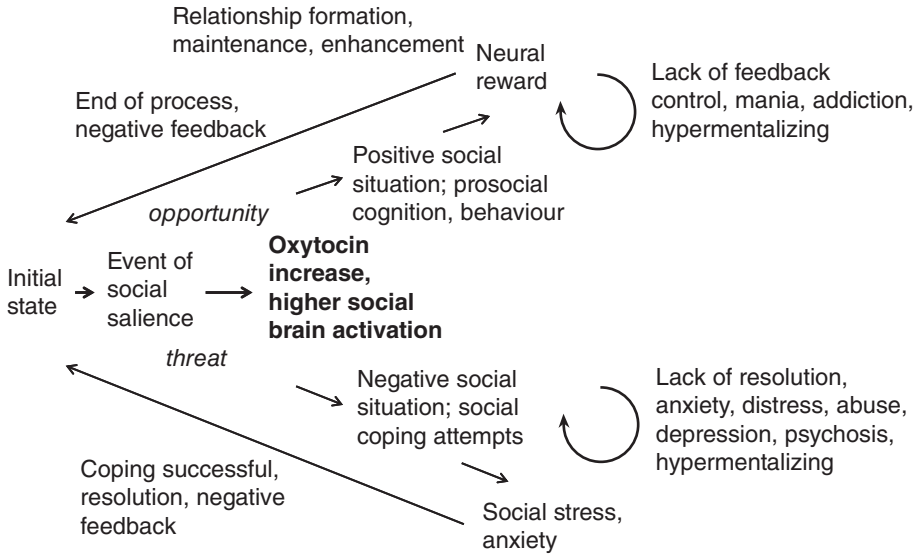


**Fig. 2.** Model for the roles of oxytocin in normal and dysregulated human social cognition. Oxytocin is secreted in response to some event of social salience, and it lowers thresholds for activation of social-brain regions of the neocortex. Positive, fitness-enhancing social situations involve neural reward and anxiety reduction *via* its effects, though prosocial bonding on the formation, maintenance and enhancement of relationships. Negative social situations elicit oxytocin production in the context of motivation for social coping attempts to alleviate deleterious circumstances, commonly involving stress and anxiety. Autism involves under-developed social cognition, and reduced function of the oxytocin system. By contrast, under this model, psychotic-affective conditions (mainly schizophrenia, bipolar disorder, and depression) can involve, in part, maladaptively hyper-developed social-cognitive phenotypes, and loss of regulatory feedback control of oxytocinergic modulation for social cognition, affect and behaviour.

complex, long-term, and difficult to resolve in any favourable way. With regard to prosocial, positive interactions, which represent forms of mutualism or altruism commonly directed towards actual or 'psychological' kin, oxytocin is expected to both motivate and reward the behaviour, through effects on increased social-brain and reward-system activation that hormonally indicate beneficial effects. In humans, most day to day social interactions are indeed expected to be positive and largely cooperative, taking place within social groups (family, friends, and ingroup members) with whom one shares different types of bonds that support mutualistic and altruistic behaviour. Such circumstances should also involve reductions in stress and anxiety (and thus lower oxytocin in socially safe and stable situations) that would, if present, indicate an unresolved, uncertain, actually or potentially fitness-reducing social situation. Oxytocin should thus, under this model, also be adaptively increased under problematic social circumstances because it focuses attention on social coping mechanisms and attempts to reach conditionally optimal solutions (Tops *et al.,* 2013); such increases may, moreover, be sustained for relatively long periods if the challenging circumstances persist. This hypothesis is concordant with recent findings that oxytocin administration increases anxiety in the context of unpredictable threats (Grillon *et al.,* 2013), and with the associations between oxytocin and relationship distress that are discussed in more detail in Section VI.

Under this framework, anxiety-associated effects of oxytocin should be restricted to situations where an individual is actively striving socially, or is faced with uncertainties that motivate the gathering and processing of social information (Declerck *et al.,* 2010), in both cases with the goal of resolving the problems in a prosocial or socially dominant, manner. In endocrinological terms, the model thus predicts increases or decreases in stress-associated cortisol levels (or stress more generally), depending on the nature and valence of the social stimuli and context. Social reward sensitivity should be increased by oxytocin in positive social situations because it facilitates social behaviour that leads to increased inclusive fitness. By contrast, in social deleterious yet unresolved situations, individuals should exhibit increased sensitivity to social 'punishment' (negative impacts on well-being), with continued expression of oxytocin-mediated social vigilance and mentalizing until a situation becomes more or less resolved. Not just social reward, but also social anxiety and stress, can thus adaptively motivate, with oxytocin providing the social focus to strive optimally for the best possible outcome, at least in neurotypical individuals (Cardoso *et al.,* 2013; Tops *et al.,* 2013).

This perspective makes clear predictions with regard to the anxiolytic (anxiety-reducing), compared to anxiogenic (anxiety-causing), effects of oxytocin, which show notable support from the literature. Most notably, higher plasma oxytocin has been linked with higher

distress or anxiety in some close social relationships, especially among females in the context of pair bonds with males (Table 1), although also in other relationships such as mothers with infants (MacKinnon *et al.,* 2014) and in the context of attachment anxiety (Weisman *et al.,* 2013). The apparent concentration or restriction of such effects to females may be related to sex differences in the importance of close and mutually supportive social relationships, and generally higher impacts of such relationships on female than male fitness (Silk *et al.,* 2010). Although the results linking oxytocin with relationship distress are well replicated, they seldom include experimental administration studies; however, comparable effects have also been reported among female prairie voles *Microtus ochrogaster*, which show higher levels of plasma oxytocin, and depression-like symptoms, after experimental social isolation (Grippo, Cushing & Carter, 2007). In contrast to such male–female interactions, females also exhibit increased 'tend and befriend' social behaviour with other females, whereby oxytocin promotes affiliative social bonds that serve to reduce anxiety and promote resolution of problematic, fitness-reducing social situations (Taylor *et al.,* 2000; Cardoso *et al.,* 2013).

Under a social-evolutionary model for the modulatory effects of oxytocin in mammalian and human social interactions, oxytocin is thus released in response to some change in the social environment that is salient to effects on inclusive fitness (Fig. 2). If the social-environmental change is perceived as beneficial, some affiliative, prosocial behaviour is increased, and reward pathways are activated, indicating that the behaviour is normally associated with increased fitness. Such affiliative behaviour usually involves some degree of mentalizing (such as individual social recognition, affirmation or enhancement of affiliation, or complex social exchange of resources), such that oxytocin lowers thresholds for activation of relevant social-brain regions. Once the reward is achieved, or ongoing, stress levels are also reduced, the goals of the mentalizing system in this context having been achieved, and plasma oxytocin levels may be expected to decline by negative feedback as the system has served its immediate function in this context. This 'positive' pathway corresponds to the most commonly observed psychological functions of oxytocin, which involve affiliation, prosocial behaviour, and reduced anxiety. As discussed in more detail below, this pathway may also, however, involve oxytocin-mediated hyper-mentalistic cognition (especially among individuals who are already socially sensitive or vigilant), increased liability to addiction (whereby this reward system is exogenously stimulated) (e.g. Buisman-Pijlman *et al.,* 2014) and the increased expression of 'negative' social emotions such as pride or contempt, that reflect positively on the self and involve social affiliation that includes some degree of dominance. In this general context, hyper-mentalistic refers to expression of excessive theory of mind (Dziobek *et al.,* 2006; Crespi & Badcock, 2008; Sharp *et al.,* 2011) that involves making assumptions or inferences about the mental states of others that are 'so far beyond observable data that the average observer will struggle to see how they are justified', and thus involve over-attribution, misinterpretation, and biases (Sharp *et al.,* 2013, p. 4).

Negative social-environmental changes, or situations, also activate the oxytocinergic system, even if only to facilitate social recognition of an individual who has just exerted social dominance over oneself (Ebner *et al.,* 2000; Anacker & Beery, 2013), or to motivate re-establishment of social contact in isolated individuals (Grippo, Cushing & Carter, 2007). Like positive events, deleterious social events are also expected to activate the mentalizing system, but here in the context of increased anxiety and distress that motivate social cognition and behaviour geared towards coping with, alleviating, or avoiding socially-driven negative effects on inclusive fitness. Responses to such events may, of course, be more or less successful, and anxiety and distress (as well as high oxytocin) may be sustained, for some period of time, if the situation cannot be easily resolved. As described below, this pathway may also engender mild or more-severe depression (accounting, potentially, for cases of elevated oxytocin in this condition), as well as some social-emotional correlates of depression such as guilt, shame and embarrassment and high levels of pathological mentalizing more generally. This pathway can also help to explain associations of high plasma oxytocin with relationship distress, especially among females, noted above, although experimental studies are required to separate causes from effects, and evaluate the hypothesis that common causes predispose to high basal oxytocin as well as anxiety, distress and depression. One recent study, however, reported that oxytocin administration clearly increased the perception of social stress (as well as increasing activation in social-brain regions including the precuneus and cingulate cortex), in the absence of increases in serum cortisol (Eckstein *et al.,* 2014), suggesting a direct causal role in this context.

### (5) Oxytocin and socially-mediated aggression

A third, less-explored dimension for effects of oxytocin involves increases in social aggression, whereby this neuropeptide reduces thresholds for defence of one's family, social relationships, or larger social group (e.g. De Dreu *et al.,* 2012; Bosch, 2013). In humans, social aggression may involve increased mentalizing to the extent that it involves recognition, evaluation and affective reactivity to social threats, and modulates the expression of physical aggression in dyads or small groups, emotional, socially threatening or socially manipulative cognition and behaviour, and complex ingroup–outgroup social dynamics with competitive

elements. Oxytocin administration has thus been implicated in social competition or aggression across several contexts, including defence of one's close relationships (DeWall *et al.,* 2014), ethnocentrism (De Dreu *et al.,* 2011), and ingroup-serving dishonesty (Radke & de Bruijn, 2012; Shalvi & De Dreu, 2014). In humans, aggression towards outgroups is tightly coupled with enhanced ingroup bonding, often in the context of moral superiority of one's ingroup and moral condemnation or 'dehumanization' of others (Lahti & Weinstein, 2005; Jack, Dawson & Norr, 2013). Studies of ethnocentrism, parochial altruism, and moralistic judgments (e.g. De Dreu *et al.,* 2010; De Dreu, 2012; Stallen *et al.,* 2012; Walter *et al.,* 2012), suggest that oxytocin effects mediate such emotions and behaviour, presumably in conjunction with aggression and bonding effects from arginine vasopressin given that oxytocin can bind to, and stimulate, arginine vasopressin receptors to some degree (Tops & Carter, 2013). All of these cases can be interpreted in the general mammalian context of defending valuable social relationships and resources.

The model and considerations described above consider effects of oxytocin largely in isolation from other hormones, which is unrealistic given the integrated regulation of mammalian social behaviour by interacting systems of peptide and steroid hormones (van Anders *et al.,* 2011; Gordon *et al.,* 2011). How, and why, do such hormones modulate or suppress the effects of oxytocin?

## V. THE OPPOSITION OF OXYTOCIN AND TESTOSTERONE

As a steroid hormone, produced in the testis and adrenal glands, that regulates the development and expression of primary and secondary sexual characteristics, testosterone differs from oxytocin in notable ways. With regard to cognition and behaviour, testosterone exhibits 'organizational' effects on brain development during the fetal stage, with the ratio of testosterone to oestradiol mediating the degree and pattern by which a chromosomally 'male' brain differs neurologically from a chromosomally 'female' one (Auyeung, Lombardo & Baron-Cohen, 2013). After birth, and especially after puberty, testosterone from the testis and adrenal glands exerts 'activational' effects on cognition and behaviour, mainly through its binding to androgen receptors. Serum testosterone levels are much higher in males than females, in contrast to levels of serum (or cerebrospinal) oxytocin, which are usually, although not always, higher in females (who are not actively reproducing) (Altemus *et al.,* 1999; Carter, 2007; Pierrehumbert *et al.,* 2010; Weisman *et al.,* 2013). Indeed, three studies have noted that oxytocin administration raised male emotional or neural responses to social stimuli to the levels of those found in untreated females (Hurlemann *et al.,* 2010; Theodoridou, Rowe & Mohr, 2013; Rilling *et al.,* 2014).

Testosterone is usually considered in the context of competition, aggressive behaviour, dominance, enhanced spatial cognition, and other traits that exhibit apparent male biases in expression. As the functions of oxytocin have begun to emerge, several authors have suggested that it appears to manifest opposite cognitive effects to those of testosterone, although such apparent diametric features were not investigated in any comprehensive way (Auyeung *et al.,* 2009, 2013; Boksem *et al.,* 2013; MacDonald *et al*., 2013a). I do so here, in the framework of the adaptive significance of each hormonal system in regulating context-specific and sex-biased social cognition and behaviour.

Table 2 shows evidence from the literature regarding opposite effects of oxytocin and testosterone on the same cognitive and behavioural phenotypes, which was compiled using documented oxytocin effects as a guide to search the literature for effects of testosterone on the same phenotype. Opposite effects of oxytocin, compared to prenatal or postnatal testosterone, are evident for a remarkable range of phenotypes, almost none of which were described in the context of such a diametric-effect hypothesis. The one commonality that appears to unite these diverse phenotypic effects of testosterone is that they all involve increased non-social or antisocial cognition and behaviour, and reduced reliance on mentalistic processing of social information. One of the clearest examples of this pattern is the effect of testosterone administration in reducing connectivity of the orbitofrontal cortex (OFC) with the amygdala, connectivity that would enhance social-brain input into emotionally driven behaviour. As noted above, oxytocin exhibits the opposite effect, increasing OFC–amygdala connectivity. Comparable diametric effects are seen for actual performance in mentalistic, empathic tasks: for example, oxytocin administration, or high-oxytocin genotypes for single nucleotide polymorphisms in the oxytocin receptor gene, are associated with better performance on reading emotions from the eye region of faces (Domes *et al.,* 2007); by contrast, testosterone administration is associated with reduced performance on the same task, with even stronger effects when an indicator of higher prenatal testosterone is also taken into account (van Honk *et al.,* 2011). Testosterone administration also leads to reduced trust (Bos, Terburg & van Honk, 2010; Boksem *et al.,* 2013), in direct opposition to the effects of oxytocin that enhance it (Kosfeld *et al.,* 2005).

Such opposite effects, and emerging evidence for physiological mechanisms whereby these two hormone systems interact, are of considerable interest because they appear to define a pivotal axis of human neuroendocrine architecture that modulates degrees and forms of sociality. The molecular mechanisms that underlie opposite effects of oxytocin and testosterone are

Table 2. Cognitive and behavioural phenotypes for which oxytocin and testosterone exhibit opposite effects, based on studies of experimental intranasal administration or measurements of serum levels. These studies represent examples of opposite effects for comparable, or the same, tests, but no studies to date have used the same experimental protocols, and the same population, to test for such patterns

| Phenotype | Oxytocin effect (administration, or serum) | Testosterone effect (administration, or serum) |
|---|---|---|
| Trust | Increased (Van IJzendoorn & Bakermans-Kranenburg, 2012) | Decreased (Bos *et al.,* 2012) |
| Generosity in 'Ultimatum Game' | Increased (Barraza & Zak, 2009) | Decreased (Zak *et al.,* 2009) |
| Performance on 'Reading Mind in The Eyes' test (Baron-Cohen *et al.,* 2001) | Increased (Domes *et al.,* 2007) | Decreased in children (fetal testosterone) (Chapman *et al.,* 2006, review); decreased in women (administration, and index of fetal testosterone) (van Honk *et al.,* 2011) |
| Visual spatial abilities | Decreased, in women (Kocoska-Maras *et al.,* 2013); high-oxytocin genotypes associated with lower mental rotation performance (Thompson, Hurd & Crespi, 2013) | Increased (Aleman *et al.,* 2004; Newman, Sellers & Josephs, 2005; Stangl, Hirshman & Verbalis, 2011) |
| Paternal care | Increased (Weisman, Zagoory-Sharon & Feldman, 2012) | Decreased (Gettler *et al.,* 2011; Rilling, 2013; Weisman, Zagoory-Sharon & Feldman, 2014) |
| Sensitivity to biological motion | Increased (Kéri & Benedek, 2009; Perry *et al.,* 2010) | Decreased (fetal testosterone) (Chapman *et al.,* 2006, review) |
| Attention to angry faces | Decreased (Domes *et al.,* 2013) | Increased (van Honk *et al.,* 1999) |
| Amygdala activation | Decreased (Baumgartner *et al.,* 2008; Rupp *et al.,* 2014) | Increased (Ackermann *et al.,* 2012; Bos *et al.,* 2013) |
| Amygdala connectivity with cortex | Increased (Riem *et al.,* 2012; Sripada *et al.,* 2013) | Decreased (van Wingen *et al.,* 2010; Volman *et al.,* 2011; Spielberg *et al.,* 2014) |
| Non-defensive aggression | Decreased (Choleris *et al.,* 2008) | Increased (Carré, McCormick & Hariri, 2011; Montoya *et al.,* 2012) |

beyond the scope of this review, but appear to involve oestrogen mediation of oxytocinergic function, interactions of testosterone with arginine vasopressin, and the functional architecture of steroid hormone pathways themselves (van Anders *et al.,* 2011; Gabor *et al.,* 2012; McCall & Singer, 2012). From a basic social-evolutionary perspective, opposite effects of oxytocin and testosterone are relatively simple to explain in that prosocial affiliation is fundamentally incompatible with competition for physical dominance, both cognitively and behaviourally (Eisenegger, Haushofer & Fehr, 2011); thus, for example, ability to compete effectively should benefit from active suppression of empathy, prosocial mentalizing, and feelings of social familiarity. The only apparent exception to this rule would be group against group competition as in humans, which is thus expected to involve unique forms of endocrine regulation compared with other animals.

Individuals interact competitively in both social and non-social contexts. In the social cases, oxytocin and arginine vasopressin serve adaptively to modify the complex, dynamic affiliative as well as agonistic (in a social context) behaviours that result. Such situations of socially-motivated aggression, and cooperation-to-compete, might be expected to involve mixtures of oxytocin and arginine vasopressin (due to its role in bonding of males; Hammock & Young, 2006; Walum *et al.,* 2008), with the latter hormone acting in concert with testosterone; however, the endocrine basis of cooperation-to-compete, as in human sports and warfare, has yet to be analysed directly, aside from an apparent role for oxytocin in bonding among team-mates (Pepping & Timmermans, 2012). By contrast, in non-social contexts, under the primary influence of testosterone, only egocentric and antisocial behaviours are relevant to maximizing fitness.

The hypothesis of oxytocin and testosterone as opposite in their effects is certainly a considerable oversimplification, and sex-specific models for how steroid and peptide hormones interact to orchestrate behaviour need to be developed (e.g. van Anders *et al.,* 2011; Rilling *et al.,* 2014), but it can help to explain broad patterns in the literature that have otherwise remained unclear, including the highly developed human social phenotype of cooperating-to-compete (Alexander, 1987; Lahti & Weinstein, 2005). Consideration of oxytocin and testosterone as exerting fundamentally opposite effects on social behaviour can also be useful in understanding hormonal mediation of human psychiatric disorders, given that such disorders frequently involve extremes of phenotypic systems (e.g. Trull, 2012), such as, for hormonal systems, high testosterone combined with low oxytocin, or the reverse.

## VI. OXYTOCIN, TESTOSTERONE, AND DISORDERS OF SOCIAL COGNITION

### (1) Oxytocin and testosterone in autism

Elucidating the normal, adaptive, psychological and evolutionary functions of oxytocin and testosterone is a prerequisite to understanding how dysregulation of these hormonal systems is associated, in different ways, with disorders of human cognition and affect (mood). The primary psychiatric disorder centrally involving underdeveloped social cognition, autism, has been strongly associated with correlates of high prenatal, and postnatal, testosterone, by diverse lines of evidence, especially through studies by S. Baron-Cohen and colleagues (reviews in Baron-Cohen *et al.,* 2011; Teatero & Netley, 2013). Correlates of high testosterone, and autism spectrum traits and diagnoses, have also been linked with reduced 'empathizing' (as the cognitive and emotional drive to understand, experience and share positive social interactions), and higher 'systemizing' (as the cognitive drive to understand rule-based, non-social and physically-based 'systems'). In this framework, autism has generally been considered to entail reduced cognitive, emotional and behavioural effects from oxytocin, and this hypothesis is supported by a broad suite of observational, experimental, and genetic results (e.g. Gregory *et al.,* 2009; Green & Hollander, 2010; Gordon *et al.,* 2013; Xu *et al.,* 2013; Hovey *et al.,* 2014). Taken together, these associations of testosterone and oxytocin with autism are concordant with models for the adaptive significance of high testosterone and low oxytocin as subserving and promoting nonsocial compared to social cognition; they also help to explain the strong male biases in the prevalence of autism, as involving combinations of high testosterone (prenatal, or both prenatal and postnatal) and low oxytocin, considering oxytocin as female-biased in its influences on affiliative and mentalization-based cognition and affect. Most broadly, both high testosterone and low oxytocin thus foster relatively 'self-oriented', egocentric and nonsocial attention and information processing (Mehta, Wuehrmann & Josephs, 2009; Wright *et al.,* 2012), as indeed exemplified by the term 'autism' itself. Studies that consider effects from both hormones together, which have yet to be conducted, should be especially useful for further progress in linking autism with hormone systems mediating brain development and function.

### (2) Oxytocin and testosterone in psychotic-affective conditions

The roles of testosterone and oxytocin in other psychiatric disorders involving dysregulated social cognition, especially the major psychotic-affective disorders schizophrenia, bipolar disorder, and depression that share symptoms and risk factors, have been less well investigated than for autism, both theoretically and empirically; indeed, conceptual, hypothetic-deductive frameworks have yet to be developed in this context, despite the obvious importance of social hormones in human psychological phenotypes. A recently developed model for understanding the psychotic-affective disorders, in comparison to autism, is that they involve forms of dysfunctional, 'hyper-developed' social cognition, as demonstrated, for example, in such phenotypes as paranoia, other social delusions, auditory hallucination, megalomania, high levels of social emotion including guilt, shame, pride, or embarrassment, high empathic drive, and high social motivation as observed in mania (Crespi & Badcock, 2008; Backasch *et al.,* 2013; Dinsdale & Crespi, 2013; Dinsdale *et al.,* 2013; Sharp *et al.,* 2013; Crespi & Leach, 2015). This model is based on the simple presumptions that evolution along the human lineage has predominantly involved increases in social cognition and emotionality (the well-supported 'social brain' hypothesis) (Dunbar & Shultz, 2007), and that all biological phenotypes can be perturbed in two opposite directions, towards either lower or higher expression of some trait, pathway, or system, both of which cause performance deficits although by different means. By this model, then, psychotic-affective disorders can be considered as generally opposite, or diametric, to autism, in symptoms, risk factors and, presumably, their hormonal correlates, as depicted in simplified form in Fig. 3. Do psychotic-affective disorders show opposite patterns to autism, with regard to oxytocin and testosterone levels?

A systematic review of testosterone and oxytocin in relation to psychotic-affective disorders is beyond the scope of this article. However, the diametric model for autism and psychotic-affective conditions, in conjunction with the adaptive roles for oxytocin and

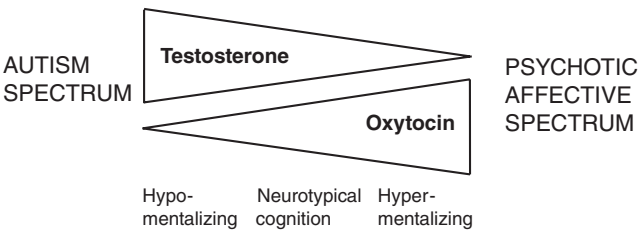


**Fig. 3.** A highly simplified model for the roles of oxytocin and testosterone in mentalizing, defined here as engaging in social cognition, and making sense of each other, and ourselves, in terms of subjective empathic and cognitive states. The model centres on the documented opposite effects of oxytocin and testosterone on mentalizing functions. It predicts that autism spectrum conditions are characterized by increased effects from testosterone, decreased effects from oxytocin, and thus reduced mentalizing; by contrast, many phenotypes of psychotic-affective conditions (mainly schizophrenia, bipolar disorder, and depression) tend to be characterized by decreased effects from testosterone, increased apparent effects from oxytocin, and dysfunctionally increased mentalizing in various forms.

testosterone discussed above, makes clear, specific, falsifiable predictions with regard to testosterone and oxytocin in these conditions, that can be evaluated with empirical information available to date.

First, psychotic-affective conditions should commonly be associated with low testosterone, including prenatal testosterone (usually indexed by digit ratios), low postnatal (plasma) testosterone, and high plasma oxytocin (Fig. 3). Higher digit ratios, as indicators of low prenatal testosterone, have been associated with schizophrenia or schizotypy in some studies (Arató *et al.,* 2004; Walder *et al.,* 2006; Voracek, 2009; Collinson *et al.,* 2010) (although other analyses have shown no such relationships; Procopio, Davies & Marriott, 2006; Gooding, Johnson & Peterman, 2010); these results are in direct contrast to the lower digit ratios reported in autism (review in Teatero & Netley, 2013). Reduced serum testosterone in schizophrenia patients (or individuals with pre-schizophrenia, 'prodromal' symptoms) has been reported consistently across a broad range of studies (Huber *et al.,* 2005; Ko *et al.,* 2007; Fernandez-Egea *et al.,* 2011; van Rijn *et al.,* 2011; Markham, 2012; Ramsey *et al.,* 2013; Trotman *et al.,* 2013), and lower testosterone has also been commonly reported in association with depression (Zarrouf *et al.,* 2009; Höfer, Lanzenberger & Kasper, 2013; Seidman & Weiser, 2013; Amanatkar *et al.,* 2014; Oulis, Masdrakis & Markianos, 2014).

Second, high oxytocin (as well as low testosterone), should be associated with tendencies towards 'hyper-mentalistic' cognition, which as discussed above involves over-interpretation, or imagination, of social cues, stimuli, and conceptualizations (e.g. Walss-Bass *et al.,* 2013); moreover, serum oxytocin should commonly be increased, compared to controls, in psychotic-affective conditions. Table 3 summarizes evidence salient to this prediction of the model, most notably listing a number of studies that show positive associations of plasma oxytocin with severity of schizophrenia symptoms, higher oxytocin among individuals with schizophrenia than in controls, and deleterious effects of oxytocin administration on mentalizing performance among individuals with normal or high social motivation or skill; indeed, positive effects of oxytocin on social cognition and skills appear largely restricted to individuals with reduced social interest or abilities prior to administration (Guastella *et al.,* 2010; Luminet *et al.,* 2011; Rosenfeld, Lieberman & Jarskog, 2011; Fischer-Shofty, Shamay-Tsoory & Levkovitz, 2013; Leknes *et al.,* 2013; Bakermans-Kranenburg & van IJzendoorn, 2013).

Higher oxytocin among individuals with depression than in controls, a pattern replicated across multiple studies, may also be explicable by high levels of (often, although by no means always, dysfunctional) mentalizing among individuals with this condition (e.g. Andrews & Thomson, 2009; Schreiter, Pijnenborg & Aan Het Rot, 2013), whose depressive states frequently involve social problems that are considered (by patients) challenging or more or less intractable (Nesse, 1999, 2004). However, this interpretation is strongly tempered by a suite of studies that show reduced oxytocin among individuals (especially females) with depression (e.g. Scantamburlo *et al.,* 2007; Ozsoy, Esel & Kula, 2009; Yuen *et al.,* 2014) (Table 3). Similarly, as also noted in Table 3, lower oxytocin has been reported among individuals with schizophrenia in some studies (e.g. Goldman *et al.,* 2008; Kéri, Kiss & Kelemen, 2009), and higher oxytocin has also been linked in one study with reduced levels of positive, and total, symptoms in schizophrenia (Rubin *et al.,* 2010). Determining the causes of such variation among studies should clarify the roles of this hormone in psychotic-affective conditions, especially with regard to the uses of oxytocin and testosterone in therapy. The model described here suggests in particular that higher oxytocin, and lower testosterone, should be associated with increased levels of hyper-developed, dysregulated, or affectively biased mentalistic cognition in schizophrenia and depression, as well as other psychotic-affective conditions. For example, a paradigmatic hyper-mentalistic symptom of schizophrenia, paranoia, explicitly involves an exaggerated 'me and them' social relationship, and so might be expected to involve unresolved, oxytocin-associated stress and anxiety given the central role of this hormone in mediating both positive, and negative, social connections, and its apparent role in shifting cognition from self to other orientation (Olff *et al.,* 2013).

### (3) Challenges in relating oxytocin and mentalizing to psychiatric conditions

Interpretation of this body of evidence relating psychotic-affective conditions to low testosterone and high oxytocin is subject to several important caveats. One of the most fundamental, in addition to the variation in results found among studies, is that most analyses of plasma oxytocin in psychotic-affective conditions and cognition, and relationship distress, are observational rather than experimental, such that the meaning of elevated oxytocin, in terms of temporal modulation of cognition and behaviour, or organizational, programming effects from early social environments, are uncertain. Moreover, in psychiatric conditions the oxytocinergic system is not necessarily expected to function normally, such that brain sensitivity and responsivity to oxytocin may be reduced or otherwise altered (e.g., MacDonald & Feifel, 2012; Ellenbogen *et al.,* 2013 Rubin *et al.,* 2014). These considerations indeed suggest that psychotic-affective conditions, and cognition, may involve some degree of 'oxytocin resistance' (high serum levels, but dysregulation of hormone responses, by analogy with insulin resistance), by mechanisms that have yet to be elucidated. The concept of oxytocin resistance may also help to explain otherwise-inexplicable

Table 3. Evidence salient to the hypothesis that high levels of plasma oxytocin are associated with psychotic-affective conditions (schizophrenia, bipolar disorder and depression), and with levels of mentalistic cognition that are higher than typical, and may involve 'hypermentalizing', in non-clinical populations and among individuals with depression or schizophrenia

| Phenotype or condition | Findings and references |
|---|---|
| Schizophrenia | Positive association of serum oxytocin levels with delusional ideation in schizophrenia patients (Walss-Bass *et al.,* 2013) |
| Schizophrenia | Plasma oxytocin levels positively associated with total schizotypy, and the interpersonal subscale (using the Schizotypal Personality Questionnaire), among healthy females (Tseng *et al.,* 2014) |
| Schizophrenia | Significant positive correlation between oxytocin levels and positive symptom severity among schizophrenia patients (Rubin *et al.,* 2014) |
| Schizophrenia | Higher oxytocin linked with reduced levels of positive, and total, symptoms in schizophrenia (Rubin *et al.,* 2010) |
| Schizophrenia | Some studies show higher plasma oxytocin in schizophrenia compared to controls, some show lower levels (Goldman *et al.,* 2008; Kéri *et al.,* 2009; Rosenfeld *et al.,* 2011; MacDonald & Feifel, 2012) |
| Bipolar disorder | Plasma oxytocin levels higher among bipolar I patients in manic episodes, and higher among patients in depressive episodes, compared to patients in remission, or controls (Turan *et al.,* 2013) |
| Depression | Some studies show higher plasma oxytocin in individuals with major depression, than in controls, some show lower levels (Scantamburlo *et al.,* 2007; Ozsoy *et al.,* 2009; Parker *et al.,* 2010; Yuen *et al.,* 2014) |
| Depression | Higher and more variable plasma oxytocin in individuals with major depression, than in controls (Cyranowski *et al.,* 2008) |
| Depression | Higher oxytocin mRNA in hypothalamus of patients with depression, compared to controls, in post-mortem study (Bao, Meynen & Swaab, 2008) |
| Depression | Higher post-prandial oxytocin associated with higher depression scores among women with anorexia (Lawson *et al.,* 2013) |
| Depression | Post-natally depressed mothers reported increased sadness under oxytocin administration compared to placebo, although they also reported a more positive relationship with their infant (Mah *et al.,* 2013) |
| Depression | Oxytocin administration was associated with increases in anxiety during therapy sessions, among males with depression (MacDonald *et al.,* 2013b) |
| Depression (non-clinical) | Individuals with high depression scores less able to inhibit processing of sad faces under oxytocin treatment (compared to placebo) (Ellenbogen *et al.,* 2013) |
| Facial emotion perception | Oxytocin administration associated with higher perceived intensity of expressions, and impaired accuracy, apparently due to oversensitivity and overinterpretation (Cardoso *et al.,* 2013) |
| Facial emotion perception | Oxytocin administration associated with increased activation of social brain regions, but lower performance among 'highly-sociable' individuals, possibly because such individuals were 'already at optimum' (Groppe *et al.,* 2013) |
| Facial emotion perception | Oxytocin administration associated with increased activation of 'social brain' regions, but decreased accuracy in emotion recognition (Voorthuis *et al.,* 2014) |
| Individual recognition | Oxytocin administration associated with bias towards unfamiliar faces being perceived as familiar (Savaskan *et al.,* 2008; Rimmele *et al.,* 2009) |
| Creativity and imagination | Plasma oxytocin and high-oxytocin genotypes associated with increased novelty-seeking, creativity, fluency, and originality (De Dreu *et al.,* 2014), as found in positive schizotypy (Acar & Sen, 2013) |
| Positive schizotypy, imagination | Single-nucleotide polymorphisms associated with high plasma oxytocin are associated with higher scores on positive schizotypy and imagination scales, in a preliminary study of a non-clinical population (Crespi & Summers, 2014) |

elevations of stress-induced oxytocin in maltreated girls, compared to boys and control girls (Seltzer *et al.,* 2014).

Second, although the roles of organizational effects of hormones on early brain development, in relation to activational effects on cognition, mood, and behaviour from variation in serum or cortical levels, have been well studied in the context of testosterone, organizational effects have yet to be elucidated for oxytocin. As a result, the roles of this hormone in neurodevelopment, which centrally mediates risks and symptoms of autism and psychotic-affective conditions, remain unclear. Similarly, the roles of variation in activational effects from testosterone, oxytocin, or other hormones in the risk and symptoms of these

conditions are largely unknown (aside from the apparent 'antipsychotic' effects of oestrogen; Kulkarni, Hayes & Gavrilidis, 2012); hormonal variation may also represent effects of common causes that underlie both cognitive-affective and endocrine phenotypes. Pleiotropic effects of testosterone, or oxytocin, system genes on reproductive and other physiological phenotypes, in relation to psychiatric phenotypes, also have yet to be elucidated, although higher fertility in first-order relatives of individuals with psychotic-affective conditions indicates that such joint genetic effects may be considerable (e.g. Power *et al.,* 2013).

Third, altered social cognition in psychotic-affective conditions (or under oxytocin or testosterone administration) has almost always been considered in terms of task performance 'deficits', rather than hypo-mentalizing compared to hyper-mentalizing. Some tests (e.g. Dziobek *et al.,* 2006; Sharp *et al.,* 2011) can differentiate between these two possibilities, but have seldom been applied. In this context, the interpretation of withdrawal from social interaction upon illness onset, and reduced mentalizing performance, especially in depression and in schizophrenia with predominantly negative symptoms, remains uncertain. Such social withdrawal appears incompatible with high oxytocin levels, unless these conditions are characterized by increases in internally directed, negatively valenced mentalizing (e.g. Sass & Parnas, 2003; Walss-Bass *et al.,* 2013), with reduced social-interaction rewards due to dysfunctions in the oxytocin–dopamine and serotonin systems (Rosenfeld *et al.,* 2011). By contrast, 'withdrawal' in autism involves never having participated socially (Kanner, 1943), from early childhood.

Considered together, these findings suggest that whereas oxytocin administration should be useful in many cases of autism (especially in early childhood) to engage and amplify this system as shown in some recent studies (Preti *et al.,* 2014), oxytocin-related therapy in psychotic-affective conditions may instead involve benefits from fostering shifts from internal, negatively valenced social cognition to positively valenced, externally directed social behaviour, whereby prosocial interactions may, in principle, be regained and normal feedbacks in the oxytocin system re-established. Moreover, in psychotic-affective conditions oxytocin may indeed, at least in some circumstances, exacerbate symptoms to the degree that it amplifies maladaptive social-cognitive states and fosters hyper-mentalistic cognition more generally. For both autism and psychotic-affective disorders, the social-evolutionary functions of oxytocin discussed above also strongly suggest that use of this hormone as therapy should involve combinations of intranasal administration with fostering of positive social bonds with family, friends, and caregivers, given the core function of this hormone in such affiliative contexts.

## VII. CONCLUSIONS

(1) Application of a social-evolutionary perspective to understanding the functions of oxytocin leads to useful insights into how, and why, this hormone mediates human social cognition and affect, with direct implications for psychiatric conditions involving altered social behaviour. Review of the social contexts of endogenous oxytocin release indicates that it promotes the formation and maintenance of affiliative, cooperative relationships in diverse situations, by increasing sensitivity to social rewards and social threats, and reducing thresholds for mentalistic cognitive and affective social-information processing. Social contexts modulated by oxytocin can thus be positive (leading to hedonic reward, and reinforcing behaviour that increases inclusive fitness), negative (motivating anxiety and social coping, to alleviate problematic situations), or aggressive (stimulating defence of one's social relationship against outsiders).

(2) The associations of testosterone with social cognition and behaviour are strikingly opposite to those of oxytocin, in that this hormone promotes egocentric, self-oriented, and competitive behaviour, compared to group-centrism, other-orientation, and cooperation. These diametric effects indicate that studies quantifying effects from both hormones together should be much more effective in explaining and predicting behaviour and cognition than studies focusing on only one of the hormones in isolation. Moreover, consistently high levels of one hormone, and low levels of the other (or comparable differences in reactivity) are expected to represent hormonal 'extremes' with regard to effects on social cognition, and may thus be associated with psychiatric disorders that centrally involve social traits.

(3) Autism appears to be characterized by high testosterone and low oxytocin, in keeping with the major features of this condition: reduced social cognition, and increased non-social cognition (low empathizing and high systemizing, by Baron-Cohen's model). Moreover, a notable, although inconsistent, suite of evidence links psychotic-affective conditions with low testosterone, high oxytocin, and dysregulated social cognition that often involves 'hyper-mentalizing', although hormonal correlates of social cognition in these disorders have yet to be investigated in theory-guided or comprehensive ways. The conceptual frameworks for understanding oxytocin and testosterone functions described here, which link adaptive significance in neurotypical individuals to dysregulation in individuals with mental conditions, provide a predictive, hypothesis-testing framework for analysing the neuroendocrine bases of human social cognition and its disorders.

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