REVIEW

The Peptide That Binds: A Systematic Review of Oxytocin and its Prosocial Effects in Humans

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Oxytocin is a neuropeptide involved in a wide variety of social behaviors in diverse species. Recent research on its effects in humans has generated an arresting picture of its role in the dynamic function of the social brain. This review presents a broad overview of this uniquely social peptide, with a particular focus on extant studies of its effects in humans. After a short discussion of the evolutionary history of the oxytocin system, critical aspects of its peripheral and central physiology, and several salient technical issues surrounding human oxytocin research, a systematic review of studies of the effects of intranasal oxytocin in humans is presented. These effects include alterations in social decision making, processing of social stimuli, certain uniquely social behaviors (e.g., eye contact), and social memory. Oxytocin's prosocial influence is then framed by an evolutionary perspective on its role in mammalian social bonding and attachment. Finally, limitations in current human oxytocin research and oxytocin's potential therapeutic applications are discussed. Key conclusions are (1) human research with intranasal oxytocin has uniquely enhanced our understanding of the microstructure and function of the human social brain, and (2) the oxytocin system is a promising target for therapeutic interventions in a variety of conditions, especially those characterized by anxiety and aberrations in social function. (HARV REV PSYCHIATRY 2010;18:1–21.)

Keywords: attachment theory, evolutionary biology, humans, oxytocin, review, social neuroscience

Oxytocin is a centrally synthesized peptide of nine amino acids that is critically involved in both central and peripheral aspects of mammalian attachment and survival.[1,2] Animal research has demonstrated oxytocin's unique role in parturition, milk letdown, and protective aggression against intruders, as well in aspects of social behavior and bonding between mother and infant and between mating pairs.[3,4] A recent surge of interest in oxytocin's central effect in humans has opened a new chapter in our understanding of the functional anatomy of human social relationships and the impact of oxytocin on the human brain. This article briefly examines important background information on the evolutionary history and physiology of the oxytocin system, addresses salient clinical and technical issues around human studies with oxytocin, systematically reviews extant studies examining the effects of intranasal oxytocin in humans, and provides a short synopsis of an evolutionary perspective on oxytocin's role in attachment. A concluding section summarizes limitations in human oxytocin research and discusses potential therapeutic applications of this uniquely social peptide. A caveat: the oxytocin system is one of the best-studied mammalian brain systems, with a vast, ever growing literature on its effects. As such, this focused

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review excludes several topics germane to an understanding of oxytocin's social functions, but not specifically addressed by extant studies of intranasal oxytocin, including the role of oxytocin in human stress, anxiety, and sexual function. These topics are addressed in more depth in several of the reviews cited herein.[5–8]

THE SCIENCE OF OXYTOCIN

Evolutionary History: A Long Love Story

The story of oxytocin begins long ago in evolutionary terms. Speaking to its central role in reproduction, oxytocin—whose name comes from the Greek word for "quick birth"—has survived an estimated 700 million years, with few modifications in either invertebrates or vertebrates.[2,9] An evolutionary precursor of oxytocin, the peptide vasotocin, controls courting sounds, sexual behavior, and birthing in reptiles.[3] It is thought that this more ancient peptide evolved in mammals into two different, but related, social neuropeptide systems: the oxytocin and arginine vasopressin systems.[9–11] Differing from oxytocin in only two of its nine amino acids, arginine vasopressin is involved in fluid balance, cardiovascular and autonomic regulation,[12] and multiple aspects of human social function, including gender-specific effects on the processing of facial emotion[13] (see Meyer-Lindenberg [2008][7] for review). Furthermore, recent reports link genetic variations in the arginine vasopressin system with long-term male pair-bonding characteristics,[14] amygdala responses to emotional stimuli,[15] and autism.[16] Other illustrative similarities and differences between these two related neuropeptide systems are comprehensively reviewed elsewhere.[7,11,17]

Systemic Action: Receptors and Regulation

Two biological distinctions regarding oxytocin merit attention. A first concerns the oxytocin "system," the functional unit that incorporates both oxytocin and its receptor.[18] Centrally, this system is part of a suite of other neurochemicals (e.g., cortisol, estrogen, opiates, and monoamines) that coordinate social behaviors and stress responses.[6] A second distinction concerns oxytocin's dual roles as both a central neurotransmitter/neuromodulator and a peripheral hormone. The central and peripheral branches of the oxytocin system clearly co-evolved to facilitate both the somatic and brain-based components of birth, nursing, and postbirth care.[3]

Recognizing a two-part receptor-hormone system is important because some of oxytocin's effects appear to be mediated via both dynamic (i.e., hormone-driven) and more static (i.e. genetically determined) alterations in receptor density and location. In pregnancy, for example, estrogen drives a dramatic increase in the density of oxytocin receptors in the uterus and mammary myoepithelium (see Russell et al. [2003][19] and Insel [1992][20] for reviews), and augments oxytocin receptor binding in certain critical brain regions (e.g., ventromedial hypothalamus).[21] Estrogen, notably, has dual regulatory functions for oxytocin, influencing transcription of both its receptors and oxytocin itself.[22] Furthermore, estrogen receptors, which are necessary for the synthesis of oxytocin receptors in the amygdala, are expressed by hypothalamic oxytocin neurons.[23] Elegant in vivo animal experiments using intracerebral microdialysis have shown that dynamic, region-specific changes in the distribution of oxytocin receptors are partly responsible for orchestrating birth, maternal behavior, anxiety, and sexual behavior.[24–26] In addition to these hormonally mediated changes, seminal research by Insel[1] has demonstrated that genetically determined, species-level differences in central oxytocin receptor location and density—not oxytocin levels—are the critical factor mediating the marked differences in pair bonding between vole species.

Extrapolating from these findings to humans, we may adduce that oxytocin's function in the human brain is affected not only by variations in its central release, but also by variations in the density, location, and function of central oxytocin receptors. These receptor variations likely occur over multiple time frames, as the result of both static and mutable influences. Pragmatically, understanding these details about oxytocin receptors frames the expanding field of human oxytocin research in at least two ways. First, though they are important, reports on oxytocin levels in different populations and conditions[27–29] provide only a partial view of the entire functional system. Second, the group of studies reviewed here that document the effects of treating humans with oxytocin has emerged in a relative vacuum of understanding about salient differences in human oxytocin receptors in specific individuals and populations. Other research tracks exploring the genetically mediated differences in oxytocin receptors[12] and the epigenetics (experience-dependent modifications) of oxytocin genes[30] are emerging to paint a more complex and nuanced picture of the variations and plasticity of the entire oxytocin system. This field of epigenetics is an especially promising area of oxytocin research that may influence our understanding of the effects of early relational experience on the future function of the oxytocin system and on attachment behavior.

Dual Roles: Peripheral and Central Effects

Oxytocin is synthesized in specialized cells in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus (see Figure 1), and serves dual roles, as a neurotransmitter/neuromodulator and a hormone.

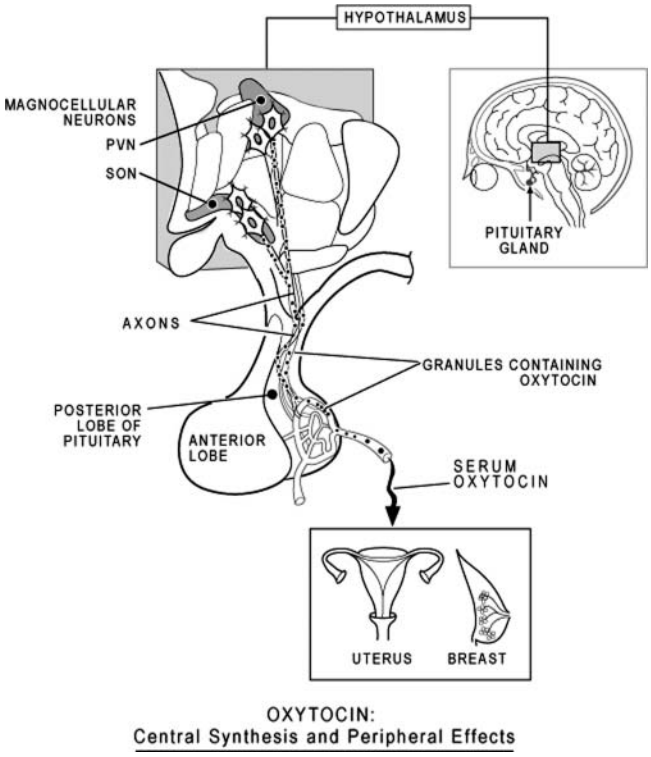

FIGURE 1. Oxytocin is synthesized in specialized cells in the PVN and SON of the hypothalamus, and serves dual roles, as both a central neurotransmitter/neuromodulator (for central effects, see Figure 2) and a peripheral hormone. Though there are receptors for oxytocin throughout the body, its primary effects are in the gravid uterus and breast, where it stimulates contractions and milk ejection. Abbreviations: PVN, paraventricular nuclei; SON, supraoptic nuclei.

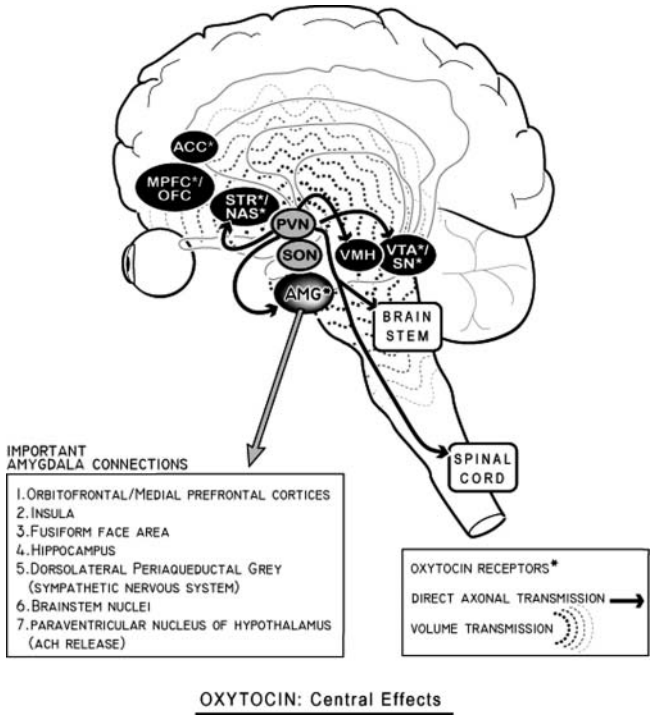

FIGURE 2. After synthesis in hypothalamic magnocellular neurons (which all project to the posterior pituitary gland (see Figure 1) and parvocellular neurons in the paraventricular nucleus (PVN) (which have central projections), oxytocin exerts its central effects via (1) direct axonal connections from the parvocellular neurons in the PVN to critical brain regions and (2) volume diffusion effects (i.e., "volume effects") in areas with oxytocin receptors. These volume effects are the result of release of oxytocin from both supraoptic nuclei and PVN (see Ludwig & Leng [2006][31] and McGregor et al. [2008][32] for reviews). As discussed in the text, the amygdala (highlighted here, with important connections) is a critical node of oxytocin's central activity in humans. Only selected oxytocin-receptor containing brain areas are shown here; these areas were selected due to their ubiquity in human studies cited in the text. For a more complete list, see reviews in Gimpi & Farenholz (2001),[2] de Bono (2003),[33] and Skuse & Gallagher (2009).[34] Abbreviations: ACC, anterior cingulate cortex; AMG, amygdala; MPFC, medial prefrontal cortex; NAS, nucleus accumbens; OFC, orbitofrontal cortex; PVN, paraventricular nucleus; SN, substantia nigra; SON, supraoptic nuclei; STR, striatum; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

Some of the oxytocin synthesized in the PVN/SON is transported in axons and released in target brain areas (e.g., hippocampus, amygdala, striatum, hypothalamus, nucleus accumbens, midbrain), where its acts as a neurotransmitter[2] (see Figure 2).

Release from the cell bodies of neurons also creates less-directed diffusion or "volume transmission" effects in brain areas with oxytocin receptors.[31] A second oxytocin pathway involves axonal transport of oxytocin to the hypophyseal bloodstream, where it enters the peripheral bloodstream for its hormonal actions, including milk letdown and uterine contractions.[31] Importantly, the central and peripheral release of oxytocin can be unyoked, and peripheral oxytocin levels may not mirror central activity or release.[31,35]

Peripheral Levels and Central Release

In humans, plasma levels of oxytocin have been related to a variety of conditions and disease states, including warm contact with a partner,[36,37] gaps in social relationships,[38] trust and trustworthiness,[39] mental stressors,[40] anxiety and hormonal responses,[41] male and female sexual responses,[8] mood disorders,[42,43] schizophrenia,[27,44] and autism.[45] However, since research tools available to animal researchers (e.g., intracerebral microdialysis, targeted delivery of oxytocin antagonists, gene knockout, and viral gene transfer) are unavailable in humans, peripheral levels have not been directly correlated with the central release in critical brain areas. As such, though the investigations mentioned

above have noted correlations between plasma oxytocin levels and different conditions, no convincing evidence of a direct relationship between central levels of oxytocin, peripheral levels of oxytocin, and psychiatric conditions has been found, and elevated levels have been found in several conditions with social anxiety as a hallmark.[46,47] Other assays of oxytocin—including its levels in cerebrospinal fluid,[28] saliva,[48] and urine[49]—share similar limitations. As such, the most direct way to assay the central actions of oxytocin in humans is via intranasal delivery, which provides a direct pathway to the brain.[50]

OXYTOCIN AND SOCIAL NEUROSCIENCE

Oxytocin's role and therapeutic potential in humans is best understood within several larger contexts, including its evolutionary history, unique biological characteristics, and effects in other mammals. Building on these bodies of knowledge, the multidisciplinary field of social neuroscience has both advanced our understanding of oxytocin's central role in humans and used oxytocin as a tool to dissect the microdynamics the social brain.[34] This second section reviews extant studies of oxytocin's effects in humans from the broad perspective of social neuroscience. Highlighted first—due to their unique and seminal contributions—are findings from the branch of social neuroscience called *social neuroeconomics*. Following that discussion is a review of studies of oxytocin's effects on the perception of social stimuli, social behavior, and social memory. These results are summarized in Table 1.

Games People Play: Social Neuroeconomics

The branch of social neuroscience called neuroeconomics has been vital to our understanding of oxytocin's effects in humans. After presenting an overview of a few basic principles in the field of neuroeconomics, we discuss oxytocin's effects in several seminal neuroeconomic experiments.

Geared toward understanding the microdynamics and neurobiology of complex, real-world decision making, social neuroeconomics is a multidisciplinary field that utilizes diverse tools, including mathematical and economic models and equations, social psychology constructs (e.g., intention detection, trust, mind reading, reputation), and experimental neuroscience techniques (functional neuroimaging, psychoactive medication, magnetic disruption of brain activity).[93,94] Two insights from social neuroeconomics especially germane to oxytocin are that (1) simple hedonic decision heuristics (i.e., humans selfishly seek to maximize gain and minimize loss) do not accurately describe real-world social decision-making, and (2) social rewards activate central reward circuitry in a way similar to other classes of survival-enhancing stimuli (i.e., food and drink).[94–96]

Neuroeconomics experiments typically involve economic exchange games. These games provide the empirical regularities necessary for experimentation while preserving the essential features of a real, consequential social interchange.[94,95] Unlike other, more complex forms of social interaction, economic games can be played in a neuroimaging environment, facilitating the digital dissection of brain areas involved in social decision making and subjective states like trust. Functional neuroimaging has been critical in our understanding the neurobiological activity of oxytocin in humans, as discussed below.

Trust and Trysts: Oxytocin in Neuroeconomic Games

In the first, groundbreaking neuroeconomic study of oxytocin, Kosfeld and colleagues[54] gave 128 healthy male subjects intranasal oxytocin or placebo and then had them play a trust/betrayal game, a two-part exercise involving two potential monetary exchanges between an investor and an anonymous trustee, who was either a human (in the "trust" version of the game) or a computer (in the "risk" version) (Figure 3).

In this game, the investor starts with a sum and can choose to transfer some of it to the trustee. This initial exchange triples the transferred sum, making such a trade—if the trustee reciprocates—potentially profitable for both sides. However, the initial, potentially lucrative expression of trust by the investor is also risky, as the trustee is under no obligation to return anything. That is, a stingy trustee could keep the entire initial investment and betray a generous investor's trust. As mentioned, the game has two versions: a socially biased "trust" version in which the trustee is a second human participant, and an impersonal "risk" version, in which the trustee is a "project" and the amount transferred back is not determined by another player in the game. Rather, investors in the "risk" version know that the back-transfer rate is pre-set by the researchers. To keep the actual risk consistent from one investor to the next, though, the researchers set the back-transfer rate in the "risk" version to be identical to the rate determined by the human participants in the "trust" version. Therefore, though the actual risk of loss or gain is the same in both versions of the game, the "trust" version has an interpersonal connotation that the "risk" version lacks.

In the "trust" version of the game, oxytocin significantly increased the amount of money that investors gave to trustees: 45% of oxytocin-treated subjects demonstrated the maximal trust level, versus 21% in the placebo group. In the impersonal "risk" version of the game, however, oxytocin did not affect the investors' decisions, indicating that oxytocin

Table 1. Human Treatment Trials with Oxytocin

	Parameter studied	Subjects (*n*) & gender	OT dose[a]	Main findings
Social cognition in normal subjects				
Heinrichs et al. (2003)[51]	Subjective calmness & endocrine response to social stress	37 M	24 IU	After a social stressor, the OT group showed decreased cortisol levels, higher ratings of calmness, & lower anxiety; the results were similar to a condition where only social support was given OT plus social support had additive effects on both endocrine & subjective ratings of stress
Heinrichs et al. (2004)[52]	Implicit & explicit memory in humans	38 M	24 IU	OT selectively impaired implicit memory for recall of relationship-related stimuli in a performance test
Kirsch et al. (2005)[53]	Neural responses to affectively charged faces & scenes	15 M	27 IU	OT subjects showed a significant reduction of activity in amygdala & amygdala-midbrain connectivity to fearful or threatening visual images, with a more prominent effect on socially salient stimuli (faces) compared to nonsocial scenes
Kosfeld et al. (2005)[54]	Trust	128 M	24 IU	OT subjects showed greater trust behavior toward human participants (compared to nonhuman recipient) in a money-transferring game
Domes et al. (2007)[55]	Neural responses to faces	13 M	24 IU	OT subjects showed a reduced response of the right amygdala to angry, happy, & fearful faces
Domes et al. (2007)[56]	"Mind reading" (intuiting mental state) from facial gestures	30 M	24 IU	OT subjects showed improved scores in the RMET (reading-the-mind-in-the eyes test) & demonstrated an increase in correct responses to difficult mind-reading questions
Zak et al. (2007)[57]	Generosity	68 M	40 IU	OT subjects were 80% more generous than placebo subjects in a money-gifting generosity game; these effects were twice as potent as the endogenous effect of altruism (one-sided giving)
Baumgartner et al. (2008)[58]	Neural activity & trusting behavior after betrayal	49 M	24 IU	OT ameliorated a betrayal-triggered decrease in trusting behavior ("trust adaptation"), associated with reduced activation of the amygdala, midbrain, & dorsal striatum
Di Simplicio et al. (2008)[59]	Processing affective information in attention, perception, & memory tasks	29 M	24 IU	OT subjects showed a slowed reaction time to identify fearful facial expressions correctly; these subjects also reduced errors in classifying positive emotions as negative ones
Ditzen et al. (2008)[60]	Behavior & physiology in couples; conflict discussion	94 M/F	40 IU	OT significantly increased the ratio of positive to negative communication behavior, & significantly reduced salivary cortisol levels after a conflict discussion between couples
Guastella et al. (2008)[61]	Cognitive processing of social valence	104 M/F	24 IU	OT subjects showed improved efficiency in recognizing angry faces over happy faces & gazed longer & more frequently toward angry faces
Guastella et al. (2008)[62]	Memory for affectively charged faces	69 M	24 IU	OT subjects showed improved recognition memory for previously seen happy faces, compared to angry & neutral faces
Guastella et al. (2008)[63]	Gaze time to the eye region of faces	52 M	24 IU	OT subjects showed increased number of fixations & total gaze time toward eye region of faces compared to placebo

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Table 1. Human Treatment Trials with Oxytocin *(Continued)*

	Parameter studied	Subjects (*n*) & gender	OT dose[a]	Main findings
Petrovic et al. (2008)[64]	Affective evaluation of faces & corresponding neural activity	27 M	32 IU	OT abolished negative affective ratings to aversely conditioned faces, & caused decreased activity in anterior medial temporal & anterior cingulate cortex Direct-gaze faces showed greater OT-mediated neural modulation than averted-gaze faces in the amygdala & fusiform gyrus
Savaskan et al. (2008)[65]	Memory for facial identity	36 18 M 18 F	20 IU	OT subjects had improved short (5-hour) & long-term (24-hour) recognition of neutral & angry faces OT lowered the false-alarm rate for not-previously-seen faces
Singer et al. (2008)[66]	Empathy for vicarious & directly experienced pain	20 M	32 IU	OT decreased activation of the amygdala in "selfish" subjects who directly received painful stimulation, but had no effects on empathy or activity in empathy-related brain regions (insula)
Unkelbach et al. (2008)[67]	Recognition of positive sexual & relationship stimuli	44 M	24 IU	OT enhanced detection & categorizing of positively valenced sexual & relationship words in a constructive recognition task
Domes et al. (2009)[68,b]	Amygdala response to fearful, angry, happy, & neutral faces	16 F	24 IU	Supporting OT's gender-specific effects, in women OT increased activity in the left amygdala, fusiform gyrus & superior temporal gyrus in response to fearful faces, & in the inferior frontal gyrus in response to angry & happy faces
Fischer-Shofty et al. (2009)[69,b]	Facial recognition ability	27 M	24 IU	OT improved subjects' ability to recognize fear, but not other emotions (happiness, sadness, anger, surprise, disgust)
Keri & Benedek. (2009)[70,b]	Perception of biological motion	20 10 M 10 F	24 IU	OT increased sensitivity to biological motion (walking figure) vs. nonbiologic motion (rotating shape)
Rimmele et al. (2009)[71,b]	Recognition memory for faces	44 M	24 IU	Pre-task OT improved familiarity memory for faces over nonsocial stimuli 24 hours later; more effortful recognition memory was not affected
Shamay-Tsoory et al. (2009)[72,b]	Emotional responses to another's gain or loss during an economic choice game	59 26 M 33 F	24 IU	Supporting the hypothesis that OT enhances salience of social cues regardless of the valence of emotion, OT-treated subjects reported both increased envy when another player gained more money than they did, & increased gloating (Schadenfreude) when they gained more than the other player
Theodoridou et al. (2009)[73,b]	Judgments of facial trustworthiness & attractiveness	96 48 M 48 F	24 IU	OT increased ratings of the trustworthiness & attractiveness of unfamiliar male & female faces in both male & female subjects
Cognitive/memory processes in normals				
Fehm-Wolfsdorf et al. (1984)[74]	Memory (word retention)	30 M	10 IU OT or AVP	Compared to both placebo & AVP (which had similar effects on memory), OT subjects experienced less learning & memory ability but felt more focused
Geenen et al. (1988)[75]	Contingent negative variation & memory	28 M	3780 mIU IV OT	OT subjects showed a decrease in CNV (contingent negative variation), an electrophysiological measure of preparatory attentive & motivational processes, both at the time of & 1 week after OT treatment
Bruins et al. (1992)[76]	Cognitive & memory processes	43 23 M 20 F	20 IU OT or AVP	OT subjects showed decreased initial storage & rate of storage in the verbal memory test, & reduced vigor in the mood profile test; vasopressin had roughly opposite effects on memory
Asperger's disorder/autism				
Hollander et al. (2003)[77]	Repetitive behaviors	15 14 M 1 F	Up to 70 U/hr IV OT	OT subjects showed a significant reduction in repetitive behaviors common to patients with autism

Table 1. Human Treatment Trials with Oxytocin *(Continued)*

	Parameter studied	Subjects (n) & gender	OT dose[a]	Main findings
Hollander et al. (2007)[78]	Affective speech comprehension	15 M	Up to 70 U/hr IV OT	OT subjects showed improvements in affective speech comprehension from pre- to post-infusion & retained the ability to accurately assign emotional significance to speech intonation
Men with attachment-related difficulties				
Meinlschmidt & Heim. (2007)[79]	Salivary cortisol	19 M	24 IU	OT subjects with early parental separation showed attenuated decreases in salivary cortisol (a measure of the central stress hormone system) over time
Buchheim et al. (2009)[80,b]	Ratings of attachment-related pictures	26 M	24 IU	In men with an insecure attachment pattern, OT increased secure, & decreased insecure, ratings
Irritable bowel syndrome				
Ohlsson et al. (2005)[81]	Constipation & associated subjective parameters	49 F	40 IU BID for 13 weeks	OT subjects had slightly improved mood, abdominal pain, & discomfort; there was a weak positive correlation between administration of OT, improvement in irritable bowel syndrome, & concomitant depression
Social anxiety disorder				
Guastella et al. (2009)[82,b]	4 self-rated scales of aspects of social anxiety; self-ratings of speech performance & appearance	25 M	24 IU	OT-treated subjects doing concomitant exposure therapy demonstrated a positive initial effect (improved self-evaluation of appearance & speech performance); these benefits, however, did not generalize into any sustained positive effect over exposure therapy alone
Obsessive-compulsive disorder				
den Boer & Westenberg. (1992)[83]	Obsessions & compulsions	12 3 M 9 F	18 & 54 IU	No effect on symptoms, though one OT subject in the 54 IU dose group showed a small decrease in checking behaviors
Epperson et al. (1996)[84]	Obsessive-compulsive disorder symptoms & mood	7 7 M 3 F	160 IU or 320 IU	No change in obsessive-compulsive disorder symptoms OT subjects had a statistically (but not clinically) significant BDI score improvement
Trichotillomania				
Epperson et al. (1996)[85]	Trichotillomania symptoms	2 F	160 IU	No difference in trichotillomania symptoms
Posttraumatic stress disorder				
Pitman et al. (1993)[86]	Physiologic responses to personal trauma prompts	43 M	20 IU OT or AVP	OT subjects had the lowest mean physiologic responses to personal combat imagery prompts, compared to placebo & AVP-treated subjects
Schizophrenia				
Bujanow (1972)[87] Bujanow (1974)[88]	Acute schizophrenia symptoms and hospitalization	Not reported	10–15 IU IV or 20–25 IU IM daily or every other day (6–10 injections)	Rapid therapeutic effect, occasionally preventing need for hospitalizations (observational reports without blinding or standardized outcome measures)
Bakharev (1984)[89]	Schizophrenia exacerbations	27 M	10 IU IM or IN every 6 hours	IV and IN oxytocin caused alleviation or marked improvement of a variety of symptoms (depression, anxiety, asthenia, apathy, anergy, sleep) and was well tolerated; currently recognized diagnostic criteria or outcome measures were not used

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Table 1. Human Treatment Trials with Oxytocin *(Continued)*

	Parameter studied	Subjects (*n*) & gender	OT dose[a]	Main findings
Sexual function				
Anderson-Hunt & Dennerstein (1994)[90]	Female sexual response (case report)	1 F	8 IU	OT subject (using intranasal OT to augment breastfeeding) experienced heightened sexual desire & intensified orgasm
Ishak et al. (2007)[91]	Anorgasmia (case report)	1 M	24 IU	OT subject—treated intracoitally—had success in restoring ejaculation
Burri et al. (2008)[92]	Endocrine & sexual function	10 M	24 IU	OT subjects showed greater increases in epinephrine plasma levels during sexual activity, & elevated plasma OT levels for >60 minutes after treatment No changes were noted in subjective sexual experience

AVP, arginine vasopressin; BDI, Beck Depression Inventory; F, female; IU, international units; M, male; OT, oxytocin; U, unit.
[a]Intranasal and once daily unless otherwise specified.
[b]These studies were added after acceptance and review of the main article. As such, they are not referenced or discussed in the text proper. Several of them (e.g., Domes et al. [2009],[68] Shamay-Tsoory et al. [2009])[72] support substantive modifications of certain hypotheses regarding the effects of oxytocin. They are included to enhance timeliness and demonstrate our complex and evolving understanding of the role of oxytocin in humans.

was exerting a specific effect on social decision making and not a generalized effect on risk taking or optimism. Also illuminating was that in the "trust" version of the game, oxytocin had no effect on the back-tranfer rate of the human trustees. This finding clarifies that oxytocin had specific effects on first-mover social "approach," which mediates the investors' decisions, and not reciprocity, which influences the decisions of trustees. Oxytocin's positive effects in this experiment can also be construed as causing a decrease in initial betrayal aversion in investors, a finding in keeping with other studies on betrayal, as discussed below. A final result—notable in the absence of an effect—was that oxytocin did not have an impact on any of the subjective states (e.g., reported mood, calmness, beliefs about the trustworthiness of others or about the likelihood of a good outcome) tested at several time points during the experiment. These findings are replicated in most extant human studies of oxytocin in normal subjects and highlight that although oxytocin biases socially sensitive decision circuits and behavior, it typically does so without affecting conscious awareness.

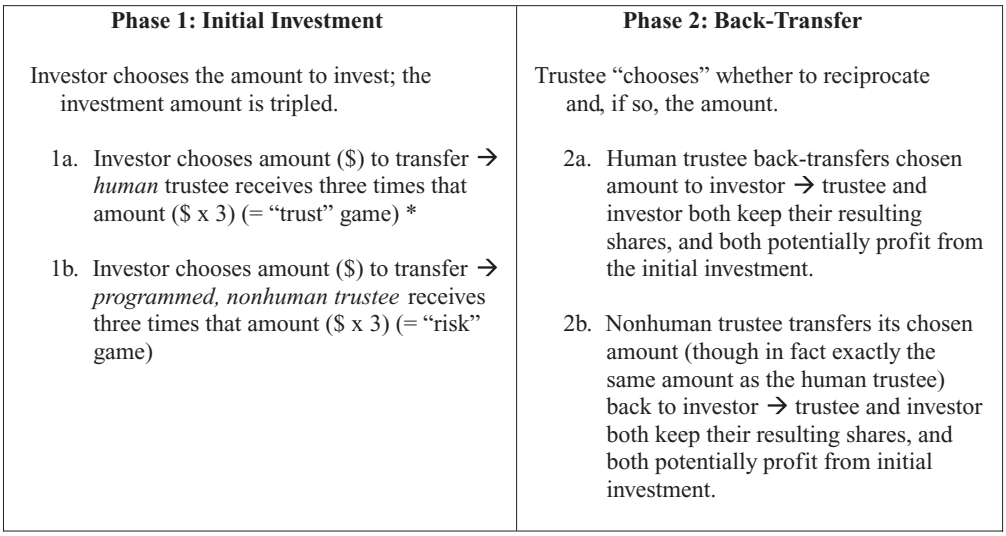

FIGURE 3. The "trust" and "risk" games. All participants received intranasal oxytocin or placebo. The only actual difference between the games is that the trustee, who receives the investment and controls the back transfers, is human only in the "trust" game. The effect of oxytocin on behavior is seen only in the initial transfer, and only when the recipient is another person. ∗ = investors' actions positively affected by oxytocin.

Phase 1: Initial Trading	Phase 2: Feedback	Phase 3: Postfeedback Play *
Group 1: "Trust" game (human recipient) Group 2: "Risk" game (programmed, nonhuman recipient)	Players have a 50-50 chance of hearing that they (a) were betrayed (by a human trustee) or (b) lost (through the programmed response of the nonhuman trustee).	Players have another round of the "trust" or "risk" game.

FIGURE 4. Variant of the "trust" and "risk" games: trust adaptation. All participants received either intranasal oxytocin or placebo. This variant of the "trust" and "risk" games examines the effect of oxytocin on betrayal aversion (trust behavior after knowledge of betrayal). The first phase is exactly the same as the first phase of the "trust" and "risk" games in Figure 3. $*$ = investors' actions positively affected by oxytocin (reduced betrayal aversion).

In a second study of trust, and using a game similar to that described above, researchers found that trustees had higher peripheral oxytocin levels when generous offers were made by human investors versus rounds when an offer—although equal in amount—was described as being decided randomly. Stated another way, oxytocin release in trustees appeared to be sensitive to the perception of magnanimous human intentions. In this experiment, higher peripheral oxytocin levels in trustees were also correlated with their subsequent trustworthy behavior. That is, the amount that trustees back-transferred (a marker of trustworthiness) was correlated with their peripheral oxytocin levels.[39] Corroborative findings regarding the role of oxytocin on "first-mover" trust or "goodwill" come from a neuroeconomic experiment in which players demonstrating more initial trust had greater neural activity than controls in the septal area and adjoining hypothalamus.[97] Each of these brain areas is rich in oxytocin receptors,[34] and the septal region may modulate the release of oxytocin and vasopressin.

A further investigation of oxytocin's effects on human trust used an ingenious variant of the above-described trust/betrayal game to explore oxytocin's effects on betrayal of trust (Figure 4).[58] After an initial phase of playing either the "trust" or "risk" variants of the game, half of the investors received feedback of a 50% incidence of either betrayal of trust (in the "trust" variant of the game) or monetary loss (in the "risk" version). As a reminder, in the "trust" version of the game, the back-transfer rate is decided by another participant, whereas in the "risk" version, the back-transfer rate is preset. As such, the feedback in the "risk" version of this game was free of human intention and the implication of betrayal. After they received this negative feedback, participants played another round of either game. This post-feedback phase allowed an examination of an effect called betrayal aversion: inhibition of generosity following a known violation of trust. Consistent with the prosocial effects on trust noted above, as well as evidence that oxytocin has amnesic effects on certain aversive experiences (reviewed below), oxytocin eliminated the anticipated negative effect of awareness of betrayal in the "trust" variation, whereas it has no effect in the "risk" variation. That is, participants who received oxytocin continued to exhibit trusting behavior in the post-betrayal phase, whereas placebo participants were more stingy in that phase. Neuroimaging revealed that the oxytocin-mediated change in post-feedback behavior was associated with decreased activity in bilateral amygdala and striatum. These subcortical sites are associated with fear responses and trust estimation of faces (amygdala) and with feedback processing and reward learning (striatum). As in the previously described games, although oxytocin affected brain activity and behavior, several measures demonstrated participants perceived no subjective effects.

Even more robust effects on social decision making were demonstrated in a related neuroeconomic experiment by Zak and colleagues,[57] who examined the effects of oxytocin on generosity using economic interchanges called the "ultimatum game" and the "dictator game" (Figure 5).

These two games are similar in that an initial decision maker (DM1) is endowed with $10, to be split, in turn, with a second player (DM2). In the simpler, dictator version, DM2 must accept any offer, whereas in the ultimatum game, DM2 can reject offers below a pre-specified minimum (the ultimatum). These rejections, though costly to DM2, punish DM1, for both players lose the money in this round. Therefore, in the ultimatum game, DM1's decision comes with an implicit awareness of DM2's capacity to judge and reject stingy offers, whereas in the dictator game, DM1's decision is not influenced by DM2's implicit expectations and emotional response. These differences allow experimenters to distinguish between the broader category of altruism (giving at a cost to oneself, assayed in both games) and a subset of altruism called generosity (giving more than the receiver expects, assayed only in the ultimatum game). In these games, generosity is defined as offers greater than the average of the minimal acceptable amount.

Oxytocin's effects in this experiment were statistically even more notable than its previously discussed effects on trust.[54] In the ultimatum game, oxytocin increased generosity by 80% over placebo: generous participants left the game

Ultimatum Game (measures generosity) *	Dictator Game (measures altruism)
Initial split: DM1 has $10, chooses amount ($A) to give away to DM2, who has a minimum amount in mind that would be "acceptable" (= the ultimatum). 1a. "acceptable" split → DM1 keeps $(10−A), DM2 keeps $A 1b. "unacceptable split" → both get nothing	DM1 has $10 and chooses the amount to give away to DM2, who has no choice but to receive the offer.

FIGURE 5. Two related economic games: the "ultimatum" and "dictator" games. All participants received intranasal oxytocin or placebo. Generosity is defined as giving greater than the average minimum acceptable offer. An oxytocin effect is seen only when DM1 has reason to consider DM2's expectations as to what is a fair or reasonable transfer. In the ultimatum game, but not in the dictator game, when a transfer from DM1 falls below DM2's established minimum, neither DM1 nor DM2 keeps anything. DM1/2 = decision maker 1 or 2. ∗ = DM1's actions positively affected by oxytocin.

with less money. In the dictator game, by contrast, oxytocin did not affect transfers, indicating that simple altruism was not affected. Consonant with demonstrations that oxytocin improves one's ability to "read the mind" of another from facial cues,[56] Zak and colleagues[57] speculated that oxytocin had its impact on generosity via neural circuits related to empathy. That is, oxytocin increased DM1's sensitivity to DM2's anticipated negative emotional response to unfair offers, and motivated generosity as an effort to diminish this expected distress. Along these lines, it has been demonstrated that stingy offers in the ultimatum game provoke negative emotional responses and activate brain regions associated with visceral disgust in receivers,[98] an effect that ultimatum game participants in the role of DM1 would necessarily simulate when deciding.

These neuroeconomic experiments convincingly demonstrate that oxytocin biases decision making in a consistently prosocial direction without affecting subjective awareness.[58] As such, oxytocin appears to be an important component of the central neurobiological systems that consistently influence human moral reasoning and decision-making in ways that are less selfish than predicted by purely economic models.[99] Besides biasing economic decisions, this network of socially sensitive neural regions—dubbed the "social brain"[100,101]—also mediates a variety of skills (e.g., visual processing of social stimuli, mentalization, emotion recognition, social memory) known as social cognition.[101] The following section reviews oxytocin's impact on the social brain network and the multifaceted process of social cognition in more depth.

Oxytocin, Faces and the Social Brain

The functional construct of an amygdala-centered "social brain" (see Skuse & Gallagher [2008][101] for review) informs a second group of studies that have explored oxytocin's impact on the processing of social stimuli—typically, face pictures. Importantly, given that much of social cognition occurs outside of awareness, many of these experiments have a functional neuroimaging arm. A seminal study in this area showed 15 healthy males socially salient, emotionally evocative pictures (e.g., angry or fearful faces) and also nonsocial pictures (e.g., threatening or fearful scenes). Intranasal oxytocin significantly reduced amygdala activation in both conditions, with the greatest dampening effect on the socially relevant facial stimuli.[53] Similar to most studies of intranasal oxytocin in normal subjects (see Table 1), subjective measures—anger, dominance or arousal, and subjective discrimination tests—showed no drug effect. In accord with connectivity analyses in animals,[102] this study also demonstrated that oxytocin affected the functional coupling of the amygdala and brain stem regions (periaqueductal grey and reticular formation) that are part of the effector regions for the autonomic and reflexive behavioral components of fear[103] (see Figure 2). These findings relate to one of the few positive treatment trials with oxytocin in a clinical psychiatric population: male veterans with PTSD. In this early trial, Pitman[86] demonstrated that intranasal oxytocin lowered physiologic reactivity (heart rate, skin conductance, and lateral frontalis electromyographic responses) to personal combat prompts. Such physiologic effects, an important part of PTSD symptomatology, may be related to amygdala-midbrain activity.[104] Subsequent studies of oxytocin in PTSD—where this effect may be beneficial in extinguishing traumatic memories—have yet to be done.

Another neuroimaging experiment using facial stimuli explored oxytocin's role in the memory for aversive social experiences.[64] In a conditioned-aversion paradigm, negative subjective responses to certain faces were induced using an electric shock. Oxytocin abolished the neural activity in medial temporal and anterior cingulate cortices associated

with aversive conditioning and also reduced the negative subjective evaluation of shock-conditioned faces.[64] Notably, oxytocin's dampening effect on amygdala activity was more prominent when faces displayed a more socially salient, direct (vs. averted) gaze. Also notable is that oxytocin in this study affected a subjective parameter, as most extant studies in unstressed normals do not find such effects (but see Heinrichs et al. [2003]).[51]

Faces are a special category of visual stimuli uniquely involved with social approach, trust, and activity in many areas of the social brain.[105] Neurobiologically, neural and behavioral responses to facial stimuli are affected by the stress hormone cortisol,[106] anxiolytic agents like selective serotonin reuptake inhibitors,[107] and benzodiazepines,[108] as well as by the successful treatment of depression.[109] Extending these findings to oxytocin, Domes and colleagues[110] demonstrated that intranasal oxytocin reduced activity in the right amygdala, irrespective of the valence of the expressed facial emotion (angry, happy, or fearful). A second study using facial stimuli found oxytocin-treated participants were less likely to classify ambiguous facial emotions (surprise, neutral) as negative (sad or disgusting). Consistent with attenuation of reflexive attention to fearful stimuli, oxytocin-treated subjects took longer to correctly identify fearful facial expressions.[59] Along with the aforementioned evidence of the impact of oxytocin on the amygdala response to faces, this finding indicates that oxytocin has effects on reflexive visual attention, especially to social stimuli. These attentional effects may allow more accurate appraisal of ambiguous social signals, a clearly prosocial bias.[59]

Visual attention to the eye region of faces—an important part of first contact with other persons—is disordered in both social anxiety[111] and autism.[112] Typically rapid and reflexive, the visual processing of faces is a multistep process that involves both automatic, bottom-up attention (sensitive to the influence of the amygdala) and more elaborate, conceptually driven, top-down processing (mediated by prefrontal structures).[101] Several experiments have explored oxytocin's role in this component of social approach. Using a visual-search paradigm with schematic happy, neutral, and angry faces, Guastella and colleagues[113] demonstrated that although angry faces both attracted and held attention more than neutral or happy faces, oxytocin did not influence the early, pre-attentive perceptual detection of threat and did not enhance early processing of positive social stimuli. These data did not support a role for oxytocin in the very early threat-detection stage of visual attention to faces, but did indicate a role in later, more cognitive stages of processing. A second experiment in this area used advanced eye-tracking technology and demonstrated that oxytocin-treated males made an increased number of fixations and directed more total gaze time toward the information-rich eye region of faces than placebo participants, an effect that may facilitate social approach, improve social cognition, and foment the formation of memory for faces.[63] Perhaps unsurprisingly in view of oxytocin's evolutionary history, even cross-species eye contact may involve oxytocin: eye contact between dog owners and their dogs increased the owner's urinary oxytocin levels more than similar interactions without eye contact.[114]

After an initial, reflexive stage of visual attention—in which we rapidly assess trust, among other qualities—we further process visual information in others' faces to discern their motives and intentions. This crucial aspect of social cognition, which has been called *mentalizing*, allows us to "read the mind" of another person. Building on studies of the role of eye regions in mind reading,[115] Domes and colleagues[56] demonstrated that oxytocin improved performance on the RMET (the reading the mind in the eyes task), a visual test that involves intuiting the emotional state of a person from a cropped picture of the eye region. Notably, this effect was most significant for the more difficult-to-read facial expressions. Given the impairment in RMET performance shown in samples of patients with first-episode schizophrenia[116] and autism-spectrum disorders,[115] oxytocin's impact on mentalization has levered enthusiasm for trials of oxytocin in these disorders.

Specifically, patients with autism have impairments in the processing of facial stimuli, abnormal amygdala responses to faces, and pathognomic impairments in real-world social behavior.[10,17] Furthermore, autism has been linked to oxytocin polymorphisms in several different populations.[117,118] In two studies examining the effects of oxytocin in this disabling disorder, Hollander and colleagues demonstrated that IV oxytocin infusions reduced repetitive behaviors[77] and improved affective speech recognition, an important part of social cognition.[78] This pair of studies is novel in two ways: they demonstrate a central effect of IV oxytocin, and they are some of the first to evidence a beneficial effect of oxytocin in a psychiatric disorder. In regard to this latter point, though several early reports from Russia document beneficial effects of intravenous, -muscular, and -nasal oxytocin in schizophrenia,[87–89] these studies did not use currently recognized diagnostic criteria and outcome measures. Trials of intranasal oxytocin in autism and schizophrenia are ongoing.

Finally, though faces and eyes are the most salient social stimuli, oxytocin also demonstrates effects on the processing of certain classes of words that may uniquely affect the social brain. Using a timed word-recognition task, Unkelbach and colleauges[67] demonstrated that oxytocin selectively facilitated the recognition of positively valenced sex and relationship words more than words in other categories. These effects are consistent with oxytocin's role in the activation of multicomponent, unconscious neural networks associated with relationships and bonding. Though these prosocial

networks likely involve the amygdala as a central node,[53,110] studies of oxytocin's impact on the automatic processing of facial stimuli,[113] as well as investigations the neural basis of other attachment-related phenomena,[119,120] suggest that direct stimulation of social reward–related pathways in oxytocin receptor–containing areas like the orbitofrontal cortex and striatum (see Figure 2) may also contribute. Similar effects can also be intimated from studies of oxytocin's impact on verbal memory, addressed below.

SOCIAL CONSEQUENCES

Oxytocin, Stress Hormones, and Social Behavior

Though oxytocin's effects on the processing of social stimuli are compelling, the ultimate test of its role in the social brain is live social interactions. These interactions, due to the manifold nature of the social brain, have the capacity to alter the neurohormonal (stress hormone) axis—effects that have broad implications for human health and development through the lifespan. A seminal study examining these interactions stressed 37 normal men with an evaluative social performance task (the Trier Social Stress Test) after being given intranasal oxytocin or placebo and either social support from a close friend or no social support. Each active intervention—oxytocin and social support—independently attenuated a post-stressor increase in cortisol and caused an increase in post-task calmness ratings, and the combination of oxytocin and social support had an additive effect.[51] Notably, there was a trend toward decreased state anxiety in the both the oxytocin–social support and the oxytocin-alone group. Taking these findings a step farther, a recent gender-balanced study by Ditzen and colleagues[121] is the most naturalistic study of oxytocin to date. In this experiment, 47 heterosexual couples received intranasal oxytocin or placebo prior to a videotaped discussion of a conflict. Oxytocin significantly affected post-stressor cortisol levels as well as the ratio of observer-rated positive-to-negative social behavior in the discussion. Importantly, this ratio is a predictor of positive long-term relationship outcomes.[122] Also noteworthy, given the gender bias in extant human oxytocin research, is that these effects were demonstrated in both men and women. A third study using live social interactions examined the effects of oxytocin on empathy and pain processing. In this study, male participants viewed their female partners receiving painful stimuli and received the same stimulation themselves. Contrary to the initial hypothesis, oxytocin had no effect on either empathy for vicarious pain or activity in empathy-related brain regions (e.g., insula). Consistent with literature reviewed above, however, oxytocin did reduce amygdala activity when participants received painful stimulation to their own hands—especially participants classified as selfish based on their behavior in an economic game.[66] Notably, amygdala attenuation was seen only in the nonsocial (self-pain) group, a contrast to the putative selectivity of oxytocin for social stimuli (but see also Kirsch et al. [2005]).[53]

These studies are part of a growing body of research that links oxytocin with the salutory biological impact of social relationships, both in the short term (e.g., decreased cortisol, decreased sympathetic tone) and long-term (e.g., longevity).[36,37,123] At a neurobiological level, these findings are consonant with oxytocin's inhibitory impact on the hypothalamus-pituitary-adrenal stress-hormone system,[124] animal studies linking oxytocin and elevated stress hormones with social isolation,[125] and human studies demonstrating a relationship between stress hormones, oxytocin, and early relational trauma.[79] In this last study, men who reported a history of early parental separation (divorce or permanent separation from their parents) demonstrated attenuated decreases in cortisol levels after administration of intranasal oxytocin compared to men without such experiences. Other human experiments demonstrate that increased oxytocin levels and improved stress responses are related to training couples in a "warm touch" intervention,[48] reports of more frequent partner hugs,[37] and partner support.[36] Decreased cerebrospinal fluid levels have been correlated with childhood abuse,[28] and decreased oxytocin responses to social support may be related to early neglect.[49] As mentioned above, these latter findings are complicated by issues regarding the method of collecting the oxytocin level (salivary vs. plasma), the dual role of oxytocin as both a response to stress and an anxiolytic hormone,[48,126] and the as yet underspecified correlation between peripheral oxytocin levels and central release.[35,127]

Together, these studies indicate that oxytocin plays an important role in the social brain, influencing social behavior, stress-hormone systems, and the processing of social stimuli, including the other-related attributional processes called theory of mind. Next, we explore what may be oxytocin's most durable function over a person's life: the formation of social memories.

Oxytocin and Social Memory

Selective social memories are essential for the early survival of caregiver-dependent mammals and are the biological foundation for a variety of sustained social attachments. From a neurobiological vantage, in fact, attachment bonds can be conceptualized as multicomponent, other-related memory networks.[128] Based on both animal and human research, oxytocin appears to function as an important component of these complex social-memory networks.

Oxytocin's effects on memory have been reported in animals since the 1960s[129] and in humans since the 1980s.[130] Animal studies indicate that oxytocin's effects on memory vary considerably based on a number of factors, including the timing of delivery, social context, gender, and dose.[131] In rodents, oxytocin is involved in memory acquisition[132] and hippocampus-dependent spatial memory,[133] and is important in social recognition and partner preference—two behavioral expressions of social memory.[100] Recent experiments in voles indicate that variations in social attachment are related to differences in oxytocin receptor density in the nucleus accumbens.[134] Furthermore, mice without a functional oxytocin system (oxytocin "knockout" mice) do not recognize conspecifics; this function is restored with oxytocin treatment.[135] Amnesic effects of oxytocin have also been demonstrated in animals: conditioned avoidance, a type of learned fear memory, is attenuated by oxytocin, which causes decreased avoidance.[136]

Early human trials investigating oxytocin's impact on memory used predominantly verbal tasks with questionable ecological applicability vis-à-vis social memory. These early studies yielded mixed results, with some reporting memory impairment,[74] especially in verbal memory and initial rate of storage,[76] and others reporting no effect,[137] leading to lukewarm early reviews of oxytocin's specific memory effects in humans.[138] These early reports of oxytocin's role in memory focused on its general effects on arousal: in one study patients rated a subjective parameter called "vigor" lower.[76] More recent experiments using verbal-memory tasks have also demonstrated mixed effects: pretreatment with oxytocin had discrete amnesic effects on words with reproduction-related meanings,[52] whereas oxytocin produced memory enhancement for words describing positive characteristics.[59]

Human attachment and social memory is largely visual, and studies utilizing more socially salient visual stimuli have more incisively clarified the potential role of oxytocin in the formation of social memory. For example, 24 hours after being treated with a pre-task dose of intranasal oxytocin, a group of healthy males were more likely to accurately remember previously seen happy faces compared to angry and neutral faces.[139] In a similar study, Rimmele and colleagues[71] demonstrated that intranasal oxytocin improved 24-hour recognition memory for faces but not for nonsocial stimuli. Most prominent were effects on judgments of familiarity, which rely not on effortful retrieval of information, but on direct sensing of memory strength. A third mixed-gender study of post-task oxytocin treatment demonstrated improved facial-identity recognition, both 30 minutes and 24 hours after treatment, for neutral and angry (but not happy) faces. Oxytocin-treated subjects also had a lower false-alarm rate and were less likely to judge not-previously-seen faces as being previously seen.[140] Notably, this study differed in design from those by Guastella[139] and Rimmle[71] in the timing (pre- or post-task) of oxytocin delivery. As such, the seemingly contradictory findings—that pre-task oxytocin improves memory for positive faces over neutral or angry ones,[139] whereas post-task oxytocin improves recognition of neutral and angry, but not happy, faces[65]—may be reconciled by positing different effects of oxytocin on the dissociable processes of encoding and consolidation of emotional information. Specific facilitatory effects of oxytocin on the initial formation of social memories—encoding—is supported by experiments demonstrating that injections of oxytocin before, but not after, social encounters restores recognition memory in oxytocin knockout mice.[141]

In the maintenance of social amity, forgetting slights may be as important as remembering faces. As such, some of oxytocin's potential amnesic effects may also have prosocial ends. In an elegant study also discussed above, Petrovic and colleagues[64] used an aversive-conditioning paradigm (faces paired with a shock) to induce a negative affective response to a group of otherwise neutral faces. Consonant with oxytocin's attenuation of betrayal-triggered decrease in trust,[58] postconditioning oxytocin abolished the expected decrement in likability for shock-conditioned faces.[64] Essentially, oxytocin-treated patients forgot that they did not like the shock-labeled faces. These findings highlight a potential prosocial consequence of the inhibitory effect of oxytocin on the human amygdala,[53,58,64,110] given the critical role of the amygdala in forming emotional memory.[142]

Although the conclusions that can be drawn regarding oxytocin's role in human social memory are tentative, and although these effects in adult humans are often subtle,[59] extant literature suggests that oxytocin may have unique effects on the formation, maintenance, and reactivation of other-related memory networks. Though it may seem contradictory, ultimately prosocial ends could emerge from more proximate facilitation of both remembering and forgetting. On the remembering side, experiments in several different mammalian species[141,143,144] indicate that oxytocin facilitates the initial formation of attachment-related memory, an effect consonant with oxytocin's vital role in birth and nursing and the critical role of the mother-infant bond in both infant survival and subsequent adult attachment.[3] In terms of the location of these effects, experiments with oxytocin knockout mice, whose social memory relies on olfactory cues, indicate that oxytocin in the medial amygdala is an essential component of oxytocin's effects on encoding social memory.[145] In humans, where visual (facial) recognition is the primary means of social recognition, the fusiform face area—critical for processing invariant aspects of faces and closely linked to the amygdala—also appears to be involved, especially in women.[68,146] Given the role of both attention and glucocorticoids in memory, previously mentioned effects

of oxytocin on visual attention and stress-hormone systems may contribute to oxytocin's amnesic effects.

On the forgetting side of the equation, once a social memory is cemented, oxytocin's purported amnesic effect—especially for aversive experiences—may also facilitate the maintenance of social bonds. Animal experiments investigating mother-infant attachment in the context of an abusive parenting style highlight the role of a hypofunctioning amygdala in fomenting even ostensibly aversive early attachment bonds[147]—important data in view of oxytocin's attenuation of amygdala activity in humans.[53,58,64,110] As such, facilitated forgetting of certain aversive relational experiences (i.e., abuse, slights,[148] childbirth)[52] may complement improved initial encoding of social memories.

Finally, once the memory network that underlies a specific social bond has been established, the role of oxytocin in other aspects of human attachment (e.g., touch,[37] warm support,[36,48] endocrine and behavioral aspects of communication-related[149] and sexual behavior)[150] may further reinforce its role in activating unconscious social-memory networks. These memory effects are deftly synthesized by Brown[128] in a comprehensive model that conceptualizes attachment bonds as multicomponent, other-related memory networks that utilize various different brain circuits and a suite of neurochemicals (including oxytocin), all toward the ultimate goal of maintaining lasting social connections.

Oxytocin and Social Bonds: An Evolutionary Perspective

As evidenced by the research reviewed above, many of oxytocin's biological functions—both peripheral and central—revolve around inherently relational events. Regarding its central effects, the ubiquity of oxytocin-rich brain regions[2] and oxytocin-responsive social behavior in diverse mammalian species[151–154] highlights oxytocin's role in the evolution of central systems that privilege prosocial behavior.[155] Because of its utility as an organizing framework to understand oxytocin's diverse, centrally mediated effects in humans, we briefly review this evolutionary perspective on social bonds and oxytocin's role in promoting them.

The evolutionary perspective on oxytocin's role in attachment and sociality draws on findings from developmental psychology, evolutionary biology, ethology, and animal research (see Gimpl & Farenholz [2001][2] and Lim & Young [2006][156] for reviews). This perspective notes the extremely long lineage of the oxytocin-vasopressin family of peptides;[9] intraspecies conservation of a "social behavior network" and oxytocin-rich brain structures;[157] species differences in aspects of sociality and pair bonding associated with oxytocin;[4,6] and the historical link between the emergence of parental nurturance, nursing, and infant attachment following childbirth.[3] Furthermore, though there are obvious differences among species (e.g., human social recognition is primarily visual, whereas olfactory stimuli are predominant in other mammals), mammalian social bonds demonstrate several homologous components at a behavioral level, including: proximity seeking, nurturance, defense of offspring and mates, selective pair-bonding, and aspects of mating behavior (see Insel & Young [2001][4] for review). In decades of animal experiments, most of these attachment-related behaviors have been associated with the oxytocin and vasopressin neuropeptide systems, whose discrete central nervous system distribution and highly plastic receptors are especially suited to modulate such behaviors.[156–158]

Most importantly, perhaps, an evolutionary perspective on oxytocin acknowledges that for altricial species (i.e., those species born needing parental care), the immediate initiation and maintenance of social bonds is a survival necessity on a par with food and other basic elements.[159] As such, natural selection has privileged the development of a variety of socially oriented neural circuits that underlie selective attention, perception-action programs, and social memory.[160] Functionally, these circuits bias mammals to reflexively and actively orient themselves toward, seek, remember, protect, and maintain specific social bonds: these are the neural ties that bind.[3] Anchored deep in the brain, these prosocial tendencies and the proximate neural circuits and neurochemistry that drive them are thought to be retooled or "exapted" from other central circuits used earlier in evolutionary time for other purposes (e.g., mating and birthing).[3,159]

In order to achieve ultimately prosocial ends, evolution had to counterbalance the asocial tendencies of more primitive survival-enhancing systems, especially sympathetic fight-or-flight circuits.[159,161] An important part of this balance is the automatic environmental and social risk assessment that Porges[159] calls the "neuroception of safety." Consistent with the nonconscious activation of prosocial behaviors noted above, oxytocin in this model is construed to be an integral part of the neurochemical milieu that creates a reflexive sense of safety in the context of social bonds. Porges gives the example of how being held immobile to nurse—a critical prosocial survival behavior—may have been exapted from older defense-related brain regions associated with freezing behavior (e.g., amygdala, periaqueductal grey; see Figure 2) by the engagement of the oxytocin system, which attenuates activity in these regions.[53,159]

As such, evolutionary models conceptualize prosocial behavior and social bonds as the result of a dynamic balance between two "safety" systems: (1) an older, "defensive," threat-sensitive system that motivates fear, risk aversion, distrust, and social distance; and (2) innately rewarding,

but more recently evolved, attachment circuits that promote a felt sense of safety via social closeness, trust, and care for others.[159,162] Clearly, a central node of the older "defensive" safety system is the amygdala, which organizes hormonal, behavioral, and perceptual reactions to threat,[103] puts a brake on social approach,[163] and, as reviewed above, demonstrates a particular sensitivity to oxytocin[53,58,64,66,110] (see Table 1). Functionally, the amygdala couples with other brain regions (e.g., hippocampus, orbitofrontal cortex, cingulate, insula, ventral striatum, somatosensory and visual cortex) to mediate context-based social cognition and exploration as well as contingent, reward-based learning and memory[164,165] (see Figure 2). Balancing these threat-sensitive circuits are the previously mentioned prosocial neural circuits that motivate the liking, wanting, and seeking components of social drives. These intrinsically prosocial circuits include dopaminergic and opiatergic drive and reward pathways in areas like the orbitofrontal cortex, ventral tegmental area, and nucleus accumbens—areas that also contain oxytocin receptors and connections.[101]

This push-pull vantage on these two evolutionary safety systems serves to link anxiolysis and the dissolution of other asocial perceptual biases like distrust, on the one hand, with an enhanced capacity to form and sustain social bonds, on the other, giving oxytocin the status of an "anxiolytic attachment peptide."[166] Uvnas-Moberg and colleagues,[161] expanding on this perspective, characterize oxytocin as a central component of an oft neglected "calm and connection system," which provides homeostasis for fight-or-flight drives and also supports beneficial social connections by biasing sensory, hormonal, autonomic, emotional, and motor systems toward calm, receptive social connection—the prototype being the bond between infant and nursing mother.

In addition to providing a framework to understand how oxytocin's myriad central effects privilege social connections and enhance survival, an evolutionary perspective links differences in the oxytocin system, both static (genetic variability between people) and dynamic (within an individual, based on social context, biological state, experience, gender, and the nature of stimuli), with differences in social behavior. Though the link between variations in the oxytocin system and attachment behavior has been demonstrated in animals,[1] and though genetic variations in the oxytocin system have been associated with autism[12] and perhaps with a trait disposition to social attachments,[167] more detailed exploration of these associations in humans is in its infancy. Although the evolution of the human cortex, learning, and culture has unyoked our social behavior from subcortical systems like oxytocin,[10] as demonstrated by the above body of research, their influence on the social perception, memory, and behavior of humans remains significant.

THERAPEUTIC POTENTIAL OF OXYTOCIN

The existing animal and human literature on oxytocin suggests several therapeutic arenas where oxytocin may prove beneficial, including: anxiety disorders (e.g., social phobia, posttraumatic stress disorder, separation anxiety disorder), disorders with prominent social dysfunction (e.g., autism, autism spectrum disorders, schizophrenia), mood disorders (e.g., postpartum depression), sexual disorders, and borderline personality disorder. Currently, central effects of oxytocin in clinical populations have been reported in autism,[77,78] posttraumatic stress disorder,[86] sexual dysfunction,[91] schizophrenia,[87–89] and a subset of chronic constipation patients with irritable bowel syndrome[81] (see Table 1). This latter study is currently the longest (13 weeks) and largest one reporting central effects of intranasal oxytocin. In a population of 49 women with chronic constipation, though oxytocin did not separate from placebo in measures of constipation, it did demonstrate a tendency to reduce abdominal pain, discomfort, and depressed mood.[81] Notable also are small negative trials of oxytocin in obsessive-compulsive disorder and trichotillomania[84,85] Given oxytocin's ancient history and the fact that perturbations in social relations are a prominent component of most major psychiatric disorders, it is likely that any therapeutic effects of oxytocin will cross current diagnostic boundaries.

More speculatively, oxytocin, by acting directly on the neural substrates of attachment, may be useful as an "augmentation agent" in individual or couples psychotherapy.[60,168] Links between psychodynamic, developmental, and neurobiological constructs[169] raise the possibility that oxytocin's pro-trust effects may diminish reflexive, brain-based defense mechanisms related to betrayal aversion.[148] These effects may be beneficial in psychotherapy, where defense mechanisms and conditioned avoidance interfere with psychotherapeutic change.[170] MDMA (3,4-methylenedioxymethamphetamine), which has oxytocinergic activity, has been investigated in this context.[171] From a broader perspective, oxytocin's role in the formation of social memories and its salutory effect when combined with social support[51] may reinforce the relational component of many therapeutic interventions.

Further advances in oxytocin's therapeutic potential may come if and when oral agents that target the central oxytocin system are developed. A simple peptide, oxytocin given orally or intravenously is rapidly degraded by peptidases in the plasma and gut. Furthermore, due to the blood-brain barrier, oxytocin in the plasma has little penetration into the central nervous system.[50] Hence, intranasal delivery—a relatively uncommon delivery system in psychiatry—is the most reliable current means to obtain demonstrable central effects.[50]

LIMITATIONS OF CURRENT HUMAN RESEARCH

The human oxytocin research reviewed herein demonstrates a myriad of interesting effects, but significant limitations exist in terms of our understanding of oxytocin's therapeutic use. First and foremost, although treatment studies in several clinical conditions are ongoing, there is a prominent lack of studies of oxytocin in psychiatric populations.

Second, issues of dosing are not clear. In this regard, endogenous oxytocin is typically released in a context-specific, pulsatile pattern, and is involved with many short-duration effects (e.g., parturition, milk letdown, orgasm, the initial phase of attachment).[31] Thinking naturalistically, in a setting like breastfeeding, phasic central release of oxytocin occurs many times a day over months to years. As such, the actual clinical effects of single-dose oxytocin—as are studied in the bulk of current human research—are likely to be small. Also worth noting as regards dosing is that oxytocin has a short plasma half-life (1–2 minutes) and a slightly longer central half-life (30 minutes) (see Ludwig & Leng [2006][31] for review), though intranasal delivery stimulates more prolonged central release,[92] and "upstream" effects may extend its biological activity, even after a single dose.[161]

Third, the safety of long-term, higher-dose use remains unknown. Despite its use as a lactation aid[172] and early reports of its safety,[81] potential negative effects are still understudied. Concerns include oxytocin's safety in females at different reproductive phases and its potential to cause electrolyte imbalances with chronic use[173]—due to oxytocin's structural similarity to arginine vasopressin and its effects in the kidneys.[174] A final limitation is that current human research has a largely male bias (see Table 1) because of the potential variability of oxytocin effects based on levels of female hormones and also because of the increased potential health risks of oxytocin for females (e.g., induction of uterine contractions). Although some of the conditions in which the oxytocin system may play a role have a male predominance (e.g., autism), others—anxiety and depression—are more common in females.[175] Redress of these shortcomings and a clearer understanding of oxytocin's therapeutic potential will emerge from research examining the effects of more chronic administration of oxytocin in specific clinical populations, including women during different phases of the life cycle.

With a vast, ever growing literature on its effects, the oxytocin system is one of the best studied mammalian brain systems. As such, this focused review has not adequately addressed a large number of topics, including: (1) studies of oxytocin plasma levels, (2) details of the complex physiology of the oxytocin system, (3) interactions between oxytocin and other neurotransmitter and hormonal systems, (4) oxytocin's role in stress and anxiety, (5) oxytocin's role in sexual behavior, (6) the relationship between oxytocin and gender, (7) the dynamics and relationships between the arginine vasopressin and oxytocin systems, (8) the role of oxytocin in the maternal brain, and (9) details of oxytocin studies in animals. These topics, all germane to oxytocin's role in humans, are addressed in more depth in several of the reviews cited here.[2,6,7]

SUMMARY

Several conclusions can be drawn from this review. First, to understand the implications of human research with oxytocin, it is valuable to understand aspects of its evolutionary history, neurobiology, and peripheral physiology. Second, given technical issues around oxytocin levels and cross-species differences, human studies using intranasal oxytocin are of particular importance. These studies demonstrate that the oxytocin system is an important component in the suite of neural systems that operate, often unconsciously, to bias humans toward prosocial ends. As such, oxytocin has effects on social perception, behavior, and social memory, and demonstrates prominent effects on the amygdala, a central nexus of the social brain.[101] Third, research with oxytocin raises important questions about the neurobiological sequelae of early relational events (epigenetics), and highlights a biological system that may contribute to interindividual and gender-based differences in prosocial behavior. Finally, given oxytocin's conservation through evolutionary time and the ancient brain structures where it has most of its effects, an evolutionary perspective on the dynamics of pair bonding and sociality uniquely frames oxytocin's impact on the brain and human behavior. Regardless of oxytocin's ultimate therapeutic utility, the study of the oxytocin system in humans has uniquely illuminated aspects of the microstructure of our uniquely social mind and brain. Following the path of oxytocin backward, both in our personal histories and in evolutionary time, we see that it has played a vital role in a long love story that began with courtship, sex, and birth.[3,155]

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