

REVIEW ARTICLE



Oxytocin and the social facilitation of placebo effects

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Significant clinical improvement is often observed in patients who receive placebo treatment in randomized double-blind placebo-controlled trials. While a proportion of this “improvement” reflects experimental design limitations (e.g., reliance on subjective outcomes, unbalanced groups, reporting biases), some of it reflects genuine improvement corroborated by physiological change. Converging evidence across diverse medical conditions suggests that clinically-relevant benefits from placebo treatment are associated with the activation of brain reward circuits. In parallel, evidence has accumulated showing that such benefits are facilitated by clinicians that demonstrate warmth and proficiency during interactions with patients. Here, we integrate research on these neural and social aspects of placebo effects with evidence linking oxytocin and social reward to advance a neurobiological account for the social facilitation of placebo effects. This account frames oxytocin as a key mediator of treatment success across a wide-spectrum of interventions that increase social connectedness, thereby providing a biological basis for assessing this fundamental non-specific element of medical care.

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INTRODUCTION

The analgesic effect of remifentanyl, a potent opioid drug routinely used in surgery to treat pain, can be substantially enhanced or abolished by verbally leading patients to expect pain relief or pain worsening during its administration [1]. This is true for subjective assays like self-reported pain intensity on a visual analog scale, and objective assays like neural activity in key nodes of the brain's pain network [1]. Such strong ‘expectation effects’ on treatment response are common in medical contexts and have been repeatedly demonstrated under well-controlled conditions using objective measures [1–13].

The fact that expectations can so radically alter treatment efficacy is mainly considered a nuisance in modern medicine. Expectation effects interfere with our ability to isolate the impact of treatment during a clinical trial, and their variance across individuals and contexts makes them difficult to predict. Much of the problem stems from the fact that expectation effects have mostly been considered as mental phenomena resistant to biological analysis. Over the last 20 years, however, research on placebo effects (detailed below) has begun to converge on evidence that expectations impact treatment effects by engaging brain reward circuitry (see [14] for a review). This newfound biological tractability has generated excitement over the possibility that a more meaningful integration of expectation effects within medicine can improve treatment efficacy, clinical outcomes, and research methods [9, 15–18].

Here, we focus on a particular aspect of this effort: the facilitation of placebo effects by affiliative interactions. Specifically, we advance the hypothesis that increased social connectedness resulting from trial participation (e.g., between a patient, their loved ones, and/or clinicians; Fig. 1A) stimulates an oxytocin-mediated upregulation of reward processing in the patient's brain,

increasing expectations of treatment success, and the placebo effects that follow (Fig. 1B). Our motivation to develop this *oxytocin placebo hypothesis* originated following completion of our randomized double-blind placebo-controlled trial of oxytocin treatment in children with autism spectrum disorder, where we observed improvements in social functioning among children receiving placebo treatment that coincided with endogenous increases in oxytocin secretion (detailed below; [19]). Our finding, together with evidence linking placebo effects to brain reward circuitry and social connection, as well as recent advances in the neurobiology of oxytocin and social reward, supports a key role for oxytocin in the social facilitation of placebo effects.

Definitions

Before addressing the neurobiological foundations of the oxytocin placebo hypothesis, we define our terms and briefly review the evidence linking placebo effects to expectations, reward processing, and social connection. We define *placebos* in line with their common understanding as “sugar pills”, or treatments that in theory lack direct therapeutic effects on a predetermined biological target. While placebos may be found outside of experimental contexts, in medicine they are most commonly used to provide negative control in placebo-controlled clinical trials. For a placebo to provide effective negative control, the placebo-control treatment group must be identical in every possible way to the active treatment group, except that the placebo treatment lacks the component of active treatment hypothesized to have an effect. In practice, this requirement is satisfied by aspects of clinical trial design that are not typically included in placebo definitions, such as randomization, blinding, and balancing [20]. This is important because without each of these other aspects being rigorously implemented, a difference in

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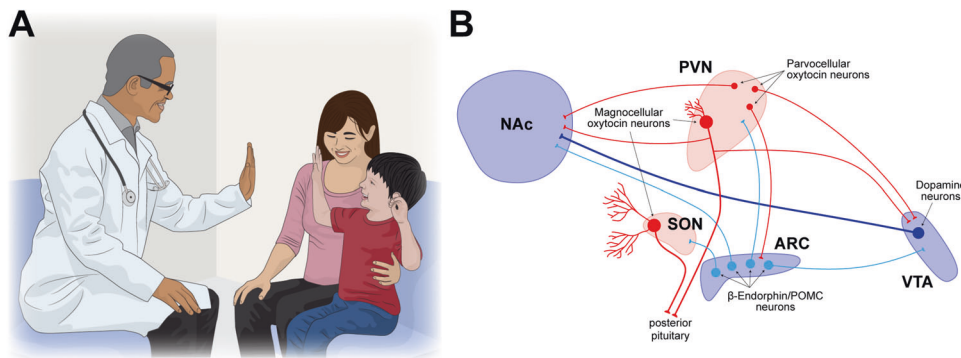


Fig. 1 Oxytocinergic modulation of reward processing and the social facilitation of placebo effects. **A** A depiction of the positive social context that often accompanies routine clinical care and participation in clinical trials. **B** A schematic depiction of brain reward circuitry implicated in placebo effects (blue) shown together with key components of the hypothalamic oxytocin system (red). Three different modes of oxytocin release are numbered: (1) neurosecretory release into systemic circulation by magnocellular projections to the posterior pituitary; (2) somato-dendritic release by magnocellular neurons into cerebrospinal fluid and extracellular space; and (3) synaptic release by parvocellular and magnocellular projections onto specific central targets. The oxytocin placebo hypothesis proposes that the social facilitation of placebo effects is primarily driven by mode 3, with the oxytocinergic projections to the VTA and NAc that modulate dopaminergic reward processing being most essential. Whether these projections are parvocellular and/or magnocellular in humans is not certain; evidence from rodent studies indicates potential species-specific differences [148, 149]. Effects of mode 3 oxytocin release on the social facilitation of placebo effects are hypothesized to be particularly strong in patients with low overall oxytocinergic tone (i.e., modes 1 and 2 are hypoactive). ARC = arcuate nucleus, NAc = nucleus accumbens, PVN = paraventricular nucleus, POMC = proopiomelanocortin, SON = supraoptic nucleus, VTA = ventral tegmental area.

outcome between a placebo-control and an active treatment group cannot be logically attributed to the difference between placebo and active treatment. This shows that although randomization, blinding, and balancing are not part of most “placebo” definitions, they are nonetheless critical to arriving at a clear definition of “placebo effects”, which are often ill-conceived as *any* significant improvement that occurs in a placebo-control group. This conception is a problem because improvements in placebo-control groups result from a variety of factors—e.g., spontaneous remission, regression to the mean, routine clinical care, reporting biases, concomitant changes in diet or exercise, etc.—many of which are unrelated to physiological responses to placebo treatment [14, 21]. For this reason, we focus on effects of placebo treatment that are evident even when all other explanations have been ruled out. Following Benedetti (2021), such *placebo effects* may be defined as clinically-relevant benefits of treatment that result from the activation of anticipatory brain mechanisms. Defining placebo effects in these terms makes it clear that the focus of their investigation should be on circumscribed objective phenomena, rather than the myriad confounding factors capable of influencing the results of a clinical trial, particularly under failures of randomization, blinding, or balancing [14].

Expectations

As described above, whether a patient expects a treatment to be successful is a key component in shaping their clinical response. Expectations refer to the anticipated likelihood of an outcome or effect [22], and may involve explicit conscious components (like believing that a treatment will work) and implicit unconscious components (e.g., a conditioned response to taking a pill), either of which can impact treatment response [23, 24]. The importance of expectations in determining placebo effects is self-evident in the design of experimental paradigms commonly used to induce them in laboratory-based research [14, 22]. In one common paradigm for inducing placebo effects, the same treatment is administered under two conditions, once with a verbal description designed to raise explicit expectations of benefit (e.g., “this is a potent painkiller”), and once with a verbal description designed to lower explicit expectations of benefit (e.g., “this is just a placebo”; [23, 25–28]). In another common paradigm, explicit expectations are manipulated using clinicaltrial type language, e.g., telling

participants “you will receive either an active treatment or a placebo” [2, 3, 11, 29]. This shows that even the possibility of receiving active treatment can be sufficient to create expectations of benefit that induce placebo effects, as often occurs in clinical trials [30–32]. A third approach for inducing placebo effects uses conditioning to generate implicit expectations. For example, a response to treatment can be conditioned by repeatedly administering an active drug solution, which is then surreptitiously replaced by saline that now produces a similar effect [23, 26, 33]. The degree to which placebo effects induced by explicit expectations resemble those induced by implicit expectations in terms of underlying neurobiology remains unresolved, but some form of expectation (or neural anticipation) is clearly essential to both. Finally, placebo effects can be induced indirectly by simply witnessing another person report benefits from placebo treatment [34], highlighting the importance of social learning in transmitting expectations (see below).

Placebo neurobiology

Recent progress in understanding the neural basis of placebo effects originated with the discovery that explicit expectations about treatment benefits correlate with activity in brain reward circuitry, particularly mesolimbic dopamine projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc; Fig. 1B; [35]). This progress has largely depended on imaging endogenous dopamine and opioid function in humans using competitive binding measures derived from positron emission tomography with radio-labeled ligands for the dopamine D₂ receptor ([¹¹C]raclopride) and the μ-opioid receptor (MOR; [¹¹C]carfentanil). The initial breakthrough in placebo neurobiology came in the context of Parkinson’s disease, when it was shown that treatment with a placebo in a clinicaltrial type paradigm stimulated endogenous dopamine activity in the striatum of patients [2], including the NAc [36] (replicated by [37]). Subsequent work extended this result to a different context—an experimental model of pain in healthy participants—finding that treatment with a placebo “analgesic” also stimulated dopamine activity in the NAc [5]. Further solidifying a link between placebo effects and reward processing, this study also found that individual differences in the NAc dopamine response to placebo treatment were correlated with individual differences in the NAc’s

general reactivity to reward (as measured in an separate experiment using a functional magnetic resonance imaging paradigm designed to stimulate NAc activity with monetary rewards [38]). Other studies of placebo effects in the context of pain have additionally implicated MOR-mediated aspects of reward processing, reporting increases in endogenous MOR activity in the NAc [3, 4, 6] and VTA [4] following treatment with a placebo analgesic. A third context in which placebo effects have been linked to reward processing is major depressive disorder, where treatment with a placebo described as a “fast-acting antidepressant” was found to stimulate increases in both dopamine and MOR activity in the NAc [7, 8]. Taken together these studies indicate that brain reward processing—particularly its dopaminergic and MOR-mediated aspects—comprises a generalizable neurobiological foundation for placebo effects arising from expected treatment benefits.

The social facilitation of placebo effects

Another key issue to consider in framing the oxytocin placebo hypothesis is the close relationship between placebo effects and the social contexts that facilitate them. When an individual enrolls in a clinical trial, it is typically because they have a medical condition that represents a significant obstacle in their life that they cannot otherwise overcome. They have often exhausted the advice and guidance of family, friends, and a variety of medical professionals. In this context, trials offer new hope brokered by experts on the leading edge of science. Although a variety of social factors contribute to hope associated with treatment—e.g., culturally propagated beliefs about health and medicine [39], the reputation of a hospital or physician [40], how a treatment is priced/marketed [12, 41], etc.—in the context of a clinical trial, hope is stimulated most directly through social interactions, maybe first indirectly via an institutionally-associated advertisement, but then always directly through conversations and meetings between patients, their loved ones, and clinicians/researchers (Fig. 1A). The information shared during these exchanges, verbally and non-verbally, consciously and unconsciously, is an important modulator of expectations and the placebo effects that follow. Clinicians who inspire trust by behaving in ways that demonstrate warmth and proficiency—e.g., by making frequent eye contact, smiling, empathizing, and actively listening, being accurate and insightful, speaking clearly and confidently, being organized, and executing procedures without error—are associated with increased placebo effects across a range of clinical outcomes [9, 42–45]. Conversely, behaviors that demonstrate a lack of interest or incompetence—making minimal eye contact, not smiling, restricting conversation, using filler words like “um”, being disorganized, and making obvious procedural errors—significantly reduce the benefits of placebo treatment [9, 42–45]. In sum, social factors can play a determining role in shaping placebo effects, with the most direct being the degree of social connection experienced during a clinical interaction. Specifically, placebo effects are increased by interactions in which a strong social connection is made, through some combination of experienced affective positivity, affection or warmth, reciprocal understanding, respect, and/or empathy¹. Conversely, interactions that lack these features decrease placebo effects.

¹More broadly, an individual’s overall level of “social connectedness” is an important predictor of well-being, morbidity, and mortality. Social connectedness can be measured by assessing structural, functional, and/or qualitative aspects of an individual’s relationships (e.g., the size of their social network, their access to social support, and affective valences), and is increased by forging new social connections of the kind described here [46, 47].

A ROLE FOR OXYTOCIN?

The potential involvement of oxytocin in placebo effects has been a topic of consideration since at least 2009 ([48, 49]; see also [14]). However, not until now has there been sufficient evidence to clarify its neurobiological basis and social specificity. Oxytocin is an essential modulator of social behavior in humans and other animals [50]. Of critical importance here, oxytocin regulates many affiliative behaviors that increase social connection and facilitate placebo effects. Oxytocin is mainly produced by magnocellular neurons that project from the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus to the posterior pituitary, from where oxytocin enters systemic circulation to induce numerous peripheral effects involved in core reproductive functions like sex, parturition, and lactation [51–53]. More subtle behavioral and perceptual effects of oxytocin, on the other hand, are regulated by its actions in the brain, where oxytocin functions as a neuromodulator. Central oxytocin effects are determined by release from the soma and dendrites of magnocellular neurons in the SON and PVN, and by projections of parvocellular neurons from the PVN to specific targets throughout the brain and spinal cord (Fig. 1B; reviewed by [50]).

Most of what we know about the role of oxytocin in acute social interactions comes from assessments of endogenous oxytocin concentrations measured in peripheral fluids (blood, saliva, or urine) or behavior measured following intranasal administration of (synthetic) oxytocin. Increases in endogenous oxytocin concentrations have been measured in the context of affiliative interactions, including receiving social support after stress [54], sharing gaze and interacting with dogs [55, 56], and moving together in synchrony [57]. Endogenous oxytocin concentrations have also been found to predict individual differences in social functioning across children with and without autism [58]. Intranasal administration studies have associated oxytocin with a variety of social behavioral and perceptual effects, including context-dependent increases in trust [59, 60], generosity [61], cooperation [62], affiliation [63], mentalization [64], emotion recognition [65], and gaze towards the faces and eyes of others ([66]; especially those displaying positive affect [67]). Together, these findings implicate oxytocin as a key factor in the type of positive social interactions that facilitate placebo effects.

Oxytocin and social reward

Primary rewards, like food and water, engage brain reward circuits that motivate and reinforce behaviors important for survival and reproduction, and there is growing evidence that being close and connected with others can function in the same manner [68, 69]. An early indication that oxytocin is involved in the rewarding aspects of social connection came from the finding that high densities of oxytocin receptors (OXTRs) in the NAc are associated with high levels of affiliative behavior in different species of rodents [70] and, to some extent, primates [71]. For example, in prairie voles, pharmacologically blocking OXTRs in the NAc disrupts social bonding [72] and maternal care [73]. More recently, in mice, it was found that oxytocin neurons in the PVN project directly to the NAc, and comprise a significant source of the oxytocin found there (Fig. 1B; [74]). Critically, the same study also found that interfering with oxytocinergic projections from the PVN to the NAc blocks place preferences conditioned by affiliative interactions, but not place preferences conditioned by cocaine, implying that the effects of NAc oxytocin on reward processing are socially specific [74]. Moreover, the affiliative interactions used to condition place preferences in this study were between “consociates”, or group members not related by familial or reproductive bonds [69]. Thus, oxytocinergic projections from the PVN to the NAc appear to regulate reward derived from non-reproductive affiliative interactions, providing a potential model for the social reward in patient-clinician relationships.

Evidence from human studies combining single-dose intranasal oxytocin administration with functional magnetic resonance imaging suggests that affiliative behaviors and perceptions are similarly supported by oxytocin signaling. Intranasal oxytocin administration increases activity in the NAc and VTA in response to viewing photographs of a romantic partner's face [75], and striatal activity more broadly in response to socially salient cues [76]. Furthermore, as in rodents, these effects exhibit social specificity, with oxytocin-induced increases in activity within the NAc and VTA being observed during the anticipation of social but not non-social rewards (a smiling face but not a grey circle; [77]). Together, these studies suggest that oxytocin potentiates the impact of social interaction on reward processing in rodents and humans.

Oxytocin facilitates dopaminergic reward

Oxytocin's effects on social reward appear to be largely mediated through dopamine [78]. In prairie voles, inhibiting dopamine D₂ receptors in the NAc has been found to block social bonding (without significant extrapyramidal reductions in locomotor activity) just like blocking OXTR does [79–82]. This suggests that the rewards of social connection depend on both oxytocin and dopamine. Moreover, this dual dependence involves interactions between oxytocin and dopamine, as inhibiting OXTR activity in the NAc blocks social bonding induced by D₂ agonists, and D₂ antagonists block social bonding induced by oxytocin (again without adverse effects on locomotion; [82]). In mice, further investigations have shown that oxytocinergic projections from the PVN modulate afferent excitatory synapses onto D1 and D2 dopamine receptor-expressing NAc neurons, providing a potential circuit-level explanation for the above-mentioned pharmacological effects [74]. Use of optogenetic and fiber photometric tools has shown that the activity of some dopamine neurons in the VTA is time-locked to specific affiliative behaviors (sniffing and contact), and that stimulating or inhibiting the subset of these neurons that project to the NAc is sufficient to increase or decrease these affiliative behaviors respectively [83]. Tying this dopaminergic control of affiliation back to oxytocin, oxytocin neurons in the PVN that project to dopamine neurons in the VTA exhibit activity that is similarly time-locked to affiliative behavior (specifically social contact; [84]). Moreover, inhibiting these VTA-projecting oxytocin neurons, or their modulation of dopaminergic neurons in the VTA, again blocks place preferences conditioned by consociate interaction but not cocaine ([84] see also [85]), mirroring the socially-specific effects of interfering with NAc-projecting PVN oxytocin neurons noted above. Finally, OXTR agonists stimulate NAc-projecting dopamine neurons in the VTA, resulting in dopamine increases in the NAc [84]. Together, these results show that oxytocin, via direct axonal projections from the PVN to the NAc and VTA, plays a key role in upregulating dopaminergic aspects of reward processing in social contexts, with the net effect of promoting rewards derived from affiliative consociate interaction.

Oxytocin and the facilitation of opioidergic reward

Like oxytocin and dopamine, opioids—particularly those that stimulate MORs—play an important role in social reward processing [86, 87]. For example, in rats, selectively stimulating MORs in the NAc produces socially-specific increases in play behavior (i.e., with conspecifics but not toys), whereas selectively stimulating the δ - or κ -opioid receptors (DORs or KORs) does not [88]. This suggests that MOR activity specifically promotes the rewards of consociate interaction, much like oxytocin. There is also evidence of interaction between oxytocin and opioids. Early work focused on the inhibition of oxytocin release by MOR activity. For example, in pregnant rats, endogenous opioids inhibit the neurosecretory release of oxytocin from magnocellular neurons in the SON until it is needed for parturition, an effect likely

mediated by MORs [89, 90]. Similar suppressive effects of MOR activity on oxytocin have been observed in rodent addiction studies, where chronic treatment with morphine (which preferentially binds MORs [91]) produces marked decreases in the oxytocin content of the SON, and to a lesser extent the NAc (but not the PVN or VTA; [92]). Conversely, systemic treatment with naloxone (which antagonizes MORs, but also KORs and DORs; [91]) has been shown to enhance the positive effects of intranasal oxytocin on facial gaze and eye contact in macaques, an effect proposed to reflect a “release” from MOR-mediated inhibition at oxytocin neurons [93]. Further evidence of oxytocin-opioid interactions comes from *Oprm1* knock-out mice, which lack the gene encoding the MOR, and which exhibit profound changes in oxytocin biology alongside major deficits in social responsivity and interaction [94–97]. Here, oxytocin seems to play a compensatory role, as *Oprm1* knock-outs have twice as many OXTRs in the NAc compared to wildtype, and some of their social deficits can be rescued, rather remarkably, with a single dose of intranasal oxytocin [97]. More evidence of functional alignment between oxytocin and opioids comes from intracerebroventricular infusions of oxytocin in prairie voles, which have been found to increase proenkephalin mRNA in the NAc [72], ultimately increasing the production of enkephalin and other opioid peptides that preferentially bind DORs and MORs [91]. Finally, there is evidence from an *in vitro* study of cultured embryonic kidney cells transfected to express MORs, showing that oxytocin enhances MOR signaling in response to a variety of agonists, potentially by binding MOR as a positive allosteric modulator [98].

Interpreting the significance of the above results for the oxytocin placebo hypothesis may appear challenging. In particular, the suppression of oxytocin by MOR activity is difficult to square with similar (or more aligned) roles in social reward. However, upon closer examination, the available evidence suggests that although MOR activity suppresses oxytocin, oxytocin may nonetheless facilitate certain aspects of MOR-mediated reward. One way for this to occur is indirectly via dopamine: well-established facilitatory interactions between dopamine and opioids in reward processing [99–103] suggest that oxytocin's capacity to upregulate mesolimbic dopamine should also stimulate opioidergic reward mechanisms. A growing distinction in the neurobiology of reward proposes that mesolimbic dopamine is primarily associated with motivational elements, such as incentive salience and “wanting”, whereas MOR activity in specific subregions of the NAc is more associated with hedonic elements like pleasure and “liking” [104]. Thus, given that an ‘appetite’ for social closeness leads to its “consumption”, oxytocin's effects on mesolimbic dopamine can be expected to indirectly promote MOR-mediated aspects of social reward. In accord with this view, positron emission tomography studies of placebo effects in humans have shown that dopaminergic and MOR-mediated NAc responses to placebo treatment are positively correlated across individuals [6]. Moreover, the dopaminergic response has been found to better track the self-reported anticipation of benefits, whereas the MOR-mediated response more closely tracks the self-reported experience of benefits [7, 8]. Finally, beyond indirect facilitation, there is clear potential for direct facilitation of MOR activity by oxytocin. Rat studies show that neurons in the arcuate nucleus (ARC) of the hypothalamus—which comprise the brain's principal source of the MOR (and DOR) agonist beta-endorphin [86, 91, 105]—are innervated by oxytocin neurons in the PVN [106], and that ARC neurons expressing beta-endorphin (or its precursor proopiomelanocortin) project to all regions implicated here in the social facilitation of placebo effects, including the VTA [107], NAc [105], PVN [108], and SON (Fig. 1B; [109]). Moreover, if oxytocin is confirmed to bind MOR as a positive allosteric modulator, oxytocin projections from the PVN may facilitate MOR signaling within the NAc itself. Thus, despite a lack of primary evidence that oxytocin facilitates MOR-mediated

aspects of social reward in vivo, oxytocin does appear well-suited to this function, indirectly via actions on mesolimbic dopamine and/or directly via actions on opioid activity in the ARC or NAC.

Implications of the Oxytocin Placebo Hypothesis for Behavioral Interventions

Compared to pharmacological treatments, placebo controls for behavioral interventions can be challenging to implement due to the dynamic nature of the social interactions on which they depend. Moreover, these social interactions themselves appear to be essential determinants of treatment success in even the most well-supported forms of behavioral intervention [110]. Early research on psychotherapeutic efficacy suggested that the relationship between therapist and client is of critical importance, perhaps even more so than a therapist's training in any particular approach or their level of experience [111]. For example, in one seminal study "treatment therapy" sessions for "disturbed" college undergraduates with highly compassionate but otherwise untrained professors of English, Philosophy, Mathematics, and History were found to be as effective as psychotherapy sessions delivered by experienced professional psychotherapists [112]. Further research has shown that effective therapist-client relationships are based, in part, on therapist behaviors that demonstrate trustworthiness, warmth, interest, and confident guidance, all of which are core components of a "therapeutic alliance" [113]. These factors, together with the positive feelings that arise in the patients as a result of their application, remain some of the best predictors of treatment success for behavioral interventions to this day [110, 114, 115], implying that the neurobiology underlying the social facilitation of placebo effects may also play an important role in the success of behavioral interventions more broadly. This is not to say that particular behavioral interventions do not carry specific benefits that are independent from increases in social connectedness—studies that have included socially supportive counseling or therapy as negative-control treatments suggest that they do [116–118]—but socially supportive control treatments also tend to be more effective than other control treatments that do less to improve social connectedness (e.g., waitlist or treatment-as-usual; [117, 119]). Accordingly, a significant component of the benefits that arise from behavioral interventions may be related to increases in social connectedness that stimulate the oxytocinergic upregulation of brain reward circuitry, increasing

sensitivity to positive social cues and expectations of clinical benefits [14, 120]. As such, deciphering between treatment benefits attributable to the biological effects of increased social connectedness versus other components of treatment is an important step towards better clinical trial designs and treatment optimization.

OXYTOCIN BIOLOGY AND THE IDENTIFICATION OF PLACEBO EFFECTS

If oxytocin underlies treatment effects driven by trial-induced increases in social connectedness, assessments of an individual's endogenous oxytocin biology may prove useful in identifying when such effects occur. Evidence in support of this possibility comes from our recent randomized double-blind placebo-controlled trial of intranasal oxytocin treatment in children with autism [19]. As is often the case in autism trials [31, 121], a large proportion of the placebo-treated individuals in our trial showed improvements in social function (measured using a 65-item parent-rated scale focused on reciprocal social behavior and communication; [122]), despite being treated with a vehicle spray that lacked oxytocin. Intriguingly, these improvements were predicted by individual differences in endogenous oxytocin biology: placebo-treated individuals with lower pre-treatment (baseline) blood oxytocin concentrations showed the most improvement (Fig. 2A), and post-trial increases from baseline in blood oxytocin concentration correlated with the amount they improved (Fig. 2B). These results are consistent with the placebo effect on social function observed in our trial being underpinned by an increase in endogenous oxytocin secretion. Although the cause of this neural response cannot be determined with certainty, an intriguing possibility is that it was driven by increased social connectedness between participants and supporting family members (patient-clinician interaction was relatively limited by comparison), whose hopeful expectations may have inspired a boost in their affiliative interactions with participants.

In considering how far beyond our trial the observed connection between placebo effects and oxytocin is likely to generalize, one important point of caution is that placebo effects are often most apparent in conditions involving specific deficits in systems implicated in placebo neurobiology. For example, the common observation of placebo effects in Parkinson's disease [30]

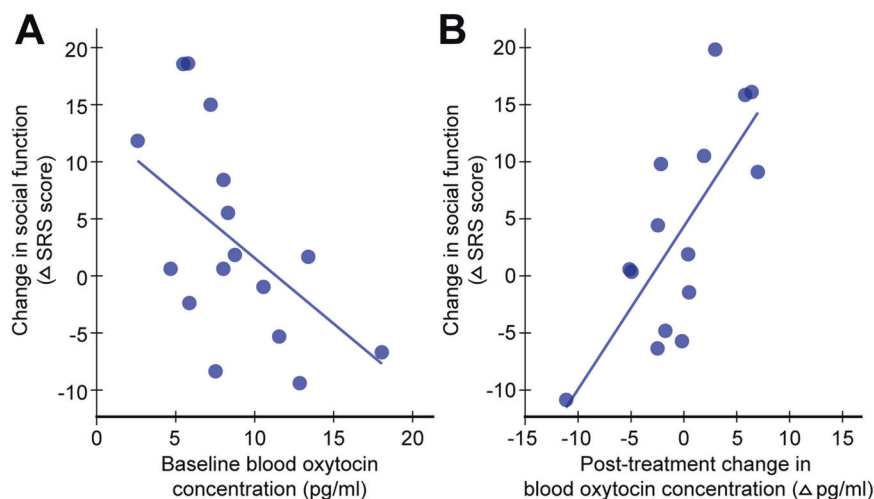


Fig. 2 Blood oxytocin concentration predicts placebo effects on social functioning in individuals with autism. **A** Pretreatment (baseline) blood oxytocin concentration plotted against change in social function (Social Responsiveness Scale [SRS] score) from before to after a 4-week placebo treatment course of twice-daily intranasal vehicle spray for $N = 16$ participants. Positive delta SRS scores indicate improvements in social function. **B** Post-treatment change in blood oxytocin concentration plotted against change in social function for 15 of the participants in **A** (no post-treatment measurement for 16th participant). Positive delta concentrations indicate endogenous increases in blood oxytocin concentration. Regression lines show least-squares fits to the data. Figure adapted from [19].

may reflect its dopaminergic etiology, and strong placebo effects on pain may be related to the role of opioids in pain suppression. Likewise, the oxytocin placebo hypothesis implies that strong placebo effects in autism trials may reflect oxytocin biology being specifically related to the social outcomes often being assessed [58]. Nevertheless, as oxytocin and social dysfunction are implicated in many neuropsychiatric disorders (e.g., schizophrenia, mood, and anxiety disorders, borderline personality disorder; [123, 124]), coping with stress [125], and also more generally in disease-associated states of social isolation, loss, or despair (especially in hospitalized patients; [126, 127]), assessments of endogenous blood oxytocin concentration and the effects of treatment-induced changes in social connectedness seem likely to be relevant to understanding placebo effects on a broad level. In particular, our data suggest that low baseline blood oxytocin concentration may represent a biomarker for high receptivity to treatments that stimulate increases in social connectedness, regardless of whether or not this is their primary aim.

Assessing change in blood oxytocin concentration from before to after treatment may also provide a way to identify different types of responses after a trial is completed, provided that the trial itself is not testing oxytocin treatment (which complicates the interpretation of blood oxytocin concentrations; [19]). For example, if corroborated by increased blood oxytocin concentration, clinical improvement following placebo treatment could represent real improvement, likely driven by increased social connectedness. In contrast, clinical improvement reported without increased blood oxytocin concentration would more likely represent unknown or spurious factors (e.g., reporting bias associated with a failure of blinding). Similarly, in patients receiving active treatment, changes in blood oxytocin concentration may improve our understanding of overall group and individual differences in response, as treatment benefits driven by increased social connectedness are not limited to individuals receiving placebo treatment. This is particularly true when an active treatment specifically engages targets implicated in placebo neurobiology (such as dopaminergic or opioidergic brain reward circuits), which can confound assessments of its efficacy in placebo-controlled comparisons [128]. Accordingly, following active treatment, clinical improvements that occur without significant changes in blood oxytocin concentration could indicate a treatment with efficacy independent of changes in social connectedness. Conversely, clinical improvements that co-occur with increases in blood oxytocin concentration, or that are dependent on baseline blood oxytocin concentration, could indicate an efficacious treatment that is likely modulated or mediated, in part, by social connectedness. Depending on the medical condition and outcome under consideration, this latter situation could represent direct effects of the active treatment (e.g., in autism or depression trials targeting social functioning), or placebo effects that mask or enhance active treatment effects (e.g., in Parkinson's trials targeting motor symptoms). Lastly, in cases where clinical improvement and change in blood oxytocin concentration correlate, baseline blood oxytocin concentration could serve as a biomarker for the likelihood of treatment efficacy or indicate the need for concomitant social or behavioral interventions.

For clinical trial methodology, we, therefore, advocate for a more individualized "personalized medicine" approach to study design and analysis (rather than a simple group comparison approach). In terms of data collection, measuring each participant's blood oxytocin concentration at the beginning and end of treatment would provide important individual-level biological data. In terms of participant randomization and allocation, matching baseline blood oxytocin concentrations between placebo-control and active treatment groups (just as one would match participants for, age, sex, ethnicity, etc.) would control for

potential effects of baseline differences in oxytocin biology on responsiveness to trial-induced increases in social connectedness. In terms of analysis, these changes would permit the inclusion of baseline and/or change in blood oxytocin concentration as a covariate to test for interactions between treatment-relevant individual differences and treatment group allocation (rather than testing allocation only) in explaining treatment responses [19]. In sum, the measurement of blood oxytocin concentration may provide a valuable tool for assessing sensitivity to placebo effects driven by increases in social connectedness prior to a trial, and for parsing different types of responses to treatment after a trial. As such, determining the breadth of these potential applications for blood oxytocin concentration, as well as their potential value in evaluations of clinical trial efficacy, are important topics for future research.

Finally, there is the possibility that exogenous oxytocin can be used to systematically influence placebo effects. A handful of studies have begun to explore this possibility by testing whether single-doses of intranasally administered oxytocin can enhance the effects of subsequently administered placebos. The evidence from such studies is presently equivocal. For men, two studies indicate that intranasal oxytocin administration enhances placebo effects induced by verbal description (for analgesia [129] and working memory [130]), while three studies indicate that it does not (for analgesia induced by verbal description combined with conditioning [131–133]). For women, the results are less ambiguous, with three studies indicating that intranasal oxytocin administration does not enhance placebo analgesia, induced by verbal description [134], or verbal description combined with conditioning ([132, 133]; controlled for menstrual phase). Interestingly, one of these studies found that, for females only, placebo analgesia was enhanced by pre-administration of a single-dose of intranasal (arginine) vasopressin [133], a structurally similar neuropeptide also implicated in social behavior and cognition [135, 136]. Although far from settled, potential sexual dimorphism in the facilitation of placebo effects by intranasal oxytocin and vasopressin administration is broadly consistent with sexually dimorphism in other socially-relevant actions of these neuropeptides [137–140]. This finding may also help explain potential differences between men and women in sensitivity to different methods of placebo-effect induction, with two recent reviews arguing that men are more susceptible to verbal description, whereas women are more susceptible to conditioning [141, 142]. Returning to the oxytocin placebo hypothesis, a potential shortcoming of existing intranasal oxytocin administration studies is their focus on experimentally-induced pain paradigms, at the potential expense of social connection. Specifically, in all but one of the aforementioned studies [130], experimenters actively administered electricity or cold to participants to cause (mild) pain. Such experimental manipulations seem likely to decrease positive affect, warmth, and trust, thereby impairing or preventing social connection [143]. Moreover, these pain paradigms typically involve experimenters actively deceiving participants, which may be detected and further impair social connection [144]. Interestingly, in each of the three studies in which intranasal oxytocin or vasopressin administration was found to enhance placebo effects, specified efforts were made to instill participants with confidence in the person describing/administering treatment, either by using an actual physician [129], or by having the experimenter wear a white lab coat indicating professional medical status [130, 133]. Given the high-degree of context sensitivity associated with the effects of intranasal oxytocin and vasopressin administration in the literature [145, 146], we should expect their capacity to modulate placebo effects to also be highly context sensitive. Accordingly, clarifying the impact of intranasally administered "social" neuropeptides on placebo effects may require experimental paradigms that not only involve measuring and controlling

for individual variation in oxytocin biology, but that also involve intentionally promoting a social connection between experimenters/clinicians and participants/patients (see e.g., [9, 147]).

CONCLUSION

The advances described here provide preliminary support for the hypothesis that oxytocinergic modulation of brain reward circuitry explains the social facilitation of placebo effects. More specifically, we have reviewed evidence that endogenous oxytocin activity associated with increased social connectedness can stimulate dopaminergic and opioidergic reward processes that are directly implicated in placebo effects across multiple conditions, thereby providing a neurobiological basis for social effects on treatment outcomes long recognized as an important aspect of medical care, despite only recently being documented in psychological terms. We further argued that in addition to its role in placebo effects, oxytocin may function as a key neurobiological mediator of treatment success across a variety of widely-used behavioral interventions in which an 'alliance' between therapist and client plays an essential role. Finally, we propose that measurements of endogenous blood oxytocin concentration can aid in the design and analysis of clinical trials that are more sensitive to individual differences, as well as potential effects of trial-induced increases in social connectedness on treatment response. Thus, although more research is needed to test specific predictions of the oxytocin placebo hypothesis, determine its breadth, and refine its neurobiological bases, its capacity to define a fundamental non-specific element of treatment success in biological terms is of great significance for medicine, particularly in the domain of treatments for disorders of mental health.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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