activity. Replicating previous studies, individual neurons in the DMFC demonstrated ramping activity during the reproduction of an interval, with faster ramping when the monkey reproduced shorter intervals [6]. Critically, neural activity during the second sample interval exhibited the predicted simulation profile: neurons demonstrated interval-dependent ramping during this epoch, prior to the response cue.

Further support for an internal model hypothesis was found across different measures of neural activity, and in their relationship with subsequent behavior. Temporal scaling was evident not only at the level of DMFC single neurons but also in the population-level neural dynamics across this region. Unlike the transient single-unit responses, the rate of change in these population dynamics scaled consistently with interval length throughout the second sample interval. These dynamics reflected the same Bayesian biases observed in monkeys' behavior: an initial bias towards the average interval duration that became less biased with more samples. Critically, these population dynamics also predicted when the monkey would saccade on the upcoming response interval, and did so above and beyond what would be predicted by the lengths of the sampled time intervals alone. Collectively, these findings are consistent with the DMFC implementing an internal model to optimize the learning of task goals and the control of neural population dynamics.

This study provides evidence that DMFC mediates the influence of prior predictions and incoming sensory evidence on planned actions, and lays the groundwork for critical tests of this proposed mechanism using causal manipulations (i.e., stimulation or inactivation). Such causal tests can also help to rule out alternative accounts of neural dynamics during the sample intervals, for instance, whether they reflect a simulated motor plan (as the authors infer) or an interval expectation (e.g., predicting the onset of the interval cue [8]). Nevertheless, by elaborating on the neuronal dynamics within DMFC during a task that requires online adjustments of learning and control, this study builds on a growing literature that implicates regions along this dorsomedial wall in the control of motor and cognitive commands [9,10].

More generally, this research provides compelling new evidence that motor and cognitive control share a common computational toolbox. Past work has suggested that both forms of control serve similar objectives (achieving a goal state within a dynamic, uncertain, and noisy environment) and that they are also both constrained by some underlying cost, limiting the amount of control that individuals can engage at a given time. As a consequence, decisions about how to allocate one's control are sensitive to whether the reward for goal achievement outweighs these costs [10]. To the extent computational and neural architecture for motor and cognitive control allocation mirror one another, the behavior and neural dynamics observed in the current task should demonstrate sensitivity to performance incentives for both forms of control.

In spite of their abundant bodies of research, the obstacle to bridging our understanding of motor and cognitive control have been similarly abundant, including limitations of tasks, measurement tools, and model organisms. This study demonstrates how a combination of computational modeling and measures of neural dynamics in the monkey can be leveraged towards this goal and, in doing so, provides a valuable path forward in mapping the joints between these two domains of control.

[1]Brown University, 190 Thayer Street, Box 1821, Providence, RI 02912, USA

*Correspondence:
amitai_shenhav@brown.edu

https://doi.org/10.1016/j.tics.2019.11.005

References

1. Manohar, S.G. *et al.* (2015) Reward pays the cost of noise reduction in motor and cognitive control. *Curr. Biol.* 25, 1707–1716
2. Tang, E. and Bassett, D.S. (2018) Colloquium: control of dynamics in brain networks. *Rev. Mod. Phys.* 90, 031003
3. Egger, S.W. *et al.* (2019) Internal models of sensorimotor integration regulate cortical dynamics. *Nat. Neurosci.* 22, 1871–1882
4. Miall, R.C. and Wolpert, D.M. (1996) Forward models for physiological motor control. *Neural Netw.* 9, 1265–1279
5. Frömer, R. *et al.* (2018) I knew that! Confidence in outcome prediction and its impact on feedback processing and learning. *bioRxiv.* Published online October 14, 2018. https://doi.org/10.1101/442822
6. Remington, E.D. *et al.* (2018) Flexible sensorimotor computations through rapid reconfiguration of cortical dynamics. *Neuron* 98, 1005–1019
7. Jazayeri, M. and Shadlen, M.N. (2010) Temporal context calibrates interval timing. *Nat. Neurosci.* 13, 1020–1026
8. Egger, S.W. *et al.* (2019) A neural circuit model for human sensorimotor timing. *bioRxiv.* Published online July 23, 2019. https://doi.org/10.1101/712141
9. Heilbronner, S.R. and Hayden, B.Y. (2016) Dorsal anterior cingulate cortex: a bottom-up view. *Annu. Rev. Neurosci.* 39, 149–170
10. Shenhav, A. *et al.* (2017) Toward a rational and mechanistic account of mental effort. *Annu. Rev. Neurosci.* 40, 99–124

Forum

Combinatorial Oxytocin Neuropharmacology in Social Cognition

Siqi Fan,[1,5]
Hannah Weinberg-Wolf,[1,5]
Matthew Piva,[1]
Olga Dal Monte,[1,2]
and Steve W.C. Chang[1,3,4,*]

The efficacy and reliability of using intranasal oxytocin (OT) to clinically enhance social functions remains

undependable. We discuss the potential benefit of concurrent administration of OT and naloxone (NAL) to robustly modulate social behavior. We further suggest that combinatorial neuropharmacology approaches should exploit the interactions between OT and serotonin to regulate social functions.

Targeting only one neuromodulator system to modulate social behavior relies on an oversimplified view of the central nervous system. In fact, no single neuromodulator system acts independently of other neuromodulators. To pharmacologically enhance social functions, it is necessary to consider how multiple neuromodulator systems interact, especially because social behaviors arise from complex sets of neural processes. Capitalizing on the interactions among different neuromodulatory systems may substantially improve neuropharmacological therapeutic interventions aimed at promoting social functions in psychiatric conditions, including autism spectrum disorders (ASD).

While it is well established that OT regulates social functions, intranasal OT has yielded mixed results in treating individuals with ASD. Such mixed findings demand a continued effort to identify innovative ways to more robustly modulate the neural substrates that OT acts on and consequent social behaviors. Informative translational research in nonhuman primates may help our progress toward this goal [1]. Here, we describe the potential benefit of concurrently blocking μ-opioid receptors when administering intranasal OT to amplify OT-mediated social functions. We then discuss another promising intervention of concurrently modulating the serotonergic and OT systems to affect social behaviors.

The opioid system has been implicated in regulating social behaviors. Excessive activation of μ-opioid receptors by morphine decreases the frequency of social contact in nonhuman primates [2]. We have also recently shown that intranasal administration of the μ-opioid receptor antagonist NAL enhances rhesus macaques' attention to conspecifics' eyes in a dose-dependent manner [3]. However, it is worthwhile to note that activating or blocking μ-opioid receptors has resulted in heterogeneous effects on social functions in both humans and nonhuman animals, which could be in part related to differences across studies in behavioral contexts and dosages. Given the intricate associations between individuals' baseline neuromodulator levels and social functions, it is critical to obtain dose–response functions to identify an individual-specific optimal dosage for promotion of social functions.

Importantly, there is a strong regulatory relationship between the central OT

Box 1. Opioid Antagonist Strongly Promotes Endogenous OT Release

Electrical stimulation of the mammalian posterior pituitary at a low frequency leads to an increase in the secretion of both OT and vasopressin [4]. A landmark study using isolated rat hypothalamic sections discovered that the rate of electrically evoked secretion of OT from the posterior pituitary can be vigorously amplified in the presence of the μ-opioid receptor antagonist NAL [4] (Figure I). Two aspects of this finding are noteworthy. First, the amplification of OT secretion from the posterior pituitary can be as large as three times greater in the presence of NAL according to this study [4]. Second, the secretion of vasopressin is not affected by NAL, indicating a specific modulation of OT by NAL [4]. This research and others [5] have led to a series of mechanistic understandings of how blocking the μ-opioid receptors in the OT-releasing cells robustly amplifies intrinsic OT secretion to the central nervous system (Figure 1A). Notably, in the human brain, genes encoding the μ-opioid receptor are highly expressed in the OT-releasing hypothalamic regions, supporting that the human brain is likely to possess a similar mechanism for the NAL-induced increase in OT secretion [3].

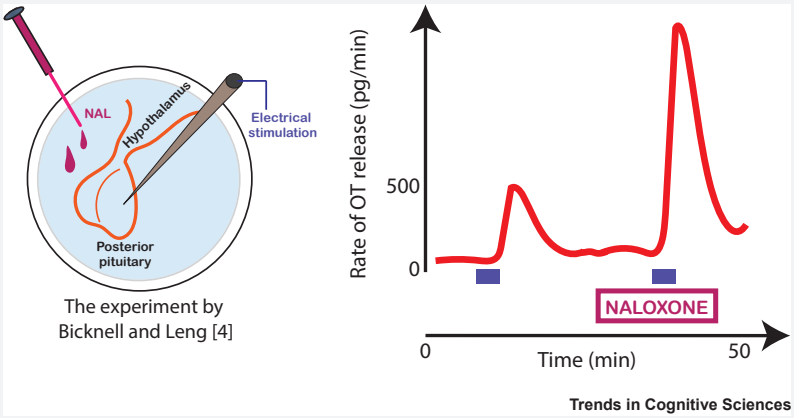

Figure I. Naloxone (NAL)-Mediated Boost in Endogenous Oxytocin (OT) Release.

A key empirical finding demonstrating an enhancement of OT release rate from the posterior pituitary in the presence of NAL. Left: A simplified experimental setup by Bicknell and Leng [4] in which isolated rat posterior pituitary sections were electrically stimulated in the presence or absence of NAL in the perfusion medium. Right: An illustration of their key empirical finding demonstrating a great enhancement of OT release rate when the electrical stimulation (blue bar) was delivered in the presence of NAL. The rate of vasopressin release from electrical stimulations was not affected by NAL.

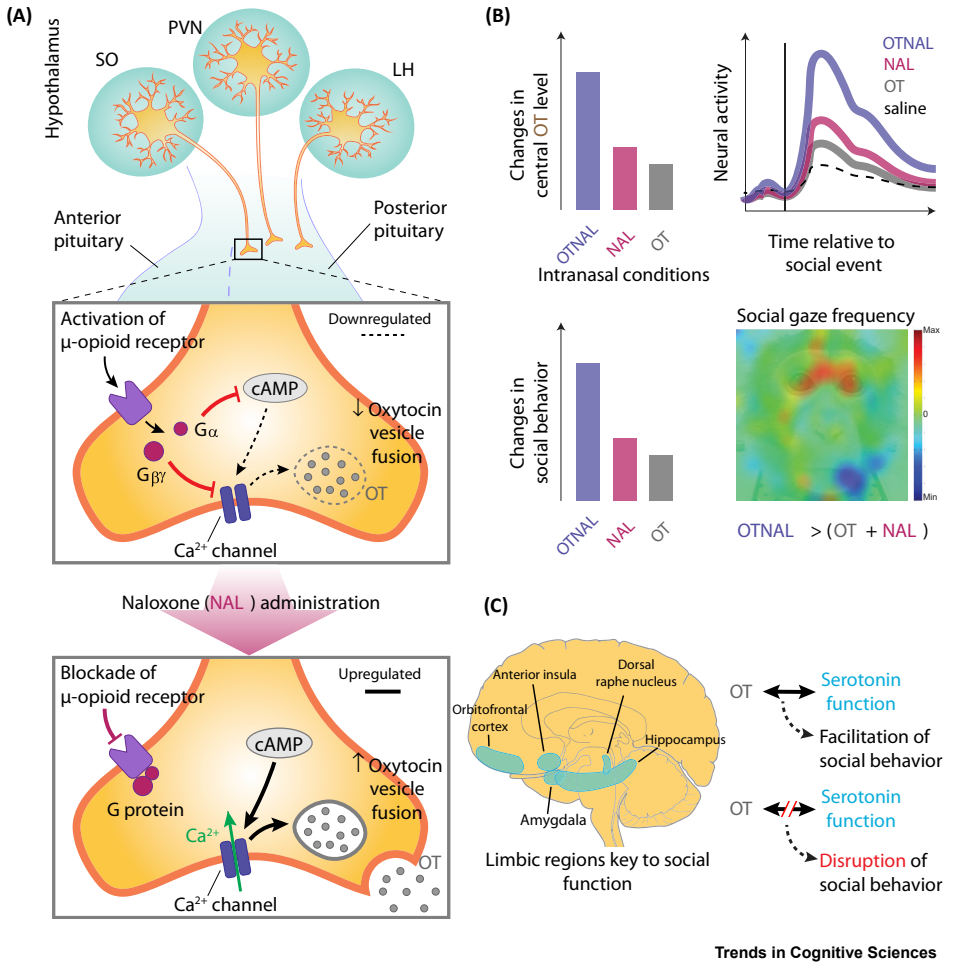

Figure 1. An Overview of the Principles Underlying Combinatorial Oxytocin (OT) Neuropharmacology.
(A) Illustrations of the cellular and synaptic mechanisms mediating the regulation of endogenous OT secretion by μ-opioid receptors (only G protein signaling at the presynaptic site is shown). SO, supraoptic nucleus; PVN, paraventricular nucleus; LH, lateral hypothalamus. (B) Hypothesized consequences arising from the administration of intranasal naloxone (NAL) with intranasal OT (OTNAL), OT alone, or NAL alone (compared with saline) on central OT levels, the neural activity of downstream brain regions, and social behavioral effects. Bottom right: One of the observed behavioral effects of OTNAL on social attention. Adapted from [3]. (C) Illustrations of how central OT functions interact with central serotonin functions, lending support for a potential benefit of co-engaging the OT and serotonin systems in social behavior.

and μ-opioid systems. Early research established that blocking μ-opioid receptors using NAL powerfully enhances OT secretion from the rat posterior pituitary (up to a threefold increase) without affecting vasopressin secretion [4] (Box 1). Many studies have documented that opioids inhibit OT secretion from hypothalamic regions through G protein and arrestin signaling (Figure 1A). Opioids act on both presynaptic and postsynaptic sites of OT-releasing cells (Figure 1A), where the μ- and κ-opioid receptor types, but not the δ-opioid receptor type, are involved in endogenous modulation of OT [5].

Individuals with ASD frequently show disrupted social gaze behavior. We have recently capitalized on the regulatory relationship between the OT and μ-opioid systems to amplify social gaze behavior in rhesus macaques. We found that concurrent administration of intranasal NAL with intranasal OT (OTNAL) causes a supralinear enhancement in overall attention directed to conspecifics' eyes as well as interindividual social gaze dynamics during spontaneous dyadic social gaze interactions [i.e., (OTNAL effect) > (OT effects) + (NAL effects)] [3] (Figure 1B). These results support the benefit of combinatorially enhancing contingent and dynamic social attention using OTNAL. Future research is required to

elucidate the neurobiological mechanisms underlying this supralinearity. We hypothesize that it is driven by augmented changes in both central OT level, which is likely to be via a combination of NAL-mediated OT secretion along with feedforward OT secretion triggered by both intranasal OT and NAL, and the consequential changes in spiking activity within the relevant neural circuits (Figure 1B). We have also reported that OT-secreting neurons in hypothalamic regions in humans are strongly colocalized with μ- and κ-opioid receptors but not δ-opioid receptors [3], further supporting that the human brain possesses a regulatory mechanism between the opioid and OT systems that can be leveraged to enhance certain social functions. Overall, administering OT under μ-opioid antagonism may be an avenue worthy of exploration to more effectively and reliably promote social functions such as social gaze behaviors in ASD.

In addition to the opioid system, the OT system interacts with the serotonin system to support social functions [6]. We have recently reported that increasing central serotonin concentrations in rhesus macaques affects social looking behavior (reviewed in [6]). Crucially, research shows that increasing rodents' central concentrations of serotonin, via either serotonin receptor agonists or intracerebroventricular injections of serotonin [5-hydroxytryptamine (5-HT)], increases peripheral OT levels (reviewed in [6]). Conversely, applying OT via microdialysis to the raphe nucleus, the region of the brain responsible for serotonin production, increases serotonin release [7]. In addition, serotonin transporter-containing fibers overlap with OT-labeled cells in the paraventricular and supraoptic nuclei of the hypothalamus in nonhuman primates (reviewed in [6]), suggesting an anatomical substrate for the mediation of interactions between the two neuromodulator systems. Empirical results like these suggest that the two neuromodulatory systems are actively coordinated (Figure 1C). It is plausible to consider that the effects of central serotonergic modulations on social functions may in part be augmented by their interactions with central OT functions.

Researchers have observed that impairments in the relationship between the serotonergic and OT systems are linked to the development of social impairment and ASD. Hyperserotonergic and hypooxytocinergic biomarkers of ASD are correlated across life [8]. Recent work has used PET imaging to show that intranasal OT administration in humans affects 5-HT1A receptor binding in the dorsal raphe nuclei and in the regions responsible for social functions, such as the amygdalar/hippocampal complex, the insula, and the orbitofrontal cortex [9] (Figure 1C). Critically, it has been shown that while concentrations of 5-HT1A receptors are comparable for ASD and typical subjects, intranasal OT increases binding potential only in the latter, but not in the former, individuals [10]. Furthermore, OT increases peripheral serotonin concentrations in serum free plasma in typical but, again, not in ASD individuals [10]. Additionally, in a rodent model of ASD, pharmacological promotion of serotonergic function increases social approach behaviors, while OT antagonists block these effects [11]. Therefore, coordination and coactivation of the serotonergic and OT systems seem to be critical for driving social functions, and the relationship between the two systems may be impaired in individuals with ASD. The limited efficacy of OT in boosting social cognition could be due, at least in part, to a dysregulation of central serotonin function in ASD. Selective serotonin reuptake inhibitors are already frequently used to treat specific symptoms in ASD. Concurrent targeting of the central OT and serotonergic systems may thus prove to be beneficial for clinical promotion of social functions. If OT-regulated release of serotonin were to be combined with an activation of central serotonin functions, targeted changes in social behavioral functions might be greater and more reliable.

In closing, the central OT system is under strong regulatory control and strategic engagement of such regulatory mechanisms may greatly improve OT-based therapeutics. Known neuromodulatory interactions between OT and opioids and between OT and serotonin advocate for the possibilities of combining OT-based therapeutics with concurrent administration of NAL or serotonin-enhancing agents to more robustly enhance social functions. Combinatorial neuropharmacology approaches might also be beneficial in other behavioral domains. For example, a recent study showed that combining ketamine and NAL administration noticeably improves the treatment of depression and comorbid alcohol use disorders [12]. With doses specifically optimized for combinatorial neuropharmacology, it might be possible to clinically amplify the effects of single neuromodulator interventions by coopting natural interactions between systems in the brain.

Acknowledgments

This work was supported by the National Institute of Mental Health (R01 MH120081, R01MH110750). We thank Olivia Meisner and Philip Putnam for helpful comments on the manuscript and thank Colin Stanton for help with illustrations.

[1]Department of Psychology, Yale University, New Haven, CT, USA

[2]Department of Psychology, University of Turin, Torino, Italy

[3]Department of Neuroscience, Yale University School of Medicine, New Haven, CT, USA

[4]Kavli Institute for Neuroscience, Yale University School of Medicine, New Haven, CT, USA

[5]Equal contributions

*Correspondence:
steve.chang@yale.edu

https://doi.org/10.1016/j.tics.2019.10.004

References

1. Putnam, P.T. *et al.* (2018) Bridging the gap between rodents and humans: the role of non-human primates in oxytocin research. *Am. J. Primatol.* 80, e22756
2. Ragen, B.J. *et al.* (2015) The effects of morphine, naloxone, and κ opioid manipulation on endocrine functioning and social behavior in monogamous titi monkeys (*Callicebus cupreus*). *Neuroscience* 287, 32–42
3. Dal Monte, O. *et al.* (2017) Oxytocin under opioid antagonism leads to supralinear enhancement of social attention. *Proc. Natl Acad. Sci. U. S. A.* 114, 5247–5252
4. Bicknell, R.J. and Leng, G. (1982) Endogenous opiates regulate oxytocin but not vasopressin secretion from the neurohypophysis. *Nature* 298, 161–162
5. Bicknell, R.J. *et al.* (1985) Neurohypophysial opioids and oxytocin secretion: source of inhibitory opioids. *Exp. Brain Res.* 60, 192–196
6. Weinberg-Wolf, H. and Chang, S.W.C. (2019) Differences in how primates monitor others: does serotonin play a central role? *Wiley Interdiscip. Rev. Cogn. Sci.* 10, e1494
7. Yoshida, M. *et al.* (2009) Evidence that oxytocin exerts anxiolytic effects via oxytocin receptor expressed in serotonergic neurons in mice. *J. Neurosci.* 29, 2259–2271
8. Hammock, E. *et al.* (2012) Examining autism spectrum disorders by biomarkers: example from the oxytocin and serotonin systems. *J. Am. Acad. Child Adolesc. Psychiatry* 51, 712–721.e1
9. Mottolese, R. *et al.* (2014) Switching brain serotonin with oxytocin. *Proc. Natl Acad. Sci. U. S. A.* 111, 8637–8642
10. Lefevre, A. *et al.* (2017) Oxytocin fails to recruit serotonergic neurotransmission in the autistic brain. *Cereb. Cortex* 28, 4169–4178
11. Arakawa, H. (2017) Involvement of serotonin and oxytocin in neural mechanism regulating amicable social signal in male mice: implication for impaired recognition of amicable cues in BALB/c strain. *Behav. Neurosci.* 131, 176–191
12. Yoon, G. *et al.* (2019) Association of combined naltrexone and ketamine with depressive symptoms in a case series of patients with depression and alcohol use disorder. *JAMA Psychiatry* 76, 337–338