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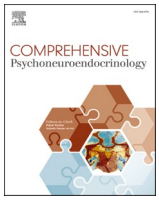

Moxie begets MOXI: The journey to a novel hypothesis about Mu-opioid and OXytocin system Interactions

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A B S T R A C T

This narrative review summarizes the early life of the author, Khalin E. Nisbett, and highlights the factors that led to her career in research and her development of two novel research hypotheses: the **M**u-opioid and **OX**ytocin system **I**nteraction (MOXI) hypothesis and **M**u-Opioid receptor antagonist and **OX**ytocin receptor **A**gonist **I**n **C**ombination (MOXAIC) treatment hypothesis. Notably, Nisbett's career began in the era after countless studies demonstrated that oxytocin is not just a female neurotransmitter and not just a female reproductive hormone, an era in which researchers are exploring the role of oxytocin in emotion regulation, social interaction, and cognitive processing across both sexes. As such, the previously held perspective that oxytocin is "just a female hormone" did not impede Nisbett's ideas. Intrigued by science, emotion regulation, and social interaction, she began to explore the role of oxytocin and opioids in emotion regulation. On the heels of earlier theories, such as the Tend-and-Befriend theory and Opioid Theory of Social Attachment, she began to develop the MOXI hypothesis, which postulates that the μ-opioid receptor and oxytocin systems interact to mediate social interaction and emotion regulation. In this narrative review, Nisbett summarizes two studies that explored (i) the role of oxytocin in anxiety- and depression-like behavior and (ii) the effect of opioid receptor blockade on the anxiolytic-like effect of oxytocin, which led to a revision of the MOXI hypothesis and postulation of the Mu−Opioid receptor antagonist and OXytocin receptor Agonist In Combination (MOXAIC) treatment hypothesis. Nisbett also discusses several limitations of these hypotheses and her current research interests and aspirations.

This personal narrative of my scientific journey is written in response to an invitation by Dr. C. Sue Carter to contribute to a Special Issue of *Comprehensive Psychoneuroendocrinology* entitled "Oxytocin – Not Just A 'Female Hormone.'" This special issue features established and early-career women scientists who have made and are committed to making significant contributions to understanding the functions of oxytocin. At the time of this writing, I held a joint appointment as a doctoral candidate in the Graduate Program in Neuroscience at the University of Illinois Chicago Graduate College and a predoctoral visiting fellow in the Neurobiology of Addiction Section of the National Institute on Drug Abuse Intramural Research Program via the National Institutes of Health Graduate Partnership Program.

"Two roads diverged in a wood, and I—

I took the one less traveled by,

And that has made all the difference."

– Robert Frost, excerpt from The Road Not Taken (1915)

The message Frost originally intended with this poem, that, in some intimate respect, the diverging roads in our lives may be equivalent [1], gives me pause. However, we will never really know because as Frost says, "way leads onto way," and we rarely ever turn back. So perhaps the alternative and more common interpretation of the final three lines of this poem is correct. Perhaps we should bravely take the road less traveled. Perhaps our courage will be rewarded.

Here is the road I have taken.

1. Milk

The first thing you must understand is that I had never seen milk curdle. Growing up in Nevis, a small island in the Caribbean, meant that my family used dried or evaporated milk for many of our meals. So, when Zoom, my favorite television series on PBS Kids, suggested that mixing orange juice with milk would cause it to separate and clot (coagulate), I was struck by awe and skepticism. There was only one solution to these conflicting feelings - I had to try it myself!

The second thing you must know is that orange juice, especially the pasteurized variety used on Zoom, was not a typical commodity in Nevis. Unfortunately, I did not understand the mechanism underlying the clotting reaction or that pasteurized orange juice could be simply

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substituted with another acidic substance. I just knew that I needed two things: milk and pasteurized orange juice. We had milk – boxes of it. We did not have pasteurized orange juice. This was not a household staple. On the contrary, my mother made freshly squeezed lemonade weekly, but this is not what was recommended by my friends on Zoom. I needed pasteurized orange juice. I was determined and my logic was clear. I proposed a plan to my parents and in my mind, it was sufficiently convincing to report that "we already have the milk." By this age, my irrepressible curiosity was mostly understood and encouraged by my parents. However, the pasteurized orange juice that I deemed necessary for this experiment was difficult to attain. I had to be persistent. After a few pleas, my father sourced 16 ounces of pasteurized orange juice so I could try the experiment and, of course, drink some too! I observed and reported to my friends and whomever else would listen that it was true: this liquid gold had the power to *change* milk. Simply unbelievable.

I describe this story for several reasons. Not only was it the first event where I can clearly remember feeling like a scientist, but it also illustrates many significant attributes of my personality as well as my family's positive influence on my upbringing, all of which are fundamental to my journey. Growing up on a small developing island translated to limited exposure to careers in science. The most obvious path for someone who loved science was medicine. Additionally, there were many experiments on PBS Kids' Zoom that I was unable to conduct because the reactants or materials were unavailable, but for this one, *we already had the milk*. This sentiment is responsible for much of my evolution because, once I set a goal, I can identify the *milk*, i.e., the resources and skills I already possess that can contribute to the outcome. Once captivated, I become endlessly inquisitive and, admittedly, sometimes very skeptical.

I also describe this story because it highlights the necessity for accessibility in science communication and training. As a child, it was unclear to me that citrus juice of any kind had the properties necessary to curdle milk. But after studying chemistry for many years, I learned that the experiment described above could have been accomplished using juice from the limes, shaddocks, and oranges that we grew in our family garden. *I had everything I needed all along!* This memory amplifies the importance of acknowledging and learning the many ways possible to achieve a goal. My desire to share what I have discovered is fueled by my interest in increasing accessibility and inspiring curiosity. Show-and-tell was my favorite activity in kindergarten, and my enthusiasm for sharing has evolved along with me. Importantly, I could not be the scientist I am today without my support system, which, fortunately, started in a loving and stimulating home. A home that would go to the ends of the earth to help me find orange juice, or any resource or skill I might need to accomplish my goal.

2. Passion

I have always valued learning and the challenges that come along with it. I was the student who reminded the teacher to give homework to the class, who asked questions that would stretch most sessions to their formal end, who read when she was bored or upset, and who asked her older brother to teach her what he learned in his courses. To you, the reader, it may seem that science was an obvious career path for me. But it was not. In primary school, I thought I might become a lawyer because I relished debates and discourse that spanned multiple topics. I also considered becoming a chef. I took pleasure in the ways that my baked goods brightened my loved ones' faces.

Being highly empathetic, I was and am often drawn to people, their experiences, and their feelings. I enjoy listening and experiencing events through the lens of others (i.e., the concept of Verstehen, originally coined by Max Weber) [2]. Encouraged by my friends who saw this side of me most, I considered becoming a therapist. In this profession, I could use my intellect and skill to serve my community. However, as an adolescent, I struggled with regulating my own emotions and was intimidated by the thought of being trusted with the emotions of others. Psychology was not offered in my school curriculum, so I only understood it as the means to becoming a therapist. I didn't yet understand the depth of the field. As a result, I decided not to pursue psychology. Still, I deeply respected therapists and counselors. My exchanges with them helped me develop my own emotional intelligence and empathy.

I was drawn to science because it became more challenging, more undiscovered as I advanced academically. In secondary school, my interest in science distilled into chemistry and physics. These subjects challenged me more than any other course in my curriculum and stimulated me more than any debate partner could. There was something about being on the precipice of new knowledge, something about questions being inexhaustible, that persuaded me. Not only that, but I also came to understand that I could use science to improve lives. Perhaps if I had known of a field of science that would incorporate both psychology and chemistry (neuroscience), I would have taken that path earlier. I did not.

Still, although I believed that the island was my oyster, I did not have a definitive vision for my future. Until the final years of secondary school, I knew what I enjoyed, and I simply did it. Eventually, I settled on becoming a gourmet chef. With the help of my Principles of Business, Food & Nutrition, and Principles of Accounting teachers, I drafted a career plan and a business proposal that would have eventually led to the opening of a gourmet restaurant and bakery. This was attainable, unique, creative, and rewarding. However, my family challenged me to pursue higher education in the sciences. They used some iteration of *you-already-have-the-milk*. The *milk*, in this case, comprised the qualities I possessed that would make me successful. Essentially, their argument was that I was *already* so bright, knowledgeable, enthusiastic, and curious. I was *already* a primary school valedictorian and on the path to becoming a secondary school valedictorian. And I was "young," so I could *just try it* and pursue the culinary arts afterward should I so choose. This took several years of dialogue that persisted beyond my secondary school graduation and throughout my tenure at the Nevis Sixth Form College. Eventually, my aunt, who was a medical doctor, and my uncle, who was a chemical engineer, were drafted into the debate by my mother, and I was ultimately convinced that I had both the time and *the milk*, so I *tried it*. Why not?

After a successful application cycle, I moved to St. Thomas to attend the University of the Virgin Islands. This was a relatively easy transition because I succeeded my sister, who still lived on the island. I was able to transfer credits from my Associate of Science degree in chemistry and mathematics from the Nevis Sixth Form College and enter as a sophomore. Within the first month of classes, I fell in love with organic chemistry and declared my major in chemistry and minor in physics. After the first semester, my organic chemistry professor, Dr. Bernard Castillo II, invited me to join his research group on the sister island, St. Croix, for the summer. Though this proposal to spend my summer conducting research on an unfamiliar island seemed unorthodox, it seemed to me that he *already had the milk*. Following a series of conversations with him, my family, and my mentors, I successfully applied to the University of the Virgin Islands Summer Research Opportunity Program. I spent that summer in Dr. Castillo's research laboratory on St. Croix, building on techniques I learned throughout the academic year. Our goal was to assess the accumulation of biotoxins (Ciguatera toxins) in the invasive lionfish and contribute to the territory's lionfish response management plan [3,4]. The first day in the Castillo laboratory filled me with a novel feeling of ecstasy that I have continued to experience throughout my research career. Dr. Castillo explained the experimental procedures and allowed me to work independently. This gave me an opportunity to explore the limits of my understanding and to problem-solve. Through another Summer Research Opportunity Program at University of the Virgin Islands, I worked under the tutelage of Dr. Yakini Brandy to extract the active ingredient (citral) from lemongrass, a plant commonly used for making tea in the Caribbean [5]. We used *in vitro* cell death assays as a first step to determine concentrations of citral that would be useful as an anti-cancer therapy. I also learned to

synthesize citral. Conversations with my mentors and experts at local and national symposia further informed what I could accomplish with a degree in chemistry. What started as a trial transformed into a desirable and attainable career path. Through my tenure at University of the Virgin Islands, I realized I could employ the creativity of a gourmet chef and my scientific aptitude in one career. Perhaps I could benefit my community by discovering natural remedies or develop novel therapies for psychiatric diseases.

I began a graduate program in chemistry at Wayne State University with the intention to learn the skills necessary for developing novel therapies for psychiatric diseases. To develop my inorganic and organic chemistry skills, I designed and synthesized photocageable drugs that had the potential to inhibit cathepsin K and L, potential therapeutic targets for the treatment of arteriosclerosis, osteoporosis, and cancer [6]. The idea was to prevent off-target effects of potent drugs by locking them in inactive conformations using Ruthenium (II) complexes (caged) until they were activated by light (uncaged). The complexes I synthesized as part of my thesis demonstrated similar efficacy when they were caged and uncaged (i.e., they were not locked in an inactive conformation when they were caged). This was a common setback, and it ran counter to our laboratory's goal. After months of surveying the literature and writing my Master's thesis, I deciphered the inconsistencies and drawbacks to the approach that we used for this class of compounds. These are summarized in my Master's thesis [6] and the related computational research manuscript [7]. It was during this period that I finally learned about neuroscience, a field that took a life science approach to psychology. Through elective coursework, including a neurobiology of addiction course with Dr. Shane Perrine, my true passion for understanding psychiatric diseases emerged. One idea was to join the pharmaceutical industry to make drugs for psychiatric diseases. However, realizing the limitations inherent in developing psychopharmaceuticals without understanding the brain, I graduated from Wayne State University with my Master of Science degree in chemistry and a newfound determination to understand the neural mechanisms underlying psychiatric disorders.

> "Our journey toward truth is often a winding and convoluted path and what we find at the end is not always the truth we expected at the beginning of the journey."
>
> – Christian Scharen, One Step Closer: Why U2 Matters to Those Seeking God

3. Purpose?

Neuroscience emerged with perfect timing. The neurobiology of psychiatric diseases course engaged my fascination with chemistry and psychology. I was intrigued by the complex and dynamic interactions they both highlighted. In chemistry, molecules interacted to form new compounds with distinct properties. In psychology, the internal milieu (genetics, personality) interacted with the external environment (social, geographical) to influence individual outcomes (behaviors, values). I found that chemistry and psychology interacted in many aspects of neuroscience, as well and I felt that my passion for these interactions led me to my purpose.

Before I even finished writing my Master's thesis, I applied to neuroscience doctoral programs. I was unsure whether I had *the milk*, but I ended my Master of Science degree in chemistry resolute that I would understand the brain and psychiatric diseases. I decided to attend the University of Illinois Chicago and was awarded the Graduate College Pathway to an Inclusive Faculty fellowship through a competition for prospective students. This fellowship granted me the flexibility to imagine my own dissertation project in a truly independent way. Though there were no ongoing research programs that matched my interest, I was fully supported by the director of the Graduate Program in Neuroscience, Dr. John Larson, and the head of the Department of Psychology, Dr. Michael Ragozzino. With the guidance of these experienced mentors, I examined burgeoning ideas and discussed thought-provoking hypotheses. After months of discussion and reading about emotion regulation and stress, I stumbled upon an enormous body of work about oxytocin, the Brain Opioid Theory of Social Attachment [8], and the Tend-and-Befriend Theory [9]. These theories illuminated my perception of stress, social interaction, and emotion regulation. The interaction between oxytocin and opioids in this capacity was largely unstudied.

4. Moxie

4.1. The Tend-and-Befriend Theory

The Tend-and-Befriend Theory, proposed by Shelley E. Taylor, offered a novel perspective on behavioral responses to stress in the context of sociality [9,10]. The tend-and-befriend stress response was proposed as an alternative to the primary physiological response to stress in males and females; that is, the fight-or-flight response that was originally suggested by Walter Cannon in 1932 [11]. Taylor estimated that the fight-or-flight theory was based on research exploring behavioral and neuroendocrine responses to physical and mental challenges, predominantly in males. Females, thought to have greater cyclical variation in neuroendocrine levels due to the reproductive cycle, were less studied, and most findings were considered difficult to interpret. The tend-and-befriend stress response may have been obscured for these reasons.

The groundwork for Taylor's theory included studies of affiliative behavior. In contrast, these studies were predominantly conducted in females because of their association with social bonding and nurturing. As a result of these studies, Taylor proposed that females, like males, had the capacity to recruit a fight-or-flight response as a reaction to stress, but that this could jeopardize them and their offspring. As such, females were likely to have evolved alternative stress responses that would maximize their and their offspring's survival; that is, to tend and to befriend. In response to stress, females exhibit nurturing activities that protect them and reduce distress in them and their offspring (tending) and affiliative activities that create and maintain social networks that can aid in the tending process (befriending). Further, Taylor posited that the tend-and-befriend stress response builds on attachment and caregiving systems that are neurobiologically mediated by the oxytocin system. Here, the oxytocin system is thought to downregulate the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis responses to stress. In addition, the oxytocin system could be modulated by sex hormones and endogenous opioid peptides that are released in the brain during stress and play an important role in modulating the endocrine stress response and regulating emotions [12,13].

4.2. The Brain Opioid Theory of Social Attachment

Anna Machin and Robin Dunbar also put forward the Brain Opioid Theory of Social Attachment [8], based on prior work by Thomas Insel [14], Jaak Panksepp [12,15], and many other researchers. This theory emphasized a function for endogenous opioids (endorphins) in social reward and social attachment. Endorphins, which are largely linked to consummatory reward and addiction, elicit feelings of euphoria and pleasure and have incentive motivational properties. As such, these peptides may also facilitate interpersonal warmth, well-being, and bliss in relationships. Further, Machin and Dunbar drew comparisons between opioid addiction and intimate relationships, highlighting the three main stages that aligned with George Koob's framework of addiction (i): euphoria, which appeared in addiction as binge intoxication and in relationships as bliss, (ii) withdrawal, which appeared in addiction as hyperkatifeia [16] and in relationships as separation distress, grief, and depression, and (iii) tolerance-habituation, which appeared in addiction as preoccupation/anticipation and in

relationships as the progression from romantic to compassionate love.

4.3. The MOXI Hypothesis

Intrigued by these theories [8,10], I decided to investigate whether an interaction between oxytocin and opioid receptor systems existed. Early work demonstrated prosocial [17–19], anxiolytic-like [17,20–25], and anti-depressive-like [26–28] effects of μ-opioid receptor agonists, and burgeoning research demonstrated similar anti-stress effects of oxytocin [29–37]. However, there was a substantial gap in the literature related to stress and emotion regulation. I hypothesized that a bidirectional relationship between the endogenous μ-opioid and oxytocin receptor systems existed; specifically, blocking one would inhibit the other, and stimulating both had potential synergistic effects. This was my initial **M**u-opioid and **OX**ytocin system **I**nteraction (MOXI) hypothesis. My research on this hypothesis began in the Department of Psychology at UIC under the tutelage of Dr. Michael Ragozzino and has continued in the Neurobiology of Addiction section at the National Institute on Drug Abuse (NIDA) Intramural Research Program (IRP) under the tutelage of Dr. George Koob. The support of Drs. Karen Colley, Jonathan Art, Sue Carter, and Leandro F. Vendruscolo has also been unparalleled.

While organizing research protocols and resources, I applied for several sources of funding to bolster our financial support because the study was taking place independently of Dr. Ragozzino's primary research program. I also contributed to an ongoing project in the Ragozzino laboratory, which we recently published [38]. The Provost's Graduate Research Award allowed us to purchase essential software and equipment to start testing my hypothesis. I also sought out mentors and collaborators from whom I could learn more and discuss my research and career plans. Crucial to my transition from UIC to NIDA IRP were Dr. Colley (Dean of the Graduate College), Dr. Art (Associate of the Graduate College), and fellow researchers who immediately understood my passion for this research project.

In my search for collaborators, I cold-emailed Dr. Carter. To my astonishment, she replied with interest, and we spoke that same day. Beyond collaboration, I gained an incredible mentor. From the beginning, Dr. Carter took a deliberate and genuine interest in my research and career.

I met Dr. Koob one month later when he visited UIC as the keynote speaker at the Department of Psychiatry's Annual Research Extravaganza. Although not in the Department of Psychiatry, I appealed to be included in his session with psychiatry graduate students, and I spoke with him about my oxytocin research. Dr. Koob connected me with a postdoctoral fellow in his Neurobiology of Addiction section at NIDA IRP, who was working on oxytocin in alcohol use disorder models. Fruitful discussions ensued. Encouraged by Dr. Carter, I reached out to Dr. Koob again about my research hypothesis and opportunities to collaborate and was offered a predoctoral fellowship, a position I currently hold, at the NIDA IRP. This opportunity to pursue my dissertation research with an internationally renowned expert at the National Institutes of Health (NIH) was beyond anything I imagined. It would simply not have been possible without the support, guidance, and backing of my devoted mentors.

Exploration of the MOXI hypothesis would not have been possible without the support of these mentors and some moxie of my own.

4.4. A brief and beautiful tangent

My first task was to evaluate the anxiolytic- and antidepressant-like effects of oxytocin in C57Bl/6J mice [39]. Using the elevated zero maze and tail suspension test, I demonstrated these effects in males. Next, I needed to test females. A lengthy debate ensued: should naturally cycling or ovariectomized females be tested? Ultimately, we tested both groups of females. This work was completed between UIC and NIDA IRP and was supported by both Dr. Ragozzino and Dr. Koob. It led to an unexpected but important series of experiments regarding the reproductive cycle and reproductive hormones. We became curious about the lower anxiety-like responses females demonstrated at baseline and their lower response to oxytocin compared to males.

To further explore these differences, we investigated the effect of the estrous cycle (the mouse reproductive cycle) and gonadal hormones (estrogen and progesterone) on oxytocin sensitivity in female mice [39]. To investigate the estrous cycle, I used vaginal lavage to identify the estrous cycle phases and clustered females into phases of proestrus/estrus and metestrus/diestrus. We found that females in proestrus/estrus were sensitive to oxytocin whereas females in metestrus/diestrus were not. Contrary to published reports [40], we did not observe a difference in baseline anxiety-like behavior in proestrus/estrus and metestrus/diestrus females. To investigate the effect of exogenous hormones in females, they were ovariectomized and supplemented or not with estrogen or progesterone. We observed a leftward shift in the dose-response curve when they were supplemented with estrogen or progesterone; that is, lower doses of oxytocin were more effective at reducing anxiety-like behavior when these hormones were administered chronically). Notably, we did not observe these effects of estrous cycle and gonadal hormones in measures of depression-like behavior (Table 1).

These data spurred questions about the different mechanisms underlying emotion regulation. Is the oxytocin system recruited differently in depression versus anxiety? Is the tail suspension test measuring other behaviors that oxytocin is affecting differentially? Would the same outcome be observed if other tests of depression-like behaviors (e.g., learned helplessness) were used? In the broader scope of psychiatric disorders and treatments, this study generated important clinical questions as well. What are the effects of menstrual cycle, hormone-mediated contraceptives, hormone supplements, and hormone blockers on the endogenous oxytocin system, efficacy of exogenous oxytocin, and FDA-approved anxiolytics and antidepressants? It is unlikely that the differences we observed are unique to oxytocin administration because other studies demonstrate similar evidence for sex-, estrous cycle-, and hormone-dependent differences [41–46], and antidepressant and anxiolytic drugs may interact with the oxytocin system [47–50].

4.5. Okay, let's focus: The MOXI Hypothesis

Still deeply curious about the oxytocin × opioid interaction, I began to explore the MOXI hypothesis in C57Bl/6J mice in the Ragozzino laboratory. The pilot experiment was conducted using β-funaltrexamine as the μ-opioid receptor antagonist with pretreatment times of 25 or 60 min and oxytocin with a pretreatment time of 15 min, both administered intracerebroventricularly. The preliminary data appeared to support the original hypothesis that β-funaltrexamine blocked the anxiolytic-like effect of oxytocin (Table 2).

Once I joined the NIDA IRP, I repeated these experiments using naloxone as the opioid receptor antagonist. Compared to β-funaltrexamine, naloxone had high blood-brain barrier permeability and was short-acting. This had the advantage of enhancing the experimental design and interpretability. However, when these experiments were performed using naloxone, we observed a completely different outcome. Instead, systemically administered naloxone potentiated the anxiolytic-like effect of oxytocin [51] (Table 2). A review of the literature revealed that, unlike naloxone, β-funaltrexamine covalently and irreversibly binds the μ-opioid receptor [52], with its effects not being specific for at least 24 h [53,54]. As such, the initial dataset remains difficult to interpret.

I next tested my hypothesis with a third μ-opioid receptor antagonist, D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2 (CTAP). CTAP is a peptide antagonist with higher potency and selectivity for μ-opioid receptors compared to naloxone [55]. Because of its low blood-brain barrier penetrance [56], it needed to be infused directly into the brain. Like naloxone, CTAP potentiated the anxiolytic-like effect of oxytocin

Table 1
Effect of oxytocin on depression- and anxiety-like behavior in C57Bl/6J mice. In a previous report, we demonstrated that oxytocin reduced depression-like behavior in all experimental groups: males, females, females in proestrus/estrus, females in metestrus/diestrus, ovariectomized females, estrogen-supplemented ovariectomized females, and progesterone-supplemented ovariectomized females [39]. Oxytocin reduced anxiety-like behavior in all experimental groups except females in metestrus/diestrus. An effect of sex was observed (i.e., oxytocin was more effective at reducing anxiety-like behavior in males compared to females). An effect of reproductive cycle was observed (i.e., oxytocin reduced anxiety-like behavior in females in proestrus/estrus but not in females in metestrus/diestrus). And a slight effect of reproductive hormones was observed (i.e., while oxytocin reduced anxiety-like behavior in all ovariectomized female experimental groups, lower doses of oxytocin were required to reduce anxiety-like behavior when ovariectomized females were supplemented with estrogen or progesterone). Shading of the arrows is used to convey oxytocin sensitivity between experimental groups (i.e., increasingly opaque arrows illustrate greater sensitivity to oxytocin).

Experimental groups	Effect of oxytocin on Depression-like behavior	Effect of oxytocin on Anxiety-like behavior
Influence of sex		
Males	↓	↓
Females	↓	↓
Influence of hormonal status: reproductive cycle		
Females in proestrus/estrus	↓	↓
Females in metestrus/diestrus	↓	X
Influence of hormonal status: reproductive hormones		
Ovariectomized females	↓	↓
Estrogen-supplemented ovariectomized females	↓	↓
Progesterone-supplemented ovariectomized females	↓	↓

Table 2
Effects of oxytocin, β-funaltrexamine, naloxone, and CTAP on baseline anxiety-like behavior and oxytocin-induced anxiolytic-like behavior in C57Bl/6J mice. Oxytocin reduced anxiety-like behavior. Consistent with my original hypothesis, β-funaltrexamine blocked the anxiolytic-like effect of oxytocin when administered 25 or 60 min before testing (these data are unpublished). However, contrary to my original hypothesis, naloxone and the μ-opioid receptor antagonist D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2 (CTAP) potentiated the anxiolytic-like effect of oxytocin [51].

Drug	Anxiety-like behavior (Baseline)	Oxytocin-induced anxiolytic-like behavior
Oxytocin	↓	**N/A**
β-funaltrexamine	↓	↓
Naloxone	X	↑
CTAP	X	↑

(Table 2). These data established an interaction between the oxytocin and μ-opioid receptor systems. However, contrary to the original hypothesis, we found that inhibiting the μ-opioid receptor system potentiated the anxiolytic-like effect of oxytocin.

4.6. The updated MOXI Hypothesis

The finding that μ-opioid receptor blockade potentiated the anxiolytic-like effect of oxytocin informed an update to the MOXI hypothesis. The initial hypothesis that activation of the endogenous μ-opioid and oxytocin receptor systems was functionally synergistic was not supported. Instead, it appeared that the μ-opioid receptor system negatively modulated the oxytocin system. After an intensive literature review, I found that at least two hypotheses could explain my findings. The first, I refer to as the hypothalamic MOXI hypothesis. It had been reported and demonstrated decades prior [57,58]. The second, I refer to as the extrahypothalamic MOXI hypothesis. This is my novel hypothesis of how the μ-opioid and oxytocin receptors might interact and it has yet to be investigated. Both are described in detail below.

4.7. The Hypothalamic MOXI Hypothesis

An early collection of studies by Gareth Leng, R. John Bicknell, Alison J. Douglas, John A. Russell, and their colleagues demonstrated that blocking μ-opioid receptors increased oxytocin release from the paraventricular and supraoptic nuclei of the hypothalamus and increased the electrical activity of oxytocin neurons in these brain regions [57,59,60]. They postulated that constitutive μ-opioid receptor activation could inhibit oxytocinergic cells and therefore, reduce the release of oxytocin (Fig. 1A), and that μ-opioid receptor blockade could disinhibit these cells and enhance oxytocin release as a result (Fig. 1B).

Based on our current understanding, this mechanism is likely specific to the paraventricular, supraoptic, and accessory nuclei of the hypothalamus (i.e., brain regions that synthesize and release oxytocin). This hypothalamic hypothesis partially explains the potentiating effect of naloxone and CTAP described in Table 2. However, I propose that another mechanism, mediated by extrahypothalamic brain regions, might explain the observed effect. Particularly, limbic brain regions, including the nucleus accumbens and central, medial, and basolateral nuclei of the amygdala, ought to be considered.

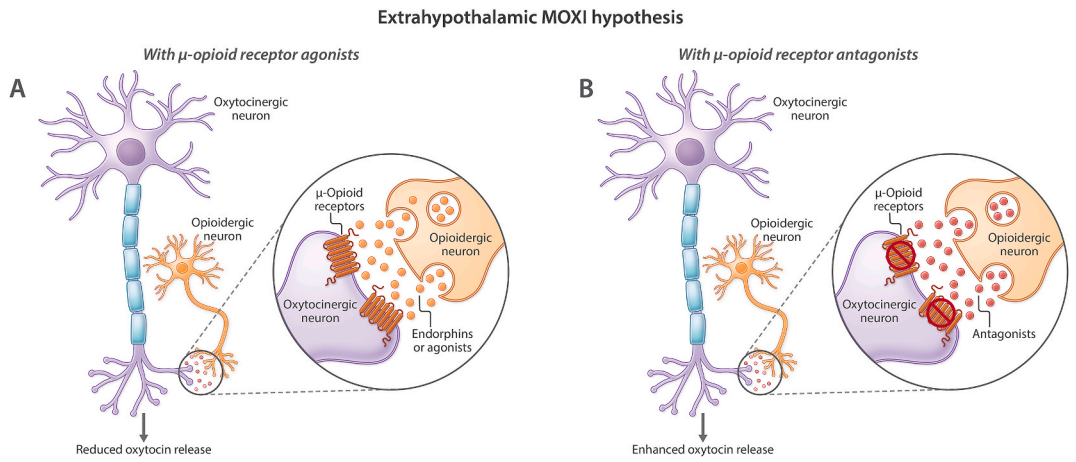

Fig. 1. Hypothalamic MOXI hypothesis. μ-Opioid receptors expressed on presynaptic terminals of hypothalamic oxytocinergic neurons can modulate the release of oxytocin throughout the brain and posterior pituitary (A, B). μ-Opioid receptors couple with inhibitory $G_{\alpha i}$ proteins. Thus, endorphins or agonists can inhibit neural transmission and reduce oxytocin release (A), and antagonists can disinhibit neural transmission and increase oxytocin release (B). This hypothesis and diagram are based on an earlier conceptualization by Clarke et al. [59].

4.8. The Extrahypothalamic MOXI Hypothesis

The extrahypothalamic hypothesis posits that μ-opioid receptors can modulate the activity of oxytocin receptor-expressing neurons (e.g., γ-aminobutyric acid-containing [GABAergic], glutamatergic, serotonergic, or dopaminergic neurons) in relevant brain regions (e.g., central nucleus of the amygdala, basolateral amygdala, nucleus accumbens, lateral septum, or ventral tegmental area). The MOXI hypothesis is based on three premises. First, both oxytocin receptors and μ-opioid receptors are expressed on the same neuron type, such as GABAergic or glutamatergic neurons [61–63]. Second, oxytocin receptors predominantly couple stimulatory $G_{\alpha q}$ proteins ($OXTR_{G\alpha q}$) but can also couple inhibitory $G_{\alpha i}$ proteins ($OXTR_{G\alpha i}$) [64]. Third, μ-opioid receptors predominantly couple inhibitory $G_{\alpha i}$ proteins ($MOR_{G\alpha i}$) [65].

This suggests that μ-opioid and oxytocin receptors have opposing functions. Specifically, activation can inhibit neuronal activity, whereas activation can stimulate neuronal activity (Fig. 2A–C). As such, μ-opioid receptor antagonism may block constitutive endorphin-mediated neuronal inhibition; that is, μ-opioid receptor antagonism may disinhibit μ-opioid receptor-expressing neurons and enhance oxytocin-induced neuronal stimulation (Fig. 2B) or neurotransmitter release (Fig. 2D). This describes the neuronal colocalization hypothesis (Fig. 2A and B) and the converging neuron hypothesis (Fig. 2C and D).

The neuronal colocalization hypothesis posits that $OXTR_{G\alpha q}$ and $MOR_{G\alpha i}$ are expressed on the same neurons in extrahypothalamic brain regions. $MOR_{G\alpha i}$ and $OXTR_{G\alpha q}$ agonists would thus have opposing effects (Fig. 2A) and blockade would increase neuronal excitability through the activation of $OXTR_{G\alpha q}$ by oxytocin (Fig. 2B). Given the synergistic effects of opioid receptor antagonists and oxytocin, I also consider potential for the heterodimerization of the respective receptors, as heterodimerization and oligomerization of both receptors have been observed previously [66–75]. The converging neuron hypothesis posits that $MOR_{G\alpha i}$ and $OXTR_{G\alpha q}$ neurons are expressed on separate neurons that then converge onto the same secondary neuron. Here, the blockade or activation of μ-opioid receptors could disinhibit or excite their respective neurons, which converge onto the same neuron as oxytocin-receptor expressing neurons to produce a synergistic effect (Fig. 2C-F).

There are multiple alternative mechanisms that can account for MOXI. Here, I propose another hypothesis that accounts for the coupling of oxytocin receptors to inhibitory $G_{\alpha i}$ proteins ($OXTR_{G\alpha i}$) that can occur in an inhibitory neural network. For example, in a predominantly GABAergic neural network, the activation of $OXTR_{G\alpha i}$ may inhibit GABA release. Thus, μ-opioid receptor-expressing GABAergic neurons may project onto oxytocin receptor-expressing GABAergic neurons. As such, μ-opioid receptor antagonism would promote GABA release and promote inhibition of the efferent oxytocin receptor-expressing neuron. $MOR_{G\alpha i}$-expressing neurons may project to $OXTR_{G\alpha i}$-expressing neurons in extrahypothalamic brain regions. In this way, the activation of both receptors would have an inhibitory action on their respective neurons (Fig. 3A), such that blockade could disinhibit GABAergic neurons and enhance the inhibition of $OXTR_{G\alpha i}$-GABAergic neurons that are important for a potentiated anxiolytic-like response (Fig. 3B).

It is important to note that neurons comprise only 10% of the total brain cell population. μ-Opioid and oxytocin receptors may be expressed on glial cells throughout the brain and some glial cells have been shown to mediate effects of oxytocin and opioids [76–81]. Thus, a role for glial cells in the MOXI hypothesis should be considered.

Currently, electrophysiological, transgenic-behavioral, and morphological studies are ongoing to decipher these potential mechanisms. A few implications of our findings and the MOXI mechanisms are discussed below.

4.9. Clinical implications of the MOXI Hypothesis: the MOXAIC Hypothesis

Early studies demonstrated that μ-opioid receptor antagonism (e.g., with naloxone and naltrexone) can increase oxytocin release via a hypothalamic mechanism (Fig. 1). I recently demonstrated that μ-opioid receptor antagonism can potentiate the anxiolytic-like effect of oxytocin (Table 2) and proposed that μ-opioid receptor blockade can enhance oxytocin function via extrahypothalamic mechanisms (Figs. 2 and 3). Accordingly, both the hypothalamic and extrahypothalamic MOXI mechanisms may synergize to promote the efficacy of **M**u-Opioid receptor antagonist and **OX**ytocin receptor **A**gonist **I**n **C**ombination (MOXAIC) treatment in psychiatric disorders and other illnesses. A recent case study demonstrated that naltrexone and oxytocin cotreatment could be used to treat hypothalamic obesity (i.e., excessive weight gain caused by injury to the hypothalamus) [82]. Another study in rhesus macaques demonstrated that naloxone and oxytocin cotreatment enhanced social attention [83], suggesting a potential therapeutic use in autism spectrum disorder and other psychosocial disorders, such as social anxiety. There may also be a potential use for adjunctive MOXAIC treatment in psychosocial therapy for the treatment of stress, affective, anxiety, and substance use disorders.

Preclinical studies demonstrate that oxytocin can reduce stress reactivity [33,84], depression-like behavior [39,85–88], anxiety-like behavior [29,35,39,89], measures of alcohol and drug dependence

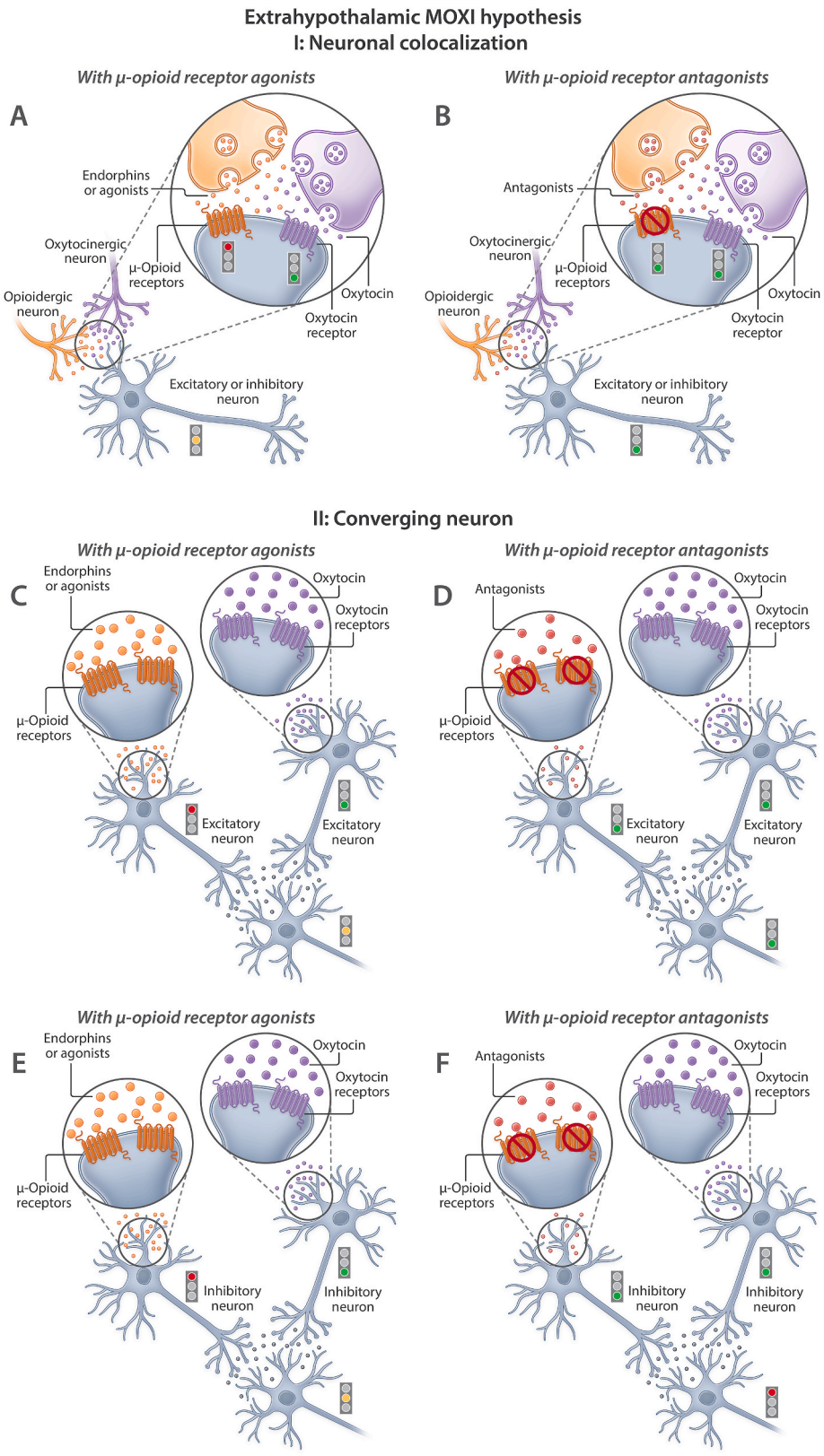

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Fig. 2. Extrahypothalamic MOXI hypotheses: neuronal colocalization and converging neuron hypotheses. μ-Opioid receptors on various neuron types (e.g., GABAergic, glutamatergic, or serotonergic neurons) can modulate the effect of oxytocin release or oxytocin receptor activation. In the neuronal colocalization hypothesis, μ-opioid receptor agonists may reduce neuron excitability by increasing inhibitory tone of the neuron (A), whereas μ-opioid receptor antagonists may have a disinhibitory effect and increase neuronal excitability by removing endorphin-induced inhibitory tone (B). In the converging neuron hypothesis, μ-opioid receptor agonists may reduce excitability of the converging μ-opioid receptor-expressing neuron and reduce neurotransmitter release onto a secondary neuron which may oppose neurotransmitter release from a converging oxytocin receptor-expressing neuron (C, E). μ-Opioid receptor antagonists may disinhibit the converging μ-opioid receptor-expressing neuron to allow for greater neurotransmitter release, which may synergize with neurotransmitter release from a converging oxytocin receptor-expressing neuron (D, F). In an excitatory neuronal network, the synergism of a μ-opioid receptor antagonist with an oxytocin receptor agonist could lead to activation of the secondary, convergent neuron (D). In an inhibitory neuronal network, this synergism could lead to inhibition of the secondary, convergent neuron (F).

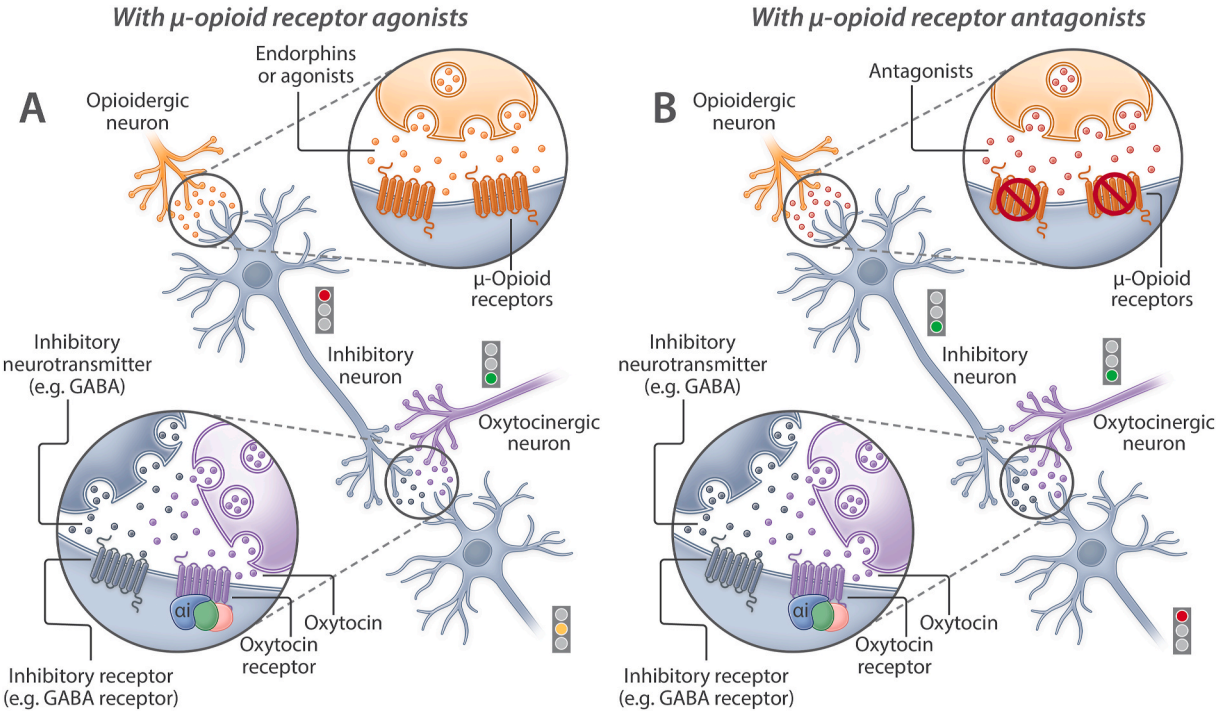

Fig. 3. Additional **MOXI hypothesis in** inhibitory **neurons.** μ-Opioid receptors expressed within an inhibitory neural netwok (e.g. GABA or Neuropeptide Y) can potentiate the effect of oxytocin or oxytocin receptor agonists. μ-Opioid receptor agonists may inhibit (hyperpotentiate) an inhibitory neuron and reduce neurotransmitter (e.g. GABA) release on a tertiary neuron (A). Thus, μ-Opioid receptor antagonists may disinhibit an inhibitory neuron and increase the release of an inhibitory neurotransmitter on a tertiary neuron. This action may synergize with the activation of $G_{\alpha i}$-coupled oxytocin receptors to completely inhibit a tertiary neuron (B).

[90–94], and hyperkatifeia [92] and can enhance cognition and social approach [95,96]. However, clinical trials have replicated these findings with low or unreliable efficacy [30,97–101]. Although the lower efficacy of oxytocin in these trials may have resulted from the route of drug administration, dose of drug, low blood-brain barrier penetrance, or low sample size, the hypothalamic and extrahypothalamic MOXI hypotheses infer a neurobiological limitation (i.e., that endorphins or constitutive μ-opioid receptor activity may block the efficacy of endogenous and exogenous oxytocin). Others have also demonstrated that oxytocin may function as a positive allosteric modulator at the μ-opioid receptor [102], which may reduce the effectiveness of oxytocin in the presence of endorphins. As such, replacing oxytocin treatment with MOXAIC treatment may be a more promising approach. Additionally, naltrexone has demonstrated high efficacy in treating opioid use disorder and preventing relapse, but it has low patient adherence because of the aversive effect of opioid receptor antagonists. The MOXI and MOXAIC treatment hypotheses also provide a promising approach for the treatment of substance use disorders and may increase patient adherence by blocking μ-opioid receptors and preventing the development of negative affective states and aversive somatic symptoms.

As these are developing hypotheses, I acknowledge several potential drawbacks. First, observations regarding the MOXI hypothesis may be context specific. This is an important consideration given that the hypothalamic MOXI hypothesis was previously supported by studies in pregnant and lactating, but not virgin female, rats [57,60,103] and in male and female rats that were subjected to osmotic stress but not stress-naive male or female rats [104]. In addition, because previous studies that may support the extrahypothalamic MOXI hypothesis [51,83] were conducted in stress-naive animals, there may be significant neural network changes that disrupt MOXI in stressed animals. Second, with respect to MOXAIC treatment, the previously mentioned drawbacks inherent in the intranasal route of oxytocin delivery [105], such as low blood-brain barrier penetrance and suboptimal dose titration, may supersede any benefits of MOXAIC treatment if the same route of administration is used for oxytocin, oxytocin receptor agonists, and/or μ-opioid receptor antagonists. Third, there is a need to determine the best ratios of effective μ-opioid receptor antagonists and doses of oxytocin receptor agonists to be used in clinical trials and preclinical studies in psychiatric disorders and related animal models, respectively. Fourth, the effects of chronic oxytocin and naltrexone treatment are not well understood. This is especially important given that chronic drug administration may desensitize target receptors (tolerance). This phenomenon is well described as a result of the administration of μ-opioid receptor agonists [106] but is understudied with respect to oxytocin

receptors [107]. It is important to note that clinically approved oxytocin and oxytocin receptor agonists demonstrate activity at vasopressin receptors [108], and clinically approved opioid receptor antagonists might have unpredictable and undesirable side effects because of their simultaneous inhibition of κ- and δ-opioid receptors [109]. Altogether, these potential drawbacks highlight that further studies are required to validate the MOXI and MOXAIC hypotheses.

5. What's next?

I remain curious about the MOXI and MOXAIC hypotheses, the previously described Tend-and-Befriend Theory, and the Brain Opioid Theory of Social Attachment, in addition to recently published concepts, such as the Allostatic Theory of Oxytocin [110] and the Oxytocin As Nature's Medicine Theory [111]. The Allostatic Theory of Oxytocin posits that oxytocin modulates social and nonsocial behaviors by facilitating adaptation and consolidation and by maintaining stability through changing environments to affect physiological and psychological wellness [110]. The Oxytocin as Nature's Medicine Theory explicates the broad functionality of oxytocin as a stress-coping molecule, an anti-inflammatory agent, and an antioxidant that can influence the immune and autonomic nervous systems to affect general health, adaptation, development, reproduction, and social behavior (e.g. bonding, altruism, and cooperation) [111].

In addition to these works, I am intrigued by Johann Hari's Lost Connections Theory [112], particularly in consideration of human ultra-sociality [113,114]. Hari's theory is based on clinical observations, research, and personal and collective anecdotes. He posits that we unknowingly depreciate our mental health as individuals and a society by neglecting important dimensions of wellness [115]. Supported by a broad literature, Hari supposes that disconnection from meaningful work [116–118], other people [117,119,120], meaningful values [121, 122], childhood trauma [123–125], status [122,126], nature [127–130], and a secure and hopeful future [121,131,132] can be determinants of psychiatric illness, in addition to genes [133–136], neuroplasticity and neuroadaptation [137] – a case that is persuasive and relatable. Ultra-sociality describes the complex social organization of a few species, including humans and some social insects (ants, termites) that are highly adaptive at a group level, having specialized divisions of labor, independent cities, and a dependence on agriculture [113,114]. Experts suggests that ultrasocial systems are upheld by cooperation and can be inhibited by competition, and that cooperation leads to "greater group productivity, more favorable interpersonal relations, better psychological health, and higher self-esteem" [113,114,138,139].

Combining these theories with my unique skillset and passion, I am motivated to understand the neurobiological and psychosocial factors that contribute to the decline of mental health in my communities and to uncover novel ways to improve global empathy, mental health, and cooperation. I am deeply curious about the relationship between social disconnectedness and psychiatric disorders.

> "If I have seen further than others, it is by standing upon the shoulders of giants."
>
> – Isaac Newton

I cannot take for granted the openness of science and the scientific community's obligation to share research findings to inform and positively affect our communities. Science has been communicated so well within the last century that we all have *more milk* than we could ask for; that is, the resources we have already acquired (knowledge, curiosity, skills, and talents) to get started on a project or mission. I am grateful to my predecessors who laid and continue to lay the groundwork to advance our understanding of each other and mental wellbeing, and I am grateful to my colleagues who build on this foundation with me. The onus is on us all to find the *orange juice* – the resources we need to attain (funding, equipment, mentors, collaborators, skills, talents) to arrive at the desired outcome.

6. Conclusion

> "Purpose is so intrinsic to whom we are that it guides us unknowingly."
>
> -Khalin E. Nisbett

Although my academic journey has been unpredictable, it has also been thrilling, and reassuring. Through the example of my many mentors, I have and will continue to serve my community, share what I have learned through research, strive to improve the lives of others, and to do all of this with all the moxie I can muster. I aspire to continue collaborating and connecting with experts and lay people to improve mental wellbeing and cooperation in our world.

CRediT authorship contribution statement

Khalin E. Nisbett: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

I declare no conflicts of interest.

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References

[1] D. Orr, The Road Not Taken: Finding America in the Poem Everyone Loves and Almost Everyone Gets Wrong, Penguin, 2015.
[2] W.T. Tucker, Max Weber's verstehen, Socio. Q. 6 (2) (1965) 157–165.
[3] A.C. Davis, L. Akins, C. Pollock, I. Lundgren, M.A. Johnston, B. Castillo, et al., Multiple drivers of invasive lionfish culling efficiency in marine protected areas, Conservation Science and Practice 3 (11) (2021) e541.
[4] S. Parkin, J. Neale, C. Brown, A.N. Campbell, F. Castillo, J.D. Jones, et al., Opioid overdose reversals using naloxone in New York City by people who use opioids: implications for public health and overdose harm reduction approaches from a qualitative study, Int. J. Drug Pol. 79 (2020) 102751.
[5] University of the Virgin Islands, UVI today. http://uvitoday.blogspot.com/2014/12/uvi-research-students-win-big-at.html, 2014.
[6] K.E. Nisbett, Design, Synthesis and Analysis of Potential Photo-Activatable Cathepsin K Inhibitors, 2017.
[7] K. Nisbett, Y.-J. Tu, C. Turro, J.J. Kodanko, H.B. Schlegel, DFT Investigation of Ligand Photodissociation in [RuII (tpy)(bpy)(py)] 2+ and [RuII (tpy)(Me2bpy)(py)] 2+ Complexes, Inorg. Chem. 57 (1) (2018) 231–240.
[8] A.J. Machin, R.I. Dunbar, The brain opioid theory of social attachment: a review of the evidence, Behaviour 148 (9–10) (2011) 985–1025.
[9] S.E. Taylor, Tend and befriend theory, Handbook of theories of social psychology 1 (2012) 32–49.
[10] S.E. Taylor, L.C. Klein, B.P. Lewis, T.L. Gruenewald, R.A. Gurung, J.A. Updegraff, Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight, Psychol. Rev. 107 (3) (2000) 411.
[11] W.B. Cannon, The Wisdom of the Body, 1939.
[12] J. Panksepp, B. Herman, T. Vilberg, P. Bishop, F. DeEskinazi, Endogenous opioids and social behavior, Neurosci. Biobehav. Rev. 4 (4) (1980) 473–487.
[13] D.J. Stein, J. van Honk, J. Ipser, M. Solms, J. Panksepp, Opioids: from physical pain to the pain of social isolation, CNS Spectr. 12 (9) (2007) 669–670.
[14] T.R. Insel, Is social attachment an addictive disorder? Physiol. Behav. 79 (3) (2003) 351–357.
[15] J. Panksepp, Affective Neuroscience: the Foundations of Human and Animal Emotions, Oxford university press, 2004.

[16] G.F. Koob, Drug addiction: hyperkatifeia/negative reinforcement as a framework for medications development, Pharmacol. Rev. 73 (1) (2021) 163–201.
[17] B.H. Herman, J. Panksepp, Effects of morphine and naloxone on separation distress and approach attachment: evidence for opiate mediation of social affect, Pharmacol. Biochem. Behav. 9 (2) (1978) 213–220.
[18] V. Trezza, R. Damsteegt, E.M. Achterberg, L.J. Vanderschuren, Nucleus accumbens μ-opioid receptors mediate social reward, J. Neurosci. 31 (17) (2011) 6362–6370.
[19] L.J. Vanderschuren, B. Spruijt, J. Van Ree, R. Niesink, Effects of morphine on different aspects of social play in juvenile rats, Psychopharmacology 117 (1995) 225–231.
[20] R. Anand, K. Gulati, A. Ray, Pharmacological evidence for the role of nitric oxide in the modulation of stress-induced anxiety by morphine in rats, Eur. J. Pharmacol. 676 (1–3) (2012) 71–74.
[21] J.C. Joshi, A. Ray, K. Gulati, Effects of morphine on stress induced anxiety in rats: role of nitric oxide and Hsp70, Physiol. Behav. 139 (2015) 393–396.
[22] A. Rezayof, S-s Hosseini, M.-R. Zarrindast, Effects of morphine on rat behaviour in the elevated plus maze: the role of central amygdala dopamine receptors, Behav. Brain Res. 202 (2) (2009) 171–178.
[23] I.-C. Shin, H.-C. Kim, J. Swanson, J.-T. Hong, K.-W. Oh, Anxiolytic effects of acute morphine can be modulated by nitric oxide systems, Pharmacology 68 (4) (2003) 183–189.
[24] R. Defrance, C. Marey, A. Kamoun, Antidepressant and anxiolytic activities of tianeptine: an overview of clinical trials, Clin. Neuropharmacol. 11 (1988) S74–S82.
[25] K. Sasaki, L.-W. Fan, L.-T. Tien, T. Ma, H.H. Loh, K. Ho, The interaction of morphine and γ-aminobutyric acid (GABA) ergic systems in anxiolytic behavior: using μ-opioid receptor knockout mice, Brain Res. Bull. 57 (5) (2002) 689–694.
[26] E. Berrocoso, K. Ikeda, I. Sora, G.R. Uhl, P. Sánchez-Blázquez, J.A. Mico, Active behaviours produced by antidepressants and opioids in the mouse tail suspension test, Int. J. Neuropsychopharmacol. 16 (1) (2013) 151–162.
[27] E. Berrocoso, P. Sánchez-Blázquez, J. Garzón, J.A. Mico, Opiates as antidepressants, Curr. Pharmaceut. Des. 15 (14) (2009) 1612–1622.
[28] B.A. Samuels, K.M. Nautiyal, A.C. Kruegel, M.R. Levinstein, V.M. Magalong, M. M. Gassaway, et al., The behavioral effects of the antidepressant tianeptine require the mu-opioid receptor, Neuropsychopharmacology 42 (10) (2017) 2052–2063.
[29] A. Blume, O.J. Bosch, S. Miklos, L. Torner, L. Wales, M. Waldherr, et al., Oxytocin reduces anxiety via ERK1/2 activation: local effect within the rat hypothalamic paraventricular nucleus, Eur. J. Neurosci. 27 (8) (2008) 1947–1956.
[30] F. De Cagna, L. Fusar-Poli, S. Damiani, M. Rocchetti, G. Giovanna, A. Mori, et al., The role of intranasal oxytocin in anxiety and depressive disorders: a systematic review of randomized controlled trials, Clinical Psychopharmacology and Neuroscience 17 (1) (2019) 1.
[31] A.J. Guastella, A.L. Howard, M.R. Dadds, P. Mitchell, D.S. Carson, A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder, Psychoneuroendocrinology 34 (6) (2009) 917–923.
[32] P. Mak, C. Broussard, K. Vacy, J.H. Broadbear, Modulation of anxiety behavior in the elevated plus maze using peptidic oxytocin and vasopressin receptor ligands in the rat, J. Psychopharmacol. 26 (4) (2012) 532–542.
[33] R.J. Windle, N. Shanks, S.L. Lightman, C.D. Ingram, Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats, Endocrinology 138 (7) (1997) 2829–2834.
[34] S. Yoon, Y.-K. Kim, The role of the oxytocin system in anxiety disorders, Adv. Exp. Med. Biol. 1191 (2020) 103–120.
[35] K. Kent, V. Arientyl, M.M. Khachatryan, R.I. Wood, Oxytocin induces a conditioned social preference in female mice, J. Neuroendocrinol. 25 (9) (2013) 803–810.
[36] K. Uvnäs-Moberg, Oxytocin may mediate the benefits of positive social interaction and emotions, Psychoneuroendocrinology 23 (8) (1998) 819–835.
[37] L.J. Young, M.M. Lim, B. Gingrich, T.R. Insel, Cellular mechanisms of social attachment, Horm. Behav. 40 (2) (2001) 133–138.
[38] P. Teneqexhi, A. Khalid, K.E. Nisbett, G.A. Job, Jr WS. Messer, M.E. Ragozzino, The partial M1 muscarinic cholinergic receptor agonist, CDD-0102A, differentially modulates glutamate efflux in striatal subregions during stereotyped motor behavior in the BTBR mouse model of autism, Under review (2023).
[39] K.E. Nisbett, L.A. Gonzalez, M. Teruel, C.S. Carter, L.F. Vendruscolo, M. E. Ragozzino, et al., Sex and hormonal status influence the anxiolytic-like effect of oxytocin in mice, Under review (2023) 1–9.
[40] T.A. Lovick, Jr H. Zangrossi, Effect of estrous cycle on behavior of females in rodent tests of anxiety, Front. Psychiatr. (2021) 1492.
[41] M.A. Wilson, R. Biscardi, Sex differences in GABA/benzodiazepine receptor changes and corticosterone release after acute stress in rats, Exp. Brain Res. 101 (1994) 297–306.
[42] M. Gulinello, S.S. Smith, Anxiogenic effects of neurosteroid exposure: sex differences and altered GABAA receptor pharmacology in adult rats, J. Pharmacol. Exp. Therapeut. 305 (2) (2003) 541–548.
[43] J. Simpson, C. Ryan, A. Curley, J. Mulcaire, J.P. Kelly, Sex differences in baseline and drug-induced behavioural responses in classical behavioural tests, Prog. Neuro Psychopharmacol. Biol. Psychiatr. 37 (2) (2012) 227–236.
[44] A. Farkouh, T. Riedl, R. Gottardi, M. Czejka, A. Kautzky-Willer, Sex-related differences in pharmacokinetics and pharmacodynamics of frequently prescribed drugs: a review of the literature, Adv. Ther. 37 (2020) 644–655.
[45] D. Reddy, S. Kulkarni, Sex and estrous cycle-dependent changes in neurosteroid and benzodiazepine effects on food consumption and plus-maze learning behaviors in rats, Pharmacol. Biochem. Behav. 62 (1) (1999) 53–60.
[46] M.A. Wilson, Influences of gender, gonadectomy 5 and estrous cycle on GABA/BZ receptors and benzodiazepine responses in rats, Brain Res. Bull. 29 (2) (1992) 165–172.
[47] K. Uvnäs-Moberg, E. Björkstrand, V. Hillegaart, S. Ahlenius, Oxytocin as a possible mediator of SSRI-induced antidepressant effects, Psychopharmacology 142 (1) (1999) 95–101.
[48] A.B. Emiliano, T. Cruz, V. Pannoni, J.L. Fudge, The interface of oxytocin-labeled cells and serotonin transporter-containing fibers in the primate hypothalamus: a substrate for SSRIs therapeutic effects? Neuropsychopharmacology 32 (5) (2007) 977–988.
[49] D. Viviani, T. Terrettaz, F. Magara, R. Stoop, Oxytocin enhances the inhibitory effects of diazepam in the rat central medial amygdala, Neuropharmacology 58 (1) (2010) 62–68.
[50] K. Yagi, T. Onaka, A benzodiazepine, chlordiazepoxide, blocks vasopressin and oxytocin release after footshocks but not osmotic stimulus in the rat, Neurosci. Lett. 203 (1) (1996) 49–52.
[51] K.E. Nisbett, L.F. Vendruscolo, G.F. Koob, μ-Opioid receptor antagonism facilitates the anxiolytic-like effect of oxytocin in mice, Transl. Psychiatry 14 (1) (2024) 125.
[52] R.B. Rothman, V. Bykov, A. Mahboubi, J.B. Long, Q. Jiang, F. Porreca, et al., Interaction of β-funaltrexamine with [3H] cycloFOXY binding in rat brain: further evidence that β-FNA alkylates the opioid receptor complex, Synapse 8 (2) (1991) 86–99.
[53] Q. Jiang, A. Seyed-Mozaffari, A. Sebastian, S. Archer, J.M. Bidlack, Preventing morphine antinociceptive tolerance by irreversible mu opioid antagonists before the onset of their antagonism, J. Pharmacol. Exp. Therapeut. 273 (2) (1995) 680–688.
[54] Q. Jiang, J. Heyman, R. Sheldon, R. Koslo, F. Porreca, Mu antagonist and kappa agonist properties of beta-funaltrexamine (beta-FNA) in vivo: long-lasting spinal analgesia in mice, J. Pharmacol. Exp. Therapeut. 252 (3) (1990) 1006–1011.
[55] T. Kramer, J. Shook, W. Kazmierski, E. Ayres, W. Wire, V. Hruby, et al., Novel peptidic mu opioid antagonists: pharmacologic characterization in vitro and in vivo, J. Pharmacol. Exp. Therapeut. 249 (2) (1989) 544–551.
[56] T.J. Abbruscato, S.A. Thomas, V.J. Hruby, T.P. Davis, Blood-brain barrier permeability and bioavailability of a highly potent and μ-selective opioid receptor antagonist, CTAP: comparison with morphine, J. Pharmacol. Exp. Therapeut. 280 (1) (1997) 402–409.
[57] A. Douglas, R. Bicknell, J. Russell, Pathways to parturition, Adv. Exp. Med. Biol. 395 (1995) 381–394.
[58] G. Leng, S.L. Meddle, A.J. Douglas, Oxytocin and the maternal brain, Curr. Opin. Pharmacol. 8 (6) (2008) 731–734.
[59] G. Clarke, P. Wood, L. Merrick, D. Lincoln, Opiate inhibition of peptide release from the neurohumoral terminals of hypothalamic neurones, Nature 282 (5740) (1979) 746–748.
[60] A. Douglas, S. Dye, G. Leng, J. Russell, R. Bicknell, Endogenous opioid regulation of oxytocin secretion through pregnancy in the rat, J. Neuroendocrinol. 5 (3) (1993) 307–314.
[61] B. Hu, C.A. Boyle, S. Lei, Oxytocin receptors excite lateral nucleus of central amygdala by phospholipase Cβ-and protein kinase C-dependent depression of inwardly rectifying K+ channels, J. Physiol. 598 (16) (2020) 3501–3520.
[62] A. Mansour, C.A. Fox, S. Burke, F. Meng, R.C. Thompson, H. Akil, et al., Mu, delta, and kappa opioid receptor mRNA expression in the rat CNS: an in situ hybridization study, J. Comp. Neurol. 350 (3) (1994) 412–438.
[63] J.M. Delfs, H. Kong, A. Mestek, Y. Chen, L. Yu, T. Reisine, et al., Expression of mu opioid receptor mRNA in rat brain: an in situ hybridization study at the single cell level, J. Comp. Neurol. 345 (1) (1994) 46–68.
[64] M. Busnelli, B. Chini, Molecular basis of oxytocin receptor signalling in the brain: what we know and what we need to know, Behav. Pharmacol. Neuropeptides: Oxytocin (2018) 3–29.
[65] M. Connor, M.J. Christie, Opioid receptor signalling mechanisms, Clin. Exp. Pharmacol. Physiol. 26 (7) (1999) 493–499.
[66] D Devost, H Zingg, Homo-and hetero-dimeric complex formations of the human oxytocin receptor, J. Neuroendocrinol. 16 (4) (2004) 372–377.
[67] S Amato, M Averna, D Guidolin, C Ceccoli, E Gatta, S Candiani, et al., Heteromerization of dopamine D2 and oxytocin receptor in adult striatal astrocytes, Int. J. Mol. Sci. 24 (5) (2023) 4677.
[68] S Amato, M Averna, D Guidolin, M Pedrazzi, S Pelassa, M Capraro, et al., Heterodimer of A2A and oxytocin receptors regulating glutamate release in adult striatal astrocytes, Int. J. of Mol. Sci. 23 (4) (2022) 2326.
[69] B Chruścicka, CS Cowan, SEW Fitzsimons, DO Borroto-Escuela, CM Druelle, P Stamou, Molecular, et al., biochemical and behavioural evidence for a novel oxytocin receptor and serotonin 2C receptor heterocomplex, Neuropharmacol. 183 (2021) 108394.
[70] B Chruścicka, SE Wallace Fitzsimons, DO Borroto-Escuela, C Druelle, P Stamou, K Nally, et al., Attenuation of oxytocin and serotonin 2A receptor signaling through novel heteroreceptor formation, ACS Chem. Neurosci. 10 (7) (2019) 3225–3240.
[71] SEW Fitzsimons, B Chruścicka, C Druelle, P Stamou, K Nally, TG Dinan, et al., A ghrelin receptor and oxytocin receptor heterocomplex impairs oxytocin mediated signalling, Neuropharmacol. 152 (2019) 90–101.
[72] BA Jordan, LA Devi, G-protein-coupled receptor heterodimerization modulates receptor function, Nature 399 (6737) (1999) 697–700.

[73] M Ugur, L Derouiche, D Massotte, Heteromerization modulates mu opioid receptor functional properties in vivo, Front. Pharmacol. 9 (2018) 416017.
[74] L Vasudevan, DO Borroto-Escuela, J Huysentruyt, K Fuxe, DK Saini, C Stove, Heterodimerization of mu opioid receptor protomer with dopamine D2 receptor modulates agonist-induced internalization of mu opioid receptor, Biomol. 9 (8) (2019) 368.
[75] PK Wrzal, D Devost, D Pétrin, E Goupil, C Iorio-Morin, SA Laporte, et al., Allosteric interactions between the oxytocin receptor and the β2-adrenergic receptor in the modulation of ERK1/2 activation are mediated by heterodimerization, Cell. Signal. 24 (1) (2012) 342–350.
[76] J. Wahis, A. Baudon, F. Althammer, D. Kerspern, S. Goyon, D. Hagiwara, et al., Astrocytes mediate the effect of oxytocin in the central amygdala on neuronal activity and affective states in rodents, Nat. Neurosci. 24 (4) (2021) 529–541.
[77] M.-H. Nam, K.-S. Han, J. Lee, J.Y. Bae, H. An, S. Park, et al., Expression of μ-opioid receptor in CA1 hippocampal astrocytes, Experimental neurobiology. 27 (2) (2018) 120.
[78] T. Maduna, E. Audouard, D. Dembélé, N. Mouzaoui, D. Reiss, D. Massotte, et al., Microglia express mu opioid receptor: insights from transcriptomics and fluorescent reporter mice, Front. Psychiatr. 9 (2019) 726.
[79] M.M. Alanazi, T. Havranek, J. Bakos, L.X. Cubeddu, A.M. Castejon, Cell proliferation and anti-oxidant effects of oxytocin and oxytocin receptors: role of extracellular signal-regulating kinase in astrocyte-like cells, Endocr. Regul. 54 (3) (2020) 172–182.
[80] A. Baudon, E.C. Creusot, F. Althammer, C.P. Schaaf, A. Charlet, Emerging role of astrocytes in oxytocin-mediated control of neural circuits and brain functions, Prog. Neurobiol. 217 (2022) 102328.
[81] M.-H. Nam, K.-S. Han, J. Lee, W. Won, W. Koh, J.Y. Bae, et al., Activation of astrocytic μ-opioid receptor causes conditioned place preference, Cell Rep. 28 (5) (2019) 1154–1166. e5.
[82] E.A. Hsu, J.L. Miller, F.A. Perez, C.L. Roth, Oxytocin and naltrexone successfully treat hypothalamic obesity in a boy post-craniopharyngioma resection, J. Clin. Endocrinol. Metabol. 103 (2) (2018) 370–375.
[83] O. Dal Monte, M. Piva, K.M. Anderson, M. Tringides, A.J. Holmes, S.W. Chang, Oxytocin under opioid antagonism leads to supralinear enhancement of social attention, Proc. Natl. Acad. Sci. USA 114 (20) (2017) 5247–5252.
[84] R.J. Windle, Y.M. Kershaw, N. Shanks, S.A. Wood, S.L. Lightman, C.D. Ingram, Oxytocin attenuates stress-induced c-fos mRNA expression in specific forebrain regions associated with modulation of hypothalamo–pituitary–adrenal activity, J. Neurosci. 24 (12) (2004) 2974–2982.
[85] J.L. Thornton, N.A. Everett, P. Webb, A.J. Turner, J.L. Cornish, S.J. Baracz, Adolescent oxytocin administration reduces depression-like behaviour induced by early life stress in adult male and female rats, Prog. Neuro Psychopharmacol. Biol. Psychiatr. (2021) 110279.
[86] T. Wang, C. Shi, X. Li, P. Zhang, B. Liu, H. Wang, et al., Injection of oxytocin into paraventricular nucleus reverses depressive-like behaviors in the postpartum depression rat model, Behav. Brain Res. 336 (2018) 236–243.
[87] H. Ji, W. Su, R. Zhou, J. Feng, Y. Lin, Y. Zhang, et al., Intranasal oxytocin administration improves depression-like behaviors in adult rats that experienced neonatal maternal deprivation, Behav. Pharmacol. 27 (8) (2016) 689–696.
[88] M. Mori, H. Shizunaga, H. Harada, Y. Tajiri, Y. Murata, K. Terada, et al., Oxytocin treatment improves dexamethasone-induced depression-like symptoms associated with enhancement of hippocampal CREB-BDNF signaling in female mice, Neuropsychopharmacology Reports 42 (3) (2022) 356–361.
[89] M. Janeček, J. Dabrowska, Oxytocin facilitates adaptive fear and attenuates anxiety responses in animal models and human studies—potential interaction with the corticotropin-releasing factor (CRF) system in the bed nucleus of the stria terminalis (BNST), Cell Tissue Res. 375 (1) (2019) 143–172.
[90] B.J. Tunstall, D. Kirson, L.J. Zallar, S.A. McConnell, J.C. Vendruscolo, C.P. Ho, et al., Oxytocin blocks enhanced motivation for alcohol in alcohol dependence and blocks alcohol effects on GABAergic transmission in the central amygdala, PLoS Biol. 17 (4) (2019) e2006421.
[91] P. Zanos, S.R. Wright, P. Georgiou, J.H. Yoo, C. Ledent, S.M. Hourani, et al., Chronic methamphetamine treatment induces oxytocin receptor up-regulation in the amygdala and hypothalamus via an adenosine A2A receptor-independent mechanism, Pharmacol. Biochem. Behav. 119 (2014) 72–79.
[92] P. Zanos, P. Georgiou, S.R. Wright, S.M. Hourani, I. Kitchen, R. Winsky-Sommerer, et al., The oxytocin analogue carbetocin prevents emotional impairment and stress-induced reinstatement of opioid-seeking in morphine-abstinent mice, Neuropsychopharmacology 39 (4) (2014) 855–865.
[93] P. Zanos, P. Georgiou, C. Weber, F. Robinson, C. Kouimtsidis, R. Niforooshan, et al., Oxytocin and opioid addiction revisited: old drug, new applications, Br. J. Pharmacol. 175 (14) (2018) 2809–2824.
[94] B.J. Tunstall, S.A. Carmack, G.F. Koob, L.F. Vendruscolo, Dysregulation of brain stress systems mediates compulsive alcohol drinking, Current opinion in behavioral sciences 13 (2017) 85–90.
[95] M. Lukas, I.D. Neumann, Social preference and maternal defeat-induced social avoidance in virgin female rats: sex differences in involvement of brain oxytocin and vasopressin, J. Neurosci. Methods 234 (2014) 101–107.
[96] M. Lukas, I. Toth, S.O. Reber, D.A. Slattery, A.H. Veenema, I.D. Neumann, The neuropeptide oxytocin facilitates pro-social behavior and prevents social avoidance in rats and mice, Neuropsychopharmacology 36 (11) (2011) 2159–2168.
[97] S. Engel, S. Laufer, C. Knaevelsrud, S. Schumacher, The endogenous oxytocin system in depressive disorders: a systematic review and meta-analysis, Psychoneuroendocrinology 101 (2019) 138–149.
[98] A.I. Mellentin, S.W. Finn, L. Skøt, D. Thaysen-Petersen, N. Mistarz, A. Fink-Jensen, et al., The effectiveness of oxytocin for treating substance use disorders: a systematic review of randomized placebo-controlled trials, Neurosci. Biobehav. Rev. (2023) 105185.
[99] D.S. Quintana, A. Lischke, S. Grace, D. Scheele, Y. Ma, B. Becker, Advances in the field of intranasal oxytocin research: lessons learned and future directions for clinical research, Mol. Psychiatr. 26 (1) (2021) 80–91.
[100] M.G. Gottschalk, K. Domschke, Oxytocin and anxiety disorders, Curr Top Behav Neurosci 35 (2018) 467–498.
[101] T.A. Thul, E.J. Corwin, N.S. Carlson, P.A. Brennan, L.J. Young, Oxytocin and postpartum depression: a systematic review, Psychoneuroendocrinology 120 (2020) 104793.
[102] Y. Meguro, K. Miyano, S. Hirayama, Y. Yoshida, N. Ishibashi, T. Ogino, et al., Neuropeptide oxytocin enhances mu opioid receptor signaling as a positive allosteric modulator, J. Pharmacol. Sci. 137 (1) (2018) 67–75.
[103] A. Douglas, I. Neumann, H. Meeren, G. Leng, L. Johnstone, G. Munro, et al., Central endogenous opioid inhibition of supraoptic oxytocin neurons in pregnant rats, J. Neurosci. 15 (7) (1995) 5049–5057.
[104] K. Shibuki, G. Leng, S. Way, Effects of naloxone and of intraperitoneal hypertonic saline upon oxytocin release and upon supraoptic neuronal activity, Neurosci. Lett. 88 (1) (1988) 75–80.
[105] G. Leng, M. Ludwig, Intranasal oxytocin: myths and delusions, Biol. Psychiatr. 79 (3) (2016) 243–250.
[106] J.T. Williams, S.L. Ingram, G. Henderson, C. Chavkin, M. von Zastrow, S. Schulz, et al., Regulation of μ-opioid receptors: desensitization, phosphorylation, internalization, and tolerance, Pharmacol. Rev. 65 (1) (2013) 223–254.
[107] C. Robinson, R. Schumann, P. Zhang, R.C. Young, Oxytocin-induced desensitization of the oxytocin receptor, Am. J. Obstet. Gynecol. 188 (2) (2003) 497–502.
[108] Z. Song, H.E. Albers, Cross-talk among oxytocin and arginine-vasopressin receptors: relevance for basic and clinical studies of the brain and periphery, Front. Neuroendocrinol. 51 (2018) 14–24.
[109] K. Raynor, H. Kong, Y. Chen, K. Yasuda, L. Yu, G.I. Bell, et al., Pharmacological characterization of the cloned kappa-, delta-, and mu-opioid receptors, Mol. Pharmacol. 45 (2) (1994) 330–334.
[110] D.S. Quintana, A.J. Guastella, An allostatic theory of oxytocin, Trends Cognit. Sci. 24 (7) (2020) 515–528.
[111] C.S. Carter, W.M. Kenkel, E.L. MacLean, S.R. Wilson, A.M. Perkeybile, J.R. Yee, et al., Is oxytocin "nature's medicine", Pharmacol. Rev. 72 (4) (2020) 829–861.
[112] J. Hari, Lost Connections: Uncovering the Real Causes of Depression-And the Unexpected Solutions, Bloomsbury, Circus London, 2018.
[113] DT Campbell. The Two Distinct Routes Beyond Kin Selection to Ultrasociality: Implications for the Humanities and Social Sciences. The Nature of Prosocial Development: Theories and Strategies, 1983, pp. 11–41.
[114] PJ Richerson, R Boyd, The evolution of human ultra-sociality. Indoctrinability, ideology, and warfare, Evol. perspect. (1998) 71–95.
[115] D.L. Stoewen, Dimensions of wellness: change your habits, change your life, Can. Vet. J. 58 (8) (2017) 861.
[116] B.A. Allan, C. Dexter, R. Kinsey, S. Parker, Meaningful work and mental health: job satisfaction as a moderator, J. Ment. Health 27 (1) (2018) 38–44.
[117] N. Dich, R. Lund, Å.M. Hansen, N.H. Rod, Mental and physical health effects of meaningful work and rewarding family responsibilities, PLoS One 14 (4) (2019) e0214916.
[118] K.A. Arnold, N. Turner, J. Barling, E.K. Kelloway, M.C. McKee, Transformational leadership and psychological well-being: the mediating role of meaningful work, J. Occup. Health Psychol. 12 (3) (2007) 193.
[119] J.T. Cacioppo, L.C. Hawkley, Social isolation and health, with an emphasis on underlying mechanisms, Perspect. Biol. Med. 46 (3) (2003) S39–S52.
[120] L. Brandt, S. Liu, C. Heim, A. Heinz, The effects of social isolation stress and discrimination on mental health, Transl. Psychiatry 12 (1) (2022) 398.
[121] D. Carmil, S. Breznitz, Personal Trauma and World View—are extremely stressful experiences related to political attitudes, religious beliefs, and future orientation? J. Trauma Stress 4 (3) (1991) 393–405.
[122] J.D. Creswell, W.T. Welch, S.E. Taylor, D.K. Sherman, T.L. Gruenewald, T. Mann, Affirmation of personal values buffers neuroendocrine and psychological stress responses, Psychol. Sci. 16 (11) (2005) 846–851.
[123] C. Heim, D.J. Newport, T. Mletzko, A.H. Miller, C.B. Nemeroff, The link between childhood trauma and depression: insights from HPA axis studies in humans, Psychoneuroendocrinology 33 (6) (2008) 693–710.
[124] C. Heim, C.B. Nemeroff, The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies, Biol. Psychiatr. 49 (12) (2001) 1023–1039.
[125] E.J. Costello, S. Mustillo, A. Erkanli, G. Keeler, A. Angold, Prevalence and development of psychiatric disorders in childhood and adolescence, Arch. Gen. Psychiatr. 60 (8) (2003) 837–844.
[126] B.G. Link, M.C. Lennon, B.P. Dohrenwend, Socioeconomic status and depression: the role of occupations involving direction, control, and planning, Am. J. Sociol. 98 (6) (1993) 1351–1387.
[127] M.C. Kondo, S.F. Jacoby, E.C. South, Does spending time outdoors reduce stress? A review of real-time stress response to outdoor environments, Health Place 51 (2018) 136–150.
[128] S.S. Corazon, U. Sidenius, D.V. Poulsen, M.C. Gramkow, U.K. Stigsdotter, Psycho-physiological stress recovery in outdoor nature-based interventions: a systematic review of the past eight years of research, Int. J. Environ. Res. Publ. Health 16 (10) (2019) 1711.

[129] S. Rodiek, Influence of an outdoor garden on mood and stress in older persons, J. Therapeut. Hortic. 13 (1) (2002) 13–21.
[130] D.G. Pearson, T. Craig, The great outdoors? Exploring the mental health benefits of natural environments, Front. Psychol. (2014) 1178.
[131] L. Zheng, S. Lippke, Y. Chen, D. Li, Y. Gan, Future orientation buffers depression in daily and specific stress, PsyCh J. 8 (3) (2019) 342–352.
[132] L. Zheng, Y. Chen, Y. Gan, Future orientation helps regulate emotion in the future, J. Appl. Soc. Psychol. 51 (9) (2021) 920–926.
[133] M. Adrian, C. Kiff, C. Glazner, R. Kohen, J.H. Tracy, C. Zhou, et al., Examining gene-environment interactions in comorbid depressive and disruptive behavior disorders using a Bayesian approach, J. Psychiatr. Res. 68 (2015) 125–133.
[134] M.C. O'Donovan, M.J. Owen, The implications of the shared genetics of psychiatric disorders, Nat. Med. 22 (11) (2016) 1214–1219.
[135] S.M. Meier, J. Deckert, Genetics of anxiety disorders, Curr. Psychiatr. Rep. 21 (2019) 1–8.
[136] J.Y. Lau, T.C. Eley, The genetics of mood disorders, Annu. Rev. Clin. Psychol. 6 (2010) 313–337.
[137] C. Pittenger, R.S. Duman, Stress, depression, and neuroplasticity: a convergence of mechanisms, Neuropsychopharmacology 33 (1) (2008) 88–109.
[138] M. Deutsch. Cooperation and Competition. Conflict, Interdependence, and Justice: The Intellectual Legacy of Morton Deutsch, 2011, pp. 23–40.
[139] DW Johnson, RT Johnson. Cooperation and competition: Theory and research, Interaction Book Company, 1989.