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Translational opportunities for circuit-based social neuroscience: advancing 21st century psychiatry

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The recent advancements of social behavioral neuroscience are unprecedented. Through manipulations targeting neural circuits, complex behaviors can be switched on and off, social bonds can be induced, and false memories can be 'incepted.' Psychiatry, however, remains tethered to concepts and techniques developed over half a century ago, including purely behavioral definitions of psychopathology and chronic, brain-wide pharmacological interventions. Drawing on recent animal and human research, we outline a circuit-level approach to the social brain and highlight studies demonstrating the translational potential of this approach. We conclude by suggesting ways both clinical practice and translational research can apply circuit-level neuroscientific knowledge to advance psychiatry, including adopting neuroscience-based nomenclature, stratifying patients into diagnostic subgroups based on neurobiological phenotypes, and pharmacologically enhancing psychotherapy.

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Introduction: the gulf between psychiatry and neuroscience

Mental illness is a leading cause of global disease burden, yet progress in treating psychiatric disorders has largely stalled since the advent of modern psychopharmacology in the 1950s and 1960s. Currently, psychiatric disorders are treated by modulating neurotransmitter activity throughout the brain via a handful of cellular and molecular targets. The majority of 'new' psychiatric pharmaceuticals are variations of old drugs with marginal improvements rather than drugs with novel mechanisms of action. This homogeneous repertoire of pharmaceuticals is ill-matched for treating heterogeneous psychiatric disorders. For example, depression is diagnosed behaviorally by the presence of at least five of nine possible symptoms and is typically treated with selective serotonin reuptake inhibitors (SSRIs). Two patients may therefore share the same diagnosis while having only a single symptom in common, yet divergent behavioral presentations often have different neurobiological etiologies and responses to treatment [1,2••]. Furthermore, as first-line treatment for at least nine different diagnoses, SSRIs serve as a sort of modern-day panacea for a myriad of conditions ranging from depression and panic disorders to bulimia and premature ejaculation. Although the focus on behavioral diagnoses and chronic, brain-wide neurotransmitter manipulation was a great advancement in the 1950s, today it is perhaps psychiatry's greatest limitation.

This clinical stagnation contrasts with the unprecedented progress of behavioral neuroscience. In rodents, it is possible to control even complex social behaviors — monogamous pair bond formation can be biased [3], distinct parental behaviors can be switched on and off [4••], and false social memories can be 'incepted' [5]. These advances have been enabled by techniques like optogenetics and chemogenetics [6,7], viral vector-mediated transgenics [8], and Cre-dependent expression systems [9] that enable the activation or inhibition of specific neural circuits and cell types with temporal precision. Understanding the circuit components regulating social behavior is a key element of the National Institute of Mental Health Strategic Plan. A challenge for psychiatry is translating these circuit-level discoveries of today into the transformative interventions of tomorrow.

Many psychiatric disorders manifest with disruptions in social cognition and behavior, and there have been great advances in understanding the neural circuit mechanisms regulating social behavior in animal models. Here, we discuss select examples of how animal research has informed our conception of the social brain, examine human research offering insight into the translational potential of this conception, and outline steps for how clinical practice can be improved by acting on the current state of neuroscientific knowledge.

Conception of the social brain from animal research

The social brain evolved to facilitate adaptive processes from reproduction to cooperation and communication,

ultimately enabling human civilization. Despite tremendous variation in social behavior across species, there is remarkable conservation in the neuromodulators regulating social behaviors. Oxytocin and vasopressin, for example, modulate social behaviors across vertebrate taxa, from flocking in birds to pair-bonding in voles. Interspecies and intraspecies variation in social behavior is related to variation in the distribution of oxytocin and vasopressin receptors in the brain [10,11]. This variation in brain receptor distribution is determined by sequence variation in the receptor genes [12,13]. In prairie voles, for instance, such sequence variation determines individual variation in striatal oxytocin receptor density [12], which predicts resiliency to early life neglect with respect to adult social bonding [14].

In mammals, social information is first processed by sensory areas including olfactory bulb for olfaction; superior colliculus, pulvinar, and primary visual cortex for vision; and primary auditory cortex for hearing. These regions express oxytocin receptors in various species, depending on the sensory pathways most relevant for a particular species' social interactions [11]. In sensory pathways, oxytocin signaling increases the salience of social stimuli by modulating neuron excitability and facilitates the flow of social information across the brain [15]. This has been hypothesized to occur in pulvinar in primates [11] and shown to occur in olfactory bulb in rodents, where oxytocin enhances social discrimination by increasing the signal-to-noise ratio of olfactory bulb output [16]. Likewise, oxytocin enhances the auditory cortex response to pup calls to promote maternal nurturing [17].

Socio-sensory information is subsequently conveyed to a network of subcortical structures including the amygdala, which is involved in the integration of information from multiple sensory modalities [18] (Figure 1). In rodents, olfactory information is transmitted to the medial amygdala, where oxytocin-dependent signaling is necessary for social recognition [10,19]. Projections from the medial amygdala to basolateral amygdala may integrate valence with social cues [20]. The medial and basolateral amygdala both project to the hippocampus, which expresses oxytocin receptors and is necessary for social recognition and memory formation [5,11]. The hippocampus projects back to basolateral amygdala and nucleus accumbens (NAc), where oxytocinergic, dopaminergic, and serotonergic innervation from the hypothalamic paraventricular nucleus, ventral tegmental area, and dorsal raphe nucleus, respectively, are necessary for social reward learning [21,22]. The NAc integrates social memories and contextual information from hippocampus, goal-directed information from prefrontal cortex (PFC), and emotional valence from amygdala to influence an organism's behavioral output through its projections to the ventral pallidum [23]. For more details on the circuitry underlying social behavior, see Refs. [10,24].

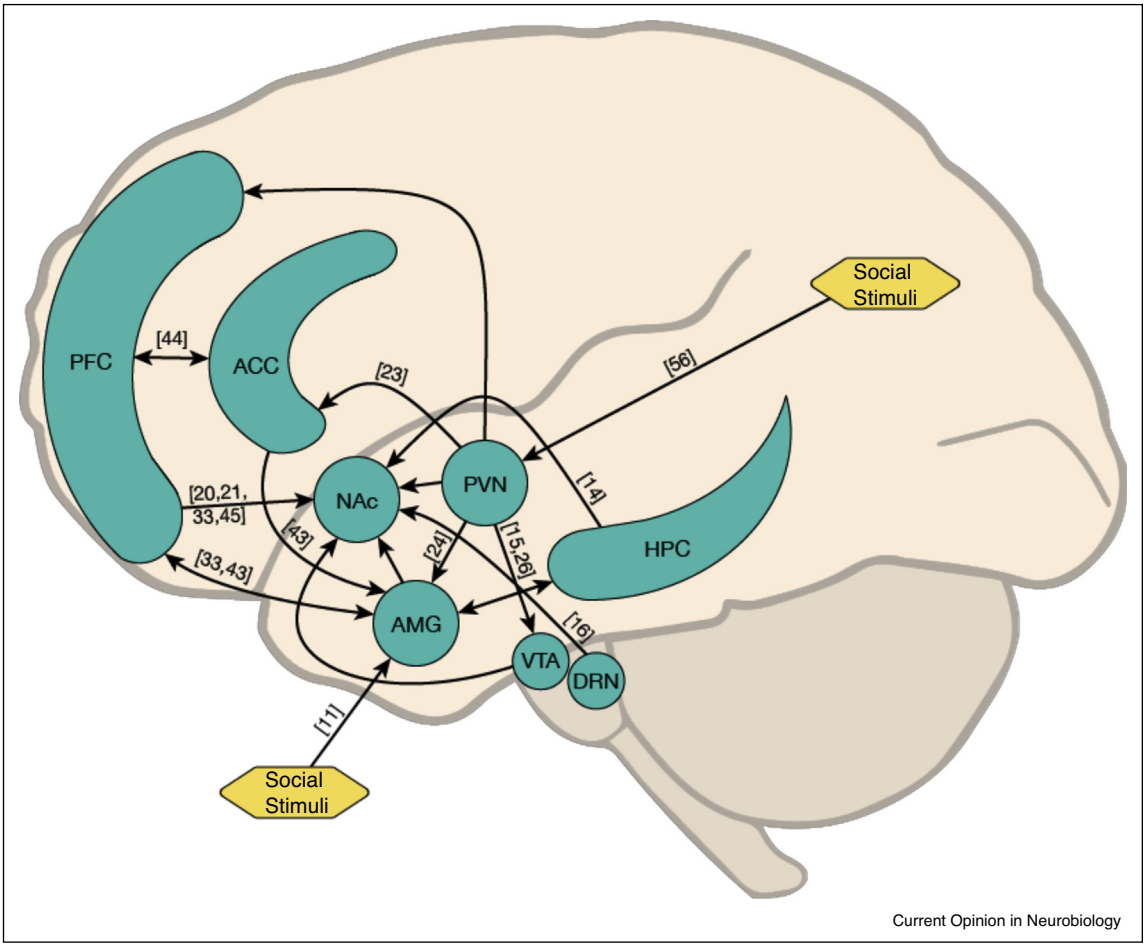
The ability to manipulate social behaviors through circuit modulation is remarkable. By activating or inhibiting specific subsets of galanin-positive neurons in the medial preoptic area, Kohl *et al.* [4••] inhibited infanticidal behavior in males and increased pup grooming in females (projections to periaqueductal gray), increased parental motivation to interact with pups (projections to ventral tegmental area), and inhibited male–male aggression (projections to medial amygdala). Okuyama *et al.* [5] identified a social engram, or collection of cells encoding a memory trace for an individual conspecific, in ventral CA1 of hippocampus; by activating this engram while administering a foot shock, they incepted a false memory that made the mice fearful of that conspecific. Inhibiting or stimulating the PFC-to-NAc projections of D1 dopamine receptor-expressing neurons impaired or restored, respectively, social recognition memories in mice [25], while stimulating PFC projections to NAc induced pair-bonding in prairie voles without mating [3]. Additionally, oxytocin signaling in insular cortex, central amygdala, and anterior cingulate cortex modulates emotion detection and responses to social affect of conspecifics [26–28].

These are but a few studies from a growing body of literature that demonstrates the ability of distinct neural circuits to robustly control specific behaviors and illustrates the potential of treating psychiatric disorders from a circuit perspective. Indeed, accumulating evidence from mouse models of autism suggests that stimulating oxytocin neurons can rescue social deficits. *Cntnap2* knockout mice show deficits in social behavior and reduced numbers of oxytocin neurons, while chemogenetic stimulation of oxytocin neurons or pharmacologically evoked release of endogenous oxytocin rescues the deficits [29]. Additionally, *Nlgn3* knockout mice show impaired social novelty preference due to decreased oxytocin signaling in ventral tegmental area [30•]. Both neural and behavioral deficits can be rescued with a MAP kinase-interacting kinase inhibitor, providing a novel translational target that affects oxytocin signaling [30•].

Insights from human research

The noninvasive nature of most human research limits its mechanistic insights. However, recent work using genetic analyses, fMRI, and intranasal oxytocin (IN-OT) administration supports the circuit-level conception of the social brain emerging from animal research and provides insight into the heterogeneity of human populations. Quintana *et al.* [31] mapped the mRNA of oxytocin pathway genes throughout human brains and found the highest expression in olfactory bulbs and pallidum, high expression in hypothalamus, thalamus, caudate, and putamen, and more moderately elevated expression in amygdala, anterior cingulum, and hippocampus. Additionally, there is strong correlation between the expression of the oxytocin receptor gene (*OXTR*) and dopamine receptors (especially D2R) and muscarinic acetylcholine receptors.

Figure 1



Select pathways involved in social cognition and associated references suggesting interventional potential.
Recent studies in both animals and humans have identified pathways in the social brain that can be modified with behavioral consequences and thus merit further investigation for therapeutic targeting. These pathways include sensory input to the amygdala (AMG) [11] and paraventricular nucleus of the hypothalamus (PVN) [57]; PVN projections to AMG [24], ventral tegmental area (VTA) [15,26], and anterior cingulate cortex (ACC) [23]; reciprocal connections between prefrontal cortex (PFC) and both AMG [33,43] and ACC [44]; ACC projections to AMG [43]; projections to nucleus accumbens (NAc) from PFC [20,21,33,45], hippocampus (HPC) [14], and the dorsal raphe nuclei (DRN) [16].

Comparing *OXTR* expression and fMRI activity associated with cognitive states revealed a robust correlation between *OXTR* expression and activity maps for 'sexual', 'motivation', 'incentive', and 'anxiety' cognitive states. These data suggest the oxytocin systems in humans and animals are similar in their anatomical distribution, interaction with other neurotransmitter systems, and role in regulating socioemotional processes.

Similar to findings in prairie voles, multiple studies suggest that genetic variation in human *OXTR* contributes to variation in behavior. Single nucleotide polymorphisms in *OXTR* are associated with impaired social memory [32], behavior in romantic relationships [33], and autism diagnosis [34]. Polymorphisms in *OXTR* also contribute to sexually dimorphic alterations in functional connectivity between the NAc and PFC [35,36]. Hypermethylation at specific sites in *OXTR* is associated not only with autism spectrum disorders (ASD), but with distinct ASD behavioral phenotypes [37•]. Moreover, these distinct clinical profiles and epigenetic biomarkers are also associated with alterations in resting state connectivity between areas critical for social cognition and behavior, such as the NAc, PFC, amygdala, and cingulate cortex.

The effects of IN-OT have been researched extensively since studies showed it promotes prosocial behavior and decreases activity in the amygdala and neural circuits associated with fear [38]. A recent meta-analysis of 82 studies including 3950 subjects confirms that the amygdala is the brain region most likely to be modulated by IN-OT followed by the insula, cingulate cortex,

inferior frontal and orbitofrontal cortices, midbrain and basal ganglia, temporal gyrus, precuneus, and occipital cortex [39]. However, results across studies are highly heterogeneous and vary based on the population and context of the study. Divergent responses to IN-OT have been associated with *OXTR* polymorphisms, gender, personality traits, attachment style, and underlying psychopathology [39,40]. Notably, IN-OT enhances the coordination of corticostriatal networks involved in social emotive, motivational, and communicative processes [41], which parallels findings in voles that show oxytocin enhances correlated activity across a network of social brain regions involved in pair-bonding [42]. Similarly, in pair-bonded men, IN-OT enhances the perceived attractiveness of their female partners' faces but not that of other equally attractive female faces [43]; in voles, pharmacologically increased oxytocin signaling enhances partner preference [44]. For reviews of lessons learned and controversies of IN-OT research, see Refs. [45,46].

In psychiatric cohorts including patients with ASD, borderline personality disorder, social anxiety disorder, posttraumatic stress disorder (PTSD), and schizophrenia, IN-OT often exerts a 'normalizing' effect on the amygdala, increasing or decreasing activity to align with that observed in healthy controls [39]. The possibility of using oxytocin to modulate specific neural circuits based on context and individual characteristics is particularly intriguing. In one study using resting state fMRI, females with PTSD displayed increased connectivity between the right basolateral amygdala and right anterior cingulate cortex while males with PTSD displayed decreased activity between the right centromedial amygdala and right ventromedial PFC [47]. In these subjects, IN-OT restored functional connectivity to levels observed in healthy controls and also decreased subjective experiences of anxiety and nervousness. Six-weeks of IN-OT treatment in ASD patients rescued social reciprocity deficits and enhanced task-dependent functional connectivity between anterior cingulate cortex and PFC [48]. In a separate study, acute IN-OT enhanced functional connectivity between PFC and NAc while viewing biological motion [49]. There are, however, failures of replication in well-powered IN-OT clinical trials for ASD that urge caution in supporting IN-OT alone as a therapy [50]. Taken together, human studies highlight the neural heterogeneity of the population and further demonstrate the potential of approaching the social brain, psychiatric disorders, and interventions from a circuit perspective.

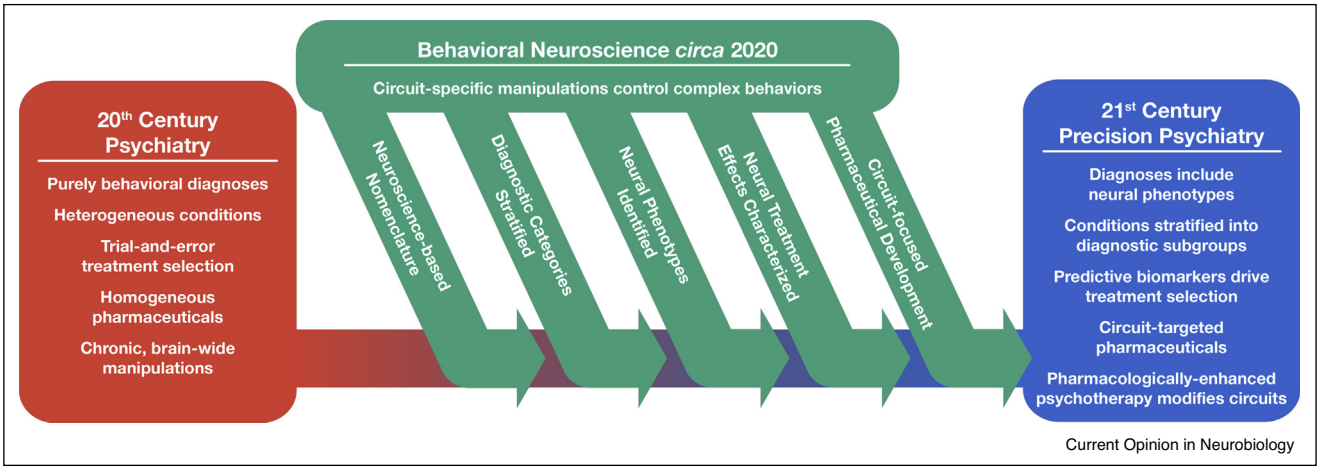
Translational implications

Psychiatry is mired in the psychopharmacological techniques of the 1950s and must move beyond nonspecific behavioral diagnoses and chronic, brain-wide pharmacological interventions to adopt more neuroscience-based diagnoses and targeted interventions. The first step is embracing neuroscience-based nomenclature, a system of classifying drugs based on pharmacological profile and neurobiological mechanism rather than diagnostic or behavioral indication [51]; clinical language that omits the neurobiological basis of diseases and treatments precludes the incorporation of neuroscientific precision into clinical practice. Similarly, the neurobiological basis of psychiatric disorders at the level of circuits should receive increased emphasis in the education of patients and medical trainees. The next generation of psychiatrists should be trained in both the behavioral pharmacological techniques employed today and the circuit neurophysiology that will drive clinical practice in the future. Regarding patients, it is worth considering that recasting psychiatric conditions in terms of 'misfiring circuits' rather than disorders of behavior might reduce stigma, a key barrier to seeking treatment [52].

A circuit-based approach also suggests immediate solutions for addressing the glaring mismatch between the heterogeneity of psychiatric disorders and the homogeneity of both diagnoses and treatments. To improve the precision of psychiatric medicine, patients within diagnostic categories must be subdivided by finding correlations between behavioral phenotypes, neural activity, genetic markers, and treatment responsiveness [1,2••,37•,40]. Simultaneously, treatments' circuit-level neural effects must be studied in addition to their behavioral effects so that more precise diagnoses can be matched with more precise treatment options. Doing so should be a top priority for psychiatry as it has been demonstrated unambiguously to be possible [1,2••,53] and the potential benefits are immense [54,55]. Additionally, more cross-species research, including reverse translation from humans to animal models, would help elucidate the mechanisms underlying clinical interventions and maximize the translational value of preclinical studies [56,57].

Psychotherapy is an alternative and effective means of treating mental illness that alters activity within neural circuits by harnessing the brain's inherent capacity for experience-dependent plasticity [58]. As pharmacology-based and psychotherapy-based interventions are independently capable of modulating circuit-level neural activity, pharmacologically enhanced psychotherapy would seem an obvious opportunity to target specific circuits more effectively and potentially reduce the need for chronic pharmacological therapy [59]. Promising results have been obtained by enhancing psychotherapy with methylenedioxymethamphetamine (MDMA; phase three clinical trial NCT03537014 is currently assessing MDMA-assisted psychotherapy for PTSD), oxytocin [60], L-DOPA [61], and other compounds (for review, see Ref. [59]). As therapeutic information in psychotherapy comes from a social source (the therapist), concurrently activating the oxytocin system is especially promising for disorders with social deficits like ASD. In rodents, social stimuli, including social touch, robustly

Figure 2



Suggested steps for advancing psychiatric practices based on recent progress in neuroscience.

activate hypothalamic oxytocin neurons and enhance social motivation, effects that could be utilized in psychotherapy [62,63•]. Oxytocin-enhanced therapy would have the combined benefits of increasing the salience of information coming from the therapist [64,65], promoting synaptic plasticity [66], and facilitating learning by modulating circuit-level neural activity [37•,67]. Despite the promising results of augmenting psychotherapy for PTSD with IN-OT [60], no studies have been reported for ASD; to date, most research on IN-OT interventions for ASD has involved administrations independent of context. Since oxytocin enhances the salience of social stimuli, we suggest that context-dependent IN-OT administration, that is preferred therapy, may be a more beneficial intervention for ASD patients than the daily, context-independent administration schedules typical of other pharmacotherapies.

The circuit-based conception of the brain, psychopathologies, and treatments also suggests new directions for translational research. For instance, a circuit-targeted approach to manipulating oxytocin signaling increases the feasibility of resetting transcriptional or translational abnormalities [30•], altering the course of neurodevelopmental disorders through interventions during developmental sensitive periods [68], or reopening critical periods in adults to enable new social learning [69••]. Moreover, single-cell sequencing has the potential to identify cell-type-specific molecular targets for the development of new pharmaceuticals that would affect specific neural circuits rather than the entire brain [70]. However, bypassing the blood–brain barrier remains a perennial problem for pharmacological interventions including IN-OT; the effect sizes in most IN-OT studies are small [46] and there are questions surrounding its ability to cross the blood–brain barrier and diffuse to subcortical structures [71,72]. We predict that the evolution of oxytocin interventions will move beyond administering exogenous oxytocin to second-generation strategies utilizing pharmaceuticals like melanocortin receptor agonists that potentiate endogenous oxytocin signaling much like how SSRIs and L-DOPA are used to potentiate serotonin and dopamine signaling [73]. Beyond the oxytocin system, emerging technologies like transcranial magnetic stimulation, deep brain stimulation, and the application of focused ultrasound to circumvent the blood–brain barrier are enabling more targeted interventions. Such innovations are critical as while psychiatric precision will always lag behind neuroscientific precision due to ethical and technological constraints, the advancement of psychiatry requires that we develop ways to approximate in humans the circuit manipulations that have proven so efficacious in animal research.

Concluding remarks

As research on the social brain has demonstrated, the potential of incorporating circuit-level approaches into the diagnosis and treatment of psychiatric disorders is no longer theoretical — it is manifestly evident. Moreover, we presently possess the technological capabilities and scientific understanding required to begin implementing this approach. The sooner circuit-level approaches are embraced, the sooner the field of psychiatry can move beyond twentieth-century behavioral pharmacology and into twenty-first-century precision medicine (Figure 2).

Author contributions

CLF and LJY conceptualized the manuscript, CLF wrote the first draft and LJY edited the manuscript.

Conflict of interest statement

Nothing declared.

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