



# Understanding the neurobiology of social behavior through exploring brain-wide dynamics of neural activity

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## ABSTRACT

Social behavior is highly complex and adaptable. It can be divided into multiple temporal stages: detection, approach, and consummatory behavior. Each stage can be further divided into several cognitive and behavioral processes, such as perceiving social cues, evaluating the social and non-social contexts, and recognizing the internal/emotional state of others. Recent studies have identified numerous brain-wide circuits implicated in social behavior and suggested the existence of partially overlapping functional brain networks underlying various types of social and non-social behavior. However, understanding the brain-wide dynamics underlying social behavior remains challenging, and several brain-scale dynamics (macro-, meso-, and micro-scale levels) need to be integrated. Here, we suggest leveraging new tools and concepts to explore social brain networks and integrate those different levels. These include studying the expression of immediate-early genes throughout the entire brain to impartially define the structure of the neuronal networks involved in a given social behavior. Then, network dynamics could be investigated using electrode arrays or multi-channel fiber photometry. Finally, tools like high-density silicon probes and miniscopes can probe neural activity in specific areas and across neuronal populations at the single-cell level.

## 1. Introduction

Social behavior is a fundamental and highly complex behavior necessary for the survival of many species, ranging from microorganisms to humans (Crespi, 2001). Among other animals, rodents are notably social creatures, exhibiting flexible and context-appropriate social behavior in their social environments (Rubenstein and Rubenstein, 2013). Specifically, laboratory rats and mice are the most common animal models used to explore brain mechanisms underlying the various types of social behavior (Ellenbroek and Yoon, 2016). In this review, we aim to emphasize the necessity of employing innovative methods and tools to understand how social behavior emerges from the integration of neural activity across different scales, occurring simultaneously within the brain. We will begin by discussing the complexity of social behavior. Subsequently, we will discuss why viewing the brain as a complex system and studying the brain in its integrality rather than examining individual brain areas or subsets of neurons separately could provide new and valuable insights into the neurobiology of social behavior. Finally, we will outline the methodologies that can be employed in social neuroscience to apply this approach effectively.

## 2. The complexity and multidimensionality of social behavior

Social behavior encompasses every mode of communication and interaction between two or more individuals (Chen and Hong, 2018). This broad definition includes a wide spectrum of social interactions essential for species survival and/or enhancing fitness, including mating, fighting, and parenting (Silk, 2007). One perspective on this broad concept is to examine social behavior through temporal stages, such as the detection of social cues, moving toward a conspecific, social investigation, and finally, the consummatory behavior phase, which may be reflected by parenting, mating, aggression, play fighting or huddling (as illustrated in Fig. 1). At each stage, animals decide whether to approach or avoid certain conspecifics, leading to coherent individual choices. The animal can rapidly switch between various stages or types of social behavior, e.g., going from allogrooming in one moment to huddling during the next one (Rojek-Sito et al., 2023).

Each of these behavioral steps can be broken down into several cognitive processes, such as detecting and perceiving social cues, evaluating the social and non-social contexts, recognizing the internal/emotional state of others, navigating in the social and spatial

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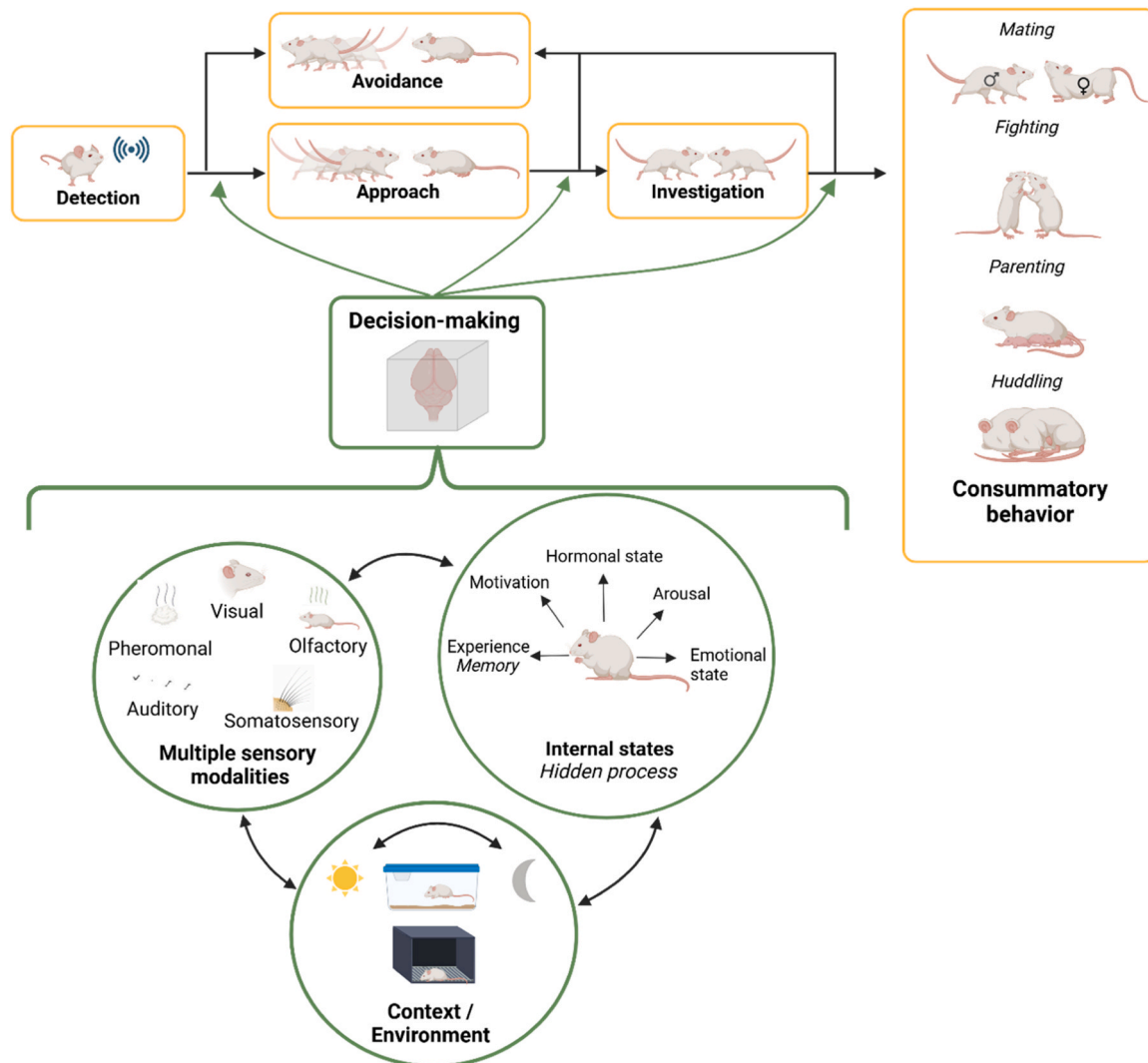
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environment, and assessing the individual's own motivation and mood states. Integrating all this information allows the individual to make an appropriate social decision. Social cues are crucial in identifying multiple characteristics of social partners, such as age (Cum et al., 2024; Rogers-Carter et al., 2019), sex (Markham and Juraska, 2007; Netser et al., 2020), strain (Jacobs et al., 2015; Jacobs and Tsien, 2014, 2012), and familiarity (Kiyokawa et al., 2014). Rodents were shown to be able to distinguish between conspecifics based on their affective state (Ferretti et al., 2019; Langford et al., 2006; Mohapatra et al., 2023; Netser et al., 2020; Scheggia et al., 2020). In many cases, one variable may influence the individual's decision on how to behave in light of the other variables. For instance, during interaction with either naïve or stressed conspecifics, adult rats approached stressed juveniles but avoided stressed adults (Rogers-Carter et al., 2019). Information regarding these variables is transmitted between individuals through multiple sensory modalities by pheromonal (Demir et al., 2020), olfactory (Arakawa et al., 2008), visual, auditory (Rao et al., 2014), and somatosensory cues (Jabarin et al., 2022).

Rodents also adjust their decisions to the context. Multiple environmental factors, such as their familiarity with the conspecific, the environmental enrichment in the encounter's location, and the social

environment in their home cage may influence their willingness to engage in social interactions (Kim et al., 2019; O'Connor et al., 2024; Prendergast et al., 2014). Additionally, the brain is a dynamic system with changes continuously occurring at many scales (e.g., neuronal activity, synaptic pruning, receptor activation/availability, neurotransmitters, etc.), all of which may affect how the brain responds to given sensory inputs and generates behavioral outputs. These hidden processes, termed "internal states," include arousal, attention, motivation, mood, and various homeostatic needs such as sleep, hunger, and thirst (Flavell et al., 2022). For example, an internal state of stress shapes how sensory information is processed and triggers appropriate behavioral and physiological responses to certain stimuli (Anderson, 2016; Bains et al., 2015; Senst et al., 2016). Thus, social behavior is significantly influenced by the internal state of the subject animal (Kennedy et al., 2014).

The brain integrates all these different variables throughout each of the temporal stages described previously. Moreover, it updates them upon recognizing new situations, whether it is the response of the other animal, changes in the environmental context, or variations in the individual's internal state (Anderson, 2016; Dewsbury, 1982; Falkner et al., 2016; Ko, 2017; Li et al., 2017). Social behavior is, therefore,



**Fig. 1.** The complexity and multidimensionality of rodents' social behavior.

Schematic explanation of the complexity of social interactions between two individual rodents. The distinct temporal stages (detection, approach, avoidance, investigation, and consummatory behavior) are shown within the yellow frames at the top of the figure. Various cognitive processes happening in parallel at each temporal stage are depicted within green circles at the bottom of the figure. These include the integration of various sensory modalities informing the subject about the other conspecific as well as regarding the particular context and environment, together with the subject's internal state.

extremely flexible and dynamic. These characteristics make exploring and understanding the neurobiological mechanisms underlying social behavior highly challenging.

### 3. From the social brain to social circuits

The "social brain" concept, which emerged in the 90 s thanks to brain functional imaging studies in humans, refers to brain areas activated during social cognition tasks. Initially, only a few brain areas were considered parts of the social brain. For example, one of the earliest reviews in this field proposed an initial set of three structures involved in social cognition: the amygdala, the orbitofrontal cortex (OFC), and the temporal lobes (Brothers, 2002). In the following years, review articles have included more structures in the social brain and added putative roles for them. For example, the fusiform face area and the superior temporal gyrus were linked to social recognition, while the amygdala and prefrontal cortex were associated with social valence evaluation (Huang et al., 2020; Iaria et al., 2008; Insel and Fernald, 2004; Schultz et al., 2003; Zhang and Li, 2018).

As tools and methodologies used for research in social neuroscience have advanced, an increasing number of brain regions have been identified as involved in social processes, such that in recent scientific review articles, more than thirty regions and subregions are implicated in social behaviors (Chen and Hong, 2018; Fernández et al., 2018; Ko, 2017; Wang et al., 2023; Wei et al., 2021). This trend of an increasing number of brain structures considered parts of the social brain is still ongoing and seems to reflect the realization that the neural basis of social behavior and cognition is highly complex and involves a large portion of the brain. At the same time, it has become clear that most of these brain structures are not exclusively dedicated to social functions and that no type of social decision-making or social information processing is localized to a single brain region (Stanley and Adolphs, 2013). Distinct amygdala nuclei, for example, are active in various emotional contexts, including social and non-social ones (Brown and Sharpey-Schafer, 1997, 1888; McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997). Similarly, the medial prefrontal cortex is involved in the representations of social stimuli (Levy et al., 2019), recognition of the internal/emotional state of others (Scheggia et al., 2020), and social decision-making, but it also plays a role in many other types of decision-making (Euston et al., 2012), as well as other functions (Friedman and Robbins, 2022). Notably, many of these brain regions are interconnected and thus may act within *ad hoc* partially overlapping functional networks during distinct types of behavior, including non-social cognitive tasks. For example, partially overlapping sets of brain regions were shown to be active during self-pain processing and empathic pain (Gross et al., 2007; Valentini et al., 2013).

Moreover, it is clear that these networks of brain structures may subserve distinct types of social behavior. For example, a recent work demonstrated that distinct projections in a circuit spanning the central amygdala, ventral tegmental area (VTA), anterior cingulate cortex, and OFC mediate the initiation and maintenance of social contact between male rats (Rojek-Sito et al., 2023). Accordingly, multiple recent review articles defined brain-wide neuronal circuits based on their various behavioral outcomes, such as mating, aggression, or maternal care (Chen and Hong, 2018; Ko, 2017; Wei et al., 2021).

We should also take into account that brain regions are not homogeneous. They comprises various cell types, such as glia and astrocytes, and different neuron populations with distinct properties, and can be of different subtypes (Yao et al., 2023). For example, the medial amygdala (MeA) is divided into four subregions: anterodorsal (MeAd), anteroventral (MeAv), posterodorsal (MeApd), and posteroventral (MeApv), each with distinct circuit connectivity and cytoarchitecture (Keshavarzi et al., 2014; Raam and Hong, 2021). MeAd and MeApd primarily contain inhibitory neurons, while MeAv and MeApv are rich in excitatory neurons (Keshavarzi et al., 2015). Recent single-cell RNA sequencing during fear learning and memory consolidation has

identified 130 distinct neuronal types across the MeA (Hochgerner et al., 2023). Such division into subregions and distinct neuronal populations probably characterizes every brain region previously implicated in social behavior.

Therefore, it seems more appropriate today to speak of multiple, partially overlapping social circuits underlying social behavior and cognition rather than a single "social brain." This concept raises new questions: how are the relevant input signals selected and distributed across the various circuits for further processing? How are the results of sensory information processing selectively routed across the densely interconnected networks to the appropriate decision-making and executive centers? How can a single brain region be involved in several different, sometimes contradicting, social behaviors? How are the numerous computational processes occurring simultaneously in spatially segregated circuits and brain areas coordinated and integrated to give rise to coherent percepts and actions?

One possible hypothesis implies the idea of specific hub regions that integrate all the information, while an alternative hypothesis suggests that such integration could occur at a brain-wide scale (Dickinson et al., 2022). As the brain is a highly connected organ, sensory information processing, internal states, and executive functions could occur in broadly distributed networks, leaving less space for the idea of a singular center where all information converges and which would serve as a supraordinate coordinating center. Notably, neither hypothesis is mutually exclusive.

### 4. Complex system approach

In light of the extensive range of brain regions and neuronal types implicated in social behavior networks, and the complex challenges of studying social behavior, it has become clear that current approaches, methods, and tools require reevaluation. To date, most research on social behavior has focused on individual brain areas, each revealing only one piece of a larger puzzle. This perspective raises the critical question: can we truly comprehend the dynamic nature of the brain by viewing it as a collection of independent elements?

One promising answer lies in leveraging methodologies and tools from the field of complexity science (Turkheimer et al., 2022). Originating from advancements in statistical physics, mathematics, and computer science, complexity theory offers a robust framework for examining intricate systems. This framework has been successfully applied to diverse systems, including metabolic networks, gene-gene interactions, as well as, the human brain (Beguerisse-Díaz et al., 2018; Razaghi-Moghadam and Nikoloski, 2020; Wein et al., 2021; Yuan and Bar-Joseph, 2020).

A complex system is characterized by four agreed-upon properties:

1. It consists of numerous components that interact with their neighbors in a relatively straightforward way. Indeed, we find numerous interacting components when examining the brain at the macroscopic level of brain regions, the mesoscale level of neuronal populations, or the microscopic level of individual neurons and their molecular changes. Brain activity involves large, distributed networks that dynamically interact and form transient states even during simple social tasks (Greene et al., 2023).
2. Complex systems are nonlinear, meaning that changes in input do not necessarily lead to proportional changes in output. Social behavior, for instance, cannot be fully explained by linear equations based solely on neuronal activity (Beguerisse-Díaz et al., 2018; Razaghi-Moghadam and Nikoloski, 2020; Wein et al., 2021; Yuan and Bar-Joseph, 2020).
3. These systems exhibit self-organization, such as the spontaneously developing coordinated oscillations and baseline activity characterizing internal brain states even in the absence of external stimuli (Vidaurre et al., 2018; Wainio-Theberge et al., 2021).

4. Complex systems show emergent behavior, which means macroscopic outcomes cannot be fully understood through microscopic interactions alone. Our current understanding of neurobiology does not comprehensively explain social behavior. However, there is an important distinction between weak and strong emergence. Strong emergence, exemplified by consciousness, suggests that new principles are needed beyond lower-level interactions (Chalmers, 2006). Conversely, weak emergence relies on computational models and complexity science to build higher-order behaviors from basic elements, highlighting the complexity of such systems while acknowledging the limits of current methods. The concept of strong emergence suggests there may be limits to what such approaches can achieve (Turkheimer et al., 2022). In contrast, the weak emergence framework supports using computational models and simulations to study the neurobiological basis of social behavior.

Viewing neural systems through the lens of complexity science aligns with contemporary neuroscience evidence and matches complex systems' properties. Complexity-driven methodologies provide powerful tools for understanding the dynamic interactions between different brain regions and how these interactions produce emergent behaviors. Connectivity lies at the heart of the complex systems approach. It is essential not only to map the structural connections within the brain but also to consider their dynamic aspects in order to fully comprehend the complexity of brain function. The connectome provides a detailed blueprint illustrating how different brain regions are anatomically interconnected, revealing the neural pathways that underpin various cognitive functions, behaviors, and physiological processes. Complexity-driven methodologies may enable us to construct a graph network of the functional connectome, which is a comprehensive map or diagram detailing the dynamic functional connectivity within the brain over time.

## 5. The challenge of studying brain-wide networks

In humans, electroencephalogram (EEG) and Functional Magnetic Resonance Imaging (fMRI) can be used to create a graph network of the brain during specific tasks. EEG studies have described the emergence of synchronized electrical oscillations between cortical regions at the millisecond timescale during social perception (Fraiman et al., 2014; Rodriguez et al., 1999). Yet, EEG can only capture electrical activity from cortical areas in low spatial resolution. fMRI studies have revealed synchronized neural activity across the brain at the timescale of seconds (Sokolov et al., 2018). Nevertheless, fMRI lacks the spatial and temporal resolution needed to understand the dynamic activity of neuronal networks, using a spatial resolution of millimeters and a typical time resolution of 1–3 seconds per image acquisition. Furthermore, fMRI cannot simultaneously provide a comprehensive view of the entire brain, as it typically focuses on specific regions at a given time. Lastly, fMRI is unsuitable for freely moving subjects, which limits its application in studying social behavior. Thus, while these methods are available for mapping brain activity in humans, they are constrained by ethical, time, and space limitations. These limitations may be solved by using animal models for the exploration of brain-wide neural activity during social behavior.

It is commonly accepted to use rodents as models for studying social behavior. Many species of rodents are highly social, and some of them, like rats and mice, are commonly used as laboratory animals, hence offer powerful experimental tools for elucidating the molecular, cellular, and neurobiological mechanisms that regulate social behavior (Hecht et al., 2012; Mogil, 2019; Wöhr and Krach, 2017). However, no method is available yet to access a complete real-time graph of all the nodes and connections of the rodent brain during social behavior. Most methods developed to study brain dynamics typically require selecting specific brain areas in advance, resulting in partial data being collected. For example, several techniques enable *in vivo* electrophysiological recording from 1 to 2 dozen brain regions simultaneously. Thus, a

crucial step is the unbiased, informed selection of regions for such recordings, which facilitates the study of the neurobiology of social behavior at a macro scale (examining interactions between remote brain areas). Once the structure of the neuronal networks involved in a given social behavior is deciphered, we can further explore its details and dynamics using electrophysiological techniques. The various existing techniques allow us to investigate the neurobiology of social behavior at multiple levels: at the macro scale (interactions between brain regions), the mesoscale (neuronal populations within a given region), and the microscopic scale (individual neurons and their subcellular compartments).

Below, we will discuss several complementary methods (illustrated in Fig. 2) currently available to gain insights into system-level brain-wide neuronal activity during social behavior in rodents.

## 6. Macro-scale level: brain-wide approach

### 6.1. Studying the whole brain expression of immediate-early genes, such as c-Fos

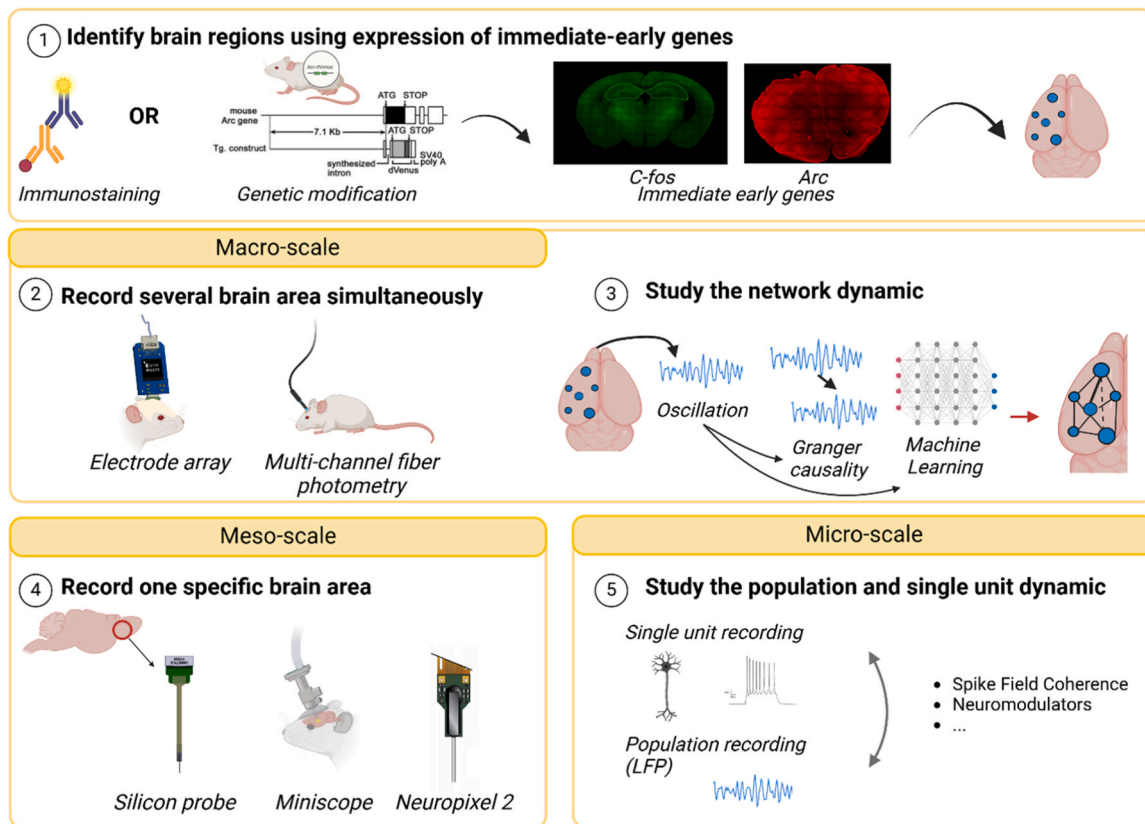
One method allowing unbiased identification of brain areas implicated in a certain type of social behavior is to map the brain-wide expression pattern of immediate-early genes such as c-Fos or Arc. The expression of immediate-early genes, especially c-Fos, in neurons, is known to be activated by recent electrical activity; hence, it may be a report of the neurons that were active during a given time window throughout the brain (Clayton, 2000; Guzowski et al., 2005). This approach, usually using either immunostaining or genetic modifications coupling the expression of a fluorescent protein to the promoter of an immediate-early gene, offers a spatially comprehensive view of recent activity across the entire brain. Unlike *in vivo* electrophysiology or calcium imaging, c-Fos analysis has limited time resolution, as the animal needs to be sacrificed during a certain time window after the task, in order to access the c-Fos expression. However, it does provide a complete picture of recent whole-brain activity at the single-cell level. This allows researchers to identify key brain structures relevant to specific social behaviors and quantitatively analyze variations in their response to distinct stimuli. For example, analysis of brain-wide neural activity via quantification of the immediate early gene c-Fos identified a pro-social neural network, including the frontal and insular cortices, that were active during the helping test (Ben-Ami Bartal et al., 2021). The striatum was selectively active while helping ingroup members but not during interactions with outgroup members. Activity in the nucleus accumbens (NAc) correlated with helping behavior (Ben-Ami Bartal et al., 2021). In a more recent study, individuals who exhibited helping behavior compared to those who did not, there was increased activity in regions associated with empathy in humans, such as the somatosensory cortex, insula, cingulate cortex, and frontal cortex, as well as in regions associated with motivation and reward, such as the NAc (Hazani et al., 2024). Additionally, adolescent rats exhibited reduced hippocampal and insular activity and increased OFC activity compared to adults in helping behavior tests (Breton et al., 2022). Such whole-brain activity maps based on immediate-early genes can generate structure-function hypotheses for further investigation through *in vivo* electrophysiological recordings and calcium imaging at higher temporal resolution. Moreover, correlating c-Fos expression between the various brain regions allows one to draw a graph of the functional network of brain regions that act in positive or negative correlation during a given behavior. However, mapping c-Fos expression does not provide insights into the dynamics of brain activity or the actual connections between these brain areas beyond these correlations.

### 6.2. Monitoring activity of multiple brain regions

#### 6.2.1. Multiple fiber photometry

Methods such as *in vivo* fiber photometry and electrophysiology have





**Fig. 2.** Complex system approach.

Summary of a proposed approach for studying the brain-wide networks underlying social behavior: In the first panel, we illustrate methods for identifying brain regions involved in social behaviors across the whole brain by assessing the expression of immediate early genes by immunostaining or genetic modification. The second panel proposes methods for macro-scale simultaneous recording from multiple selected brain areas and various analyses used to understand the connectivity between these areas and their respective weights and roles in the networks. The third panel suggests methods for studying specific brain areas with higher resolution to access the mesoscale level. The last panel suggests methods to better understand the relationship between neuronal populations and single-cell recording, thus combining mesoscale and micro-scale analyses. Overall, this approach aims to provide a comprehensive understanding of the neural networks that underlie social behaviors.

the capability to record neuronal activity in any brain area. Still, traditionally, their main limitation has been the number of brain areas that could be recorded simultaneously. However, new tools have been developed to address this limitation.

In 2015, a method known as frame-projected independent fiber photometry was introduced to record fiber photometry signals from several brain areas simultaneously (Guo et al., 2015). Using this method, researchers identified synchronous activity across multiple cortical and limbic regions on a timescale of 100 ms during exposure to social novelty (Kim et al., 2019). In 2019, another laboratory published a paper demonstrating the recording of networks comprising 12–48 brain areas and optically perturbing subsets of regions using optogenetic manipulation (Sych et al., 2019). Perturbation of ventral thalamic nuclei resulted in distributed network modulation and behavioral deficits; in a texture discrimination behavior, the number of missed and False alarms increased (Sych et al., 2019). The big advantage of multi-site fiber photometry recordings over electrophysiology is the ability to record from specific neuronal populations using genetically encoded calcium or voltage indicators. For example, a recent elegant study recorded activity from *Esr1*-positive neurons in 12 limbic brain areas using fiber photometry during social behavior in male mice (Guo et al., 2023). The findings of this study revealed that social activity-coupled signals were widely distributed in this limbic network of brain areas and could be decoded from the network activity. Specifically, MeA showed increased activity during each episode of social investigation, while the ventromedial hypothalamus (Vmh) demonstrated the fastest and largest response during attacks. Functional connectivity among nearly all

recorded brain areas drastically increased during attacks, with 12 out of 13 brain areas showing increased activity. Cross-region correlation analysis revealed significant increases in network functional connectivity during the initiation phase of social action, whereas late copulation was associated with a dissociated network state. Based on these response patterns, the researchers proposed a mating-biased network and an aggression-biased network to mediate male sexual and aggressive behaviors, respectively.

Multiple studies using fMRI, EEG, or multi-site fiber-photometry indicate a synchronization among different brain regions during various social behaviors (Guo et al., 2023; Kim et al., 2016; Sokolov et al., 2018), thus suggesting that every behavior is a phenotypical manifestation of some well-orchestrated brain-wide network activity. This raises new questions: how are these brain areas organized at a network scale? Are brain-wide dynamics necessary for expressing internal states, or are they merely consequences of activity within a highly interconnected network of brain regions? However, due to their relatively low temporal resolution, these methods cannot fully answer those questions regarding the mechanisms behind the emergence of this synchronized network. Such information may be supplied by brain-wide electrophysiological recordings, as will be described below.

#### 6.2.2. Neuronal oscillations and social behavior in rodents

Synchronized neuronal population activity, characterizing many behavioral tasks and emotional states, gives rise to network oscillations (Buzsáki, 2006). Such oscillations are categorized into different frequency bands, such as theta (4–10 Hz), beta (12–30 Hz), and gamma

(30–80 Hz), each thought to serve distinct functions across various brain regions (Akam and Kullmann, 2014; Buzsáki and Draguhn, 2004). These oscillations are reflected by extracellularly recorded local field potentials (LFPs), with the "power" of rhythmic LFP signals reflecting the magnitude of these oscillations at a single location. Theta oscillations have been extensively studied over several decades and are associated with active information processing and stimulus-related activities (Buzsáki, 2002; Jones and Wilson, 2005; Jutras et al., 2013). Recent studies in rodents have implicated theta oscillations in various cognitive and emotional functions, such as spatial navigation, motor activity, emotional conditioning, and memory consolidation (Berry and Seager, 2001; Buzsáki, 2002; Karalis et al., 2016; Likhtik et al., 2014; Popa et al., 2010). Additionally, synchronized theta oscillatory activity has been found not only in response to external stimuli but also during anticipation of tasks requiring rapid motor responses, suggesting its role in task preparation (Roelfsema et al., 1997). Researchers suggested that theta oscillations organize and synchronize spiking activity over brain-wide distributed circuits (Benchenane et al., 2010; Courtin et al., 2014; Mague et al., 2022).

In contrast to theta rhythmicity, gamma rhythmicity is considered a bottom-up process associated with the synchronous activity of local inhibitory networks (Benchenane et al., 2011; Palva and Palva, 2018). Overall, neuronal oscillations are considered a mechanism that synchronizes spiking activity across brain regions and can enhance information transfer between them (Buzsáki et al., 2012; Deffains et al., 2016).

In the context of social behavior, both theta and gamma oscillations are modulated by the presence of social stimuli. For example, the dorsomedial prefrontal cortex (dmPFC) and basolateral amygdala (BLA) exhibit increased theta oscillation power and decreased gamma power when mice interact with a stimulus mouse. In mouse models with reduced social interactions, the dmPFC showed a higher increase in theta power when they exhibited social avoidance behavior. In contrast, in wild-type mice, the dmPFC and BLA decrease theta power during social approach to a target mouse. Frequency-specific optogenetic manipulations that replicate social approach-related LFP patterns have been shown to restore social interaction behavior in socially deficient mice (Kuga et al., 2022).

Since theta oscillations are well-known to be involved in modulating social behavior, they seem to be a key candidate for propagating information that encompasses both the internal state and social context (Karalis and Sirota, 2022). Moreover, LFP theta rhythmicity induced in the rat brain during a free social interaction test has persisted for a while after removing the social stimulus from the arena. These findings led to the hypothesis that self-generated oscillatory activity in the theta-frequency range may serve as a correlate of internal states (Tendler and Wagner, 2015). Interestingly, many fundamental behaviors, such as breathing and locomotion, are regulated by neural activity within the theta frequency range (Bender et al., 2015; Tort et al., 2018). These behavior outputs are key observable variables from which the internal state of the mice can be inferred (Marques et al., 2020). Accordingly, theta rhythmicity is thought to reflect top-down processes associated with internal states such as arousal and attention, which are regulated by brain-wide active neuromodulators across brain networks (Clayton et al., 2015; Fiebelkorn and Kastner, 2019; Knyazev, 2007).

### 6.2.3. Coordination of brain-wide neural activity by neuromodulators

The impact of neuromodulators on behavior has been extensively studied (Bargmann, 2012; Bargmann and Marder, 2013; Flavell et al., 2013; Harris-Warrick and Marder, 1991; Kennedy et al., 2014; Marder, 2012; Nusbaum and Blitz, 2012; Taghert and Nitabach, 2012; Zelikowsky et al., 2018). Neuromodulators occupy an ideal position to explain complex behavior as they can modulate neural circuits through rapid actions, such as increased excitability and long-lasting effects (Van den Pol, 2012). Neuromodulatory centers, such as the medial raphe nuclei (serotonin) or locus coeruleus (noradrenaline), can also have

brain-wide effects over long distances and receive diverse synaptic inputs while sending diffuse projections to many brain regions (Ren et al., 2018; Saper et al., 2010; Weissbourd et al., 2014). One neuromodulator extensively implicated in the context of social behavior is the hypothalamic neuropeptide oxytocin. It is released during mating (Waldherr and Neumann, 2007). Blocking oxytocin receptors in the NAc prevents the formation of partner preference induced by mating, whereas administering oxytocin in the NAc is sufficient to induce partner preference in female prairie voles (Liu and Wang, 2003). The release of oxytocin in the NAc core during social interaction is indispensable for social interaction-induced conditioned preference (Dölen et al., 2013). Moreover, the collective knowledge of neuromodulators, particularly exemplified by the role of oxytocin in social behavior, supports the idea that neuromodulators often act in combination rather than through a single modulator for a single action. Indeed, the facilitating effects of oxytocin and dopamine on partner preference are interdependent; an antagonist of the D2 dopamine receptor in the NAc can abolish partner preference induced by oxytocin and vice versa (Liu and Wang, 2003). Globally, neurons that populate a given circuit are usually heterogeneous and can differentially express several receptors of neuromodulators. Thus, neuronal circuits may be modulated by emergent states produced by the effects of multiple interacting neuromodulators (Bargmann, 2012; Courtiol et al., 2021; Daw et al., 2002; Doya, 2002; Marder, 2012). Notably, theta rhythmicity in various brain regions, such as the hippocampus and prefrontal cortex, was shown to be regulated by distinct neuromodulators (Benchenane et al., 2010; Gu and Yakel, 2022; Vertes and Kocsis, 1997). One way by which neuromodulators may regulate the behavioral effects of brain-wide oscillatory neuronal activity is by modulating the coherence of such activity between various brain regions.

### 6.2.4. Communication between brain areas through neural coherence

Brecht et al. (1998) conducted one of the first studies to provide evidence of synchronized LFP rhythmicity among widely distributed brain structures, including the primary visual cortex, the optic tectum, and the suprasylvian cortex, by simultaneously recording from those areas in anesthetized paralyzed cats (Brecht et al., 1998). Since then, LFP coherence analysis has become broadly used to determine if two brain regions exhibit synchronized neuronal oscillatory activity (Bowyer, 2016). This led to the development of the coherence metric and the emergence of the concept of communication through neural coherence, which suggests that neural communication between remote brain regions and distributed circuits is supported by neuronal synchronization (Fries, 2005). Coordinated oscillations have been shown to play a role in information transfer between neurons (Akam and Kullmann, 2014; Buschman and Kastner, 2015; Voytek and Knight, 2015), dynamic changes in synchronization can flexibly alter the pattern of communication within a neuronal network (Fries, 2015). This concept of dynamic functional connectivity is supported by the fact that research has indicated that pathologies associated with social deficits are linked to altered functional connectivity. For example, such a phenomenon has been demonstrated in humans with autism spectrum disorder (ASD), which exhibit a pronounced reduction in gamma band power in the left hemisphere (Castelli et al., 2002; Koshino et al., 2005; Villalobos et al., 2005), as well as a reduction in the power and coherence of slow brain rhythms, such as alpha (8–12 Hz) and theta rhythms (Barttfeld et al., 2013; Coben et al., 2008; Doesburg et al., 2013; Isler et al., 2010; Kikuchi et al., 2015; Machado et al., 2015; Murias et al., 2007).

One possible explanation for the emergence of coherence in neural systems is spike-field coherence (SFC) (Zarei et al., 2018). SFC is a neurophysiological measure that quantifies the temporal relationship between the firing of neurons and the oscillatory activity within a specific frequency band (Fries et al., 2002, 2001; Grasse and Moxon, 2010; Hagan et al., 2012). This measure provides insights into how individual neurons integrate and interact with larger network dynamics and, hence, could be crucial for bridging the gap between macroscopic and

microscopic scales of neural activity. It helps connect large-scale brain oscillations observed at the macro level with individual neurons' detailed, micro-level activity, providing a more comprehensive understanding of neural dynamics. However, SFC analysis requires high-quality signals to detect neuronal spikes reliably. This can be challenging with multi-electrode arrays, particularly where individual neuron signals are not discernible. In such cases, the precision of spike detection may be compromised, making it difficult to assess spike-field relationships accurately. Thus, as discussed later, it may be more relevant to mesoscale recordings using Neuropixels probes.

#### 6.2.5. Exploring brain-wide neural activity in animal models during social interactions using electrode arrays

Multi-site brain recordings from behaving animals have revealed that during social encounters, most, if not all, brain regions exhibit higher levels of theta and gamma power compared to baseline (Kuga et al., 2022; Tendler and Wagner, 2015). Specifically, social encounters are associated with enhancing brain rhythmic activity, particularly in the theta range, across all brain regions. This enhancement reflects an internal brain state associated with social arousal (Tendler and Wagner, 2015). Additionally, changes in theta rhythmicity are directly proportional to the novelty of the social partner and may be considered a neuronal correlate of short-term social memory (Liebe et al., 2012). Recent studies in mice have also shown that theta and gamma rhythmicity are driven by an encounter-induced global brain state that shows similar temporal dynamics across tasks independent of the behavioral dynamics. However, the change in theta coherence during the encounter period differed significantly between tasks, thus reflecting the social context more than other variables (Mohapatra et al., 2024). Moreover, *Cntnap2*-KO mice, a mouse model of autism spectrum disorder (ASD), exhibited higher LFP theta and gamma rhythmicity than C57BL/6 J mice, even at rest. Specifically, *Cntnap2*-KO mice showed a greater increase in theta coherence during the social discrimination test compared to baseline, particularly between the prelimbic medial prefrontal cortex (PrL) and the hypothalamic paraventricular nucleus (PVN) (Mohapatra et al., 2023). This increased coherence indicates that these two brain areas are more synchronized during the social discrimination test in *Cntnap2*-KO mice than C57BL/6 J wild-type mice (Mohapatra et al., 2023). Another recent study showed that the PrL and Nac increased their connectivity in the high theta band while individuals were cooperating during a cooperative test (Conde-Moro et al., 2024).

Overall, these results are in accordance with the concept of a complex system, which implies that the outputs result from how the elements of the system interact rather than from how much they vary individually. This suggests that the collective behavior and emergent properties of the system are more significant than the individual variations of its components.

Several mathematical tools are used in the field of social neuroscience to address this issue. Some tools have been developed and adapted to study the brain at the network level rather than just a sum of pairwise interactions between brain areas. Linear Factor Models, including principal component analysis (PCA) and independent component analysis, are a widely used method in neuroscience to analyze brain network data (Cunningham and Yu, 2014; Udell et al., 2016). These methods simplify the interpretation of data from various modalities by analyzing extracted features such as power spectra from LFP or cross-spectral covariance matrices from multi-site LFP recordings. They are particularly useful for studying LFPs and selecting relevant frequency bands without bias. For example, in a study on LFPs recorded during social interactions in bats, the authors used PCA to identify which frequency bands were most involved, as no prior literature was available on this topic. They selected the 1–29 Hz and 30–150 Hz ranges across all recording channels, bats, and sessions. These ranges robustly captured the maximum amount of variance possible, allowing for an effective analysis of the data dimensions (Zhang and Yartsev, 2019).

Another tool, called Granger causality analysis, determines whether

one time series can predict another one (Bressler and Seth, 2011; Granger, 1969). Granger causality analysis is used to identify causal connectivity between the brain-wide LFP recordings. For instance, such analysis of LFP signals recorded from several brain regions in various social contexts showed that the ventral dentate gyrus plays a significant role in coordinating context-specific rhythmic activity (Mohapatra et al., 2024). Moreover, *Cntnap2*-KO mice exhibited increased Granger causality of theta rhythmicity between the PrL and the PVN across all types of contexts (Free Social Interaction, Isolated state preference, Social Preference, Sex Preference) (Mohapatra et al., 2023). It is important to note that despite advancements, Granger causality is limited by its assumptions of linearity and stationarity, its sensitivity to model specification, and its inability to handle nonparametric, multivariate, and nonstationary data while accounting for unmeasured variables (Shojaie and Fox, 2022). Moreover, we typically cannot incorporate directed communication between brain regions using existing measures like Granger causality with Linear Factor Models (LFMs) because these measures are incompatible with the assumptions of LFMs. To address this limitation, a novel measure called the Directed Spectrum has been introduced to estimate directed communication in the frequency domain (Gallagher et al., 2021). DS measures are compatible with LFMs and can accurately recover latent brain networks, demonstrating superior performance compared to other directed communication measures like Spectral Granger causality (Gallagher et al., 2017). This advancement offers the potential to incorporate the concept of causality between brain regions into network models, facilitating a deeper understanding of the interactions among different areas of the brain.

#### 6.2.6. Using machine learning for studying brain-wide neural activity during social behavior in rodents

It is often useful to describe system dynamics as “states” or attractors, which are regional activity patterns between which the system oscillates (Kelso, 1995). One research group has developed a machine learning approach, termed “cross-spectral factor analysis” (CSFA), to capture neural dynamics from raw neural data during changing behavioral and state conditions (Gallagher et al., 2017). This approach utilizes LFP activity data recorded from multiple brain regions across various frequencies. CSFA breaks down the observed signal into factors defined by unique spatio-spectral properties, allowing for mapping LFP signals to a lower dimensional space while retaining relevant information. They also introduced a semi-supervised approach called discriminative CSFA (dCSFA), which facilitates the design of causal follow-up experiments (Mague et al., 2022). Empirical results demonstrate that CSFA achieves comparable performance in classifying mouse genotype and behavioral context compared to existing methods, but it is more easily interpretable (Gallagher et al., 2017). Model outputs are termed ‘Electomes,’ which are patterns that reflect the electrical functional connectome or networks within the brain. These features include spectral power, synchrony, and phase-directionality. The model outputs also allow one to assess the activity of each Electome Factor over time. Notably, individual brain areas or circuits can participate in multiple Electome Factors, facilitating functional interactions among them and contributing to the emergence of a global brain state.

Extracting Electomes using the dCSFA method from LFP data records from 8 brain areas during social behavior revealed that the network is organized by theta oscillations originating from the prelimbic cortex and amygdala, converging on the VTA (Mague et al., 2022). This network encodes both social versus object conditions and individual social preferences across populations. Interestingly, the network generalizes on a mouse-by-mouse basis to encode individual differences in social behavior in healthy animals but fails to do so in a high-confidence genetic model of autism. These findings highlight the brain's integration of distributed activity across timescales to encode an appetitive brain state underlying individual differences in social behavior. The authors hypothesize the existence of network-level mechanisms involving the synchronization of oscillations that integrate cellular firing across brain



regions and timescales (milliseconds to seconds) to collectively encode an appetitive brain state underlying individual differences in social behavior.

In a more recent article, the same research group defined a brain-wide network that encodes an aggressive internal state within and across mice by recording twelve brain areas and using the same approach (Grossman et al., 2022). Multiple brain regions failed to independently encode attack behavior across mice and contexts (11 brain areas). The aggressive state is encoded at the network level, with predictive efficacy exceeding that of ventral hippocampal activity. This network is organized by prominent theta and beta oscillations, originating from the OFC and medial dorsal thalamus and converging on the VMH and MeA. The aggressive brain state is encoded by decreased activity in the network. Additionally, network activity is conserved when animals are isolated in their home cages, so the network encodes their trait aggression, not solely their aggression behavior. Furthermore, the model was generalized to mice with different genetic backgrounds and subjected to a new aggression context.

Thus, probing the macro-scale level with complementary techniques such as brain-wide c-Fos expression mapping, multi-site fiber photometry and electrophysiology of multiple brain areas allows for the unbiased identification of critical brain regions involved in social behaviors, facilitating a deeper understanding of the complex and dynamic neuronal networks underlying these behaviors.

## 7. Probing the meso- and micro-scale levels

### 7.1. Neural population and single-cell recordings

Understanding the mesoscale level of brain organization is pivotal, especially once macro-scale network dynamics have been revealed and hub regions or enhancer regions identified. The network dynamics are likely to emerge from integrating macro-scale internal states and the processing of environmental and social information that occurs at the mesoscale with the behavior of individual neurons. Using tools that enable observing neuronal population behavior alongside single-unit analysis offers a pathway to unravel the mechanisms underlying physiological social networks' emergence at both the meso- and micro-scale levels. Several methods today allow us to access population and single-unit activities. These include silicon probes (Jun et al., 2017), miniscopes (Zhang et al., 2019), and high-density multi-contact probes (Juavinett et al., 2019). Here, we will detail the use of high-density multi-contact probes, such as the Neuropixels probe. These probes, containing hundreds to thousands of contacts, seem to be the next development in this field. Although limited in their capacity to access multiple regions simultaneously due to their vertical shaft distribution, multi-shaft probes, such as the Neuropixels 2 system, can record from four shanks in parallel, thus enabling recordings from a broader range of brain regions (Steinmetz et al., 2021). While this remains constrained to a subset of the brain, they still offer the advantage of unbiased recording from brain areas aligned along the same axis (Jun et al., 2017; Mora Lopez et al., 2017). With potentially thousands of neurons recorded simultaneously at single-cell resolution, these probes provide a comprehensive view of neural activity with high spatial and temporal resolution.

In a recent study employing Neuropixels probes, researchers found that 42 percent of neurons in the BLA of the subject rat responded to one of four stimuli presented (male or female rat, object, or rice) (Mazuski and O'Keefe, 2022). Half of these neurons exclusively responded to a single stimulus class. The authors thus proposed that BLA neurons identify specific etiologically relevant events. Additionally, a recent investigation using large-scale electrophysiological recordings across multiple brain regions revealed that the state of thirst was encoded as a low-dimensional population state (Allen et al., 2019). This encoded state influenced both spontaneous and cue-evoked neural activity, notably enhancing the rate and duration of task-responsive activity. These

findings underscore the concept of broadly distributed neural activity intricately interwoven with internal states. Moreover, another recent study employed silicon probes across diverse cortical and subcortical brain regions, uncovering the presence of an intracerebral respiratory corollary discharge (Karalis and Sirota, 2022). This discharge effectively modulated neural activity across the observed brain areas. Remarkably, the rhythmicity of breathing appeared to serve as a global pacemaker for the brain, facilitating the integration and segregation of information flow and processing across distributed circuits during offline states. By synthesizing insights from these studies, we can hypothesize that internal states may delineate functional sub-networks of neurons within and across brain regions and neural circuits, thereby influencing social behavior outputs based on the animal's internal state, which is itself influenced by the context.

Thus, despite its constraints, High-density multi-contact probe technology opens significant avenues by providing extremely fine spatial resolution at the level of individual neurons over a relatively large area covering several brain areas.

### 7.2. Optogenetic and chemogenetic manipulations of neuronal population activity

Alongside the above-mentioned electrophysiological methods, optogenetics and chemogenetics provide a complementary approach. Optogenetics allows for genetically defined, light-based control of neurons and has been widely used in social neuroscience studies. This technique has evolved rapidly in recent years, now encompassing a wide range of tools that enable the depolarization and hyperpolarization of neurons, as well as prolonged activity modulation through on-off light delivery systems (Airan et al., 2009; Berndt et al., 2009; Oh et al., 2010; Stierl et al., 2011). Additionally, it is now relatively easy to target specific subpopulations of neurons by combining genetically modified mice with viral vector-mediated gene delivery (Packer et al., 2013). For example, the ventrolateral subdivision of the VMH (VMHvl) receives projections from the bed nucleus of the stria terminalis (BNST), and activating Esr1-positive neurons in the VMHvl of male and female mice leads to aggression (Hashikawa et al., 2017; Lee et al., 2014). However, activating Esr1-negative neurons within the VMHvl is insufficient to induce aggression (Lee et al., 2014). Weaker optogenetic excitation of these neurons promoted mounting behavior towards both males and females. Nevertheless, these results should be interpreted cautiously, as VMHvl neurons display complex dynamics within a molecularly defined subpopulation (Falkner et al., 2016; Karigo et al., 2021; Remedios et al., 2017). While optogenetic and chemogenetic techniques allow for targeted manipulation of state-promoting neurons, they may not fully replicate the natural dynamics of these cells. Still, they can be effective methods for validating the identification of hub regions following analysis at a macroscale level. Moreover, combining these genetic methods with electrophysiological recordings using miniscopes in the VMHvl, for example, could address this issue by exploring how state-triggering specific neuronal populations fluctuate across various timescales (Aly, 2020; Zimmerman et al., 2017).

Overall, understanding how social brain functional networks dynamically emerge and lead to adaptive social decision-making in animal models requires macro-scale, meso-scale, and micro-scale recordings of brain activity using tools such as multiple fiber photometry, electrode arrays, silicon or Neuropixel probes and miniscopes, as well as optogenetic and chemoogenetic manipulations of specific neuronal populations.

## 8. The promise of brain stimulation approach for neurological disorders

As mentioned above, ASD is associated with disruptions in brain dynamics, but this is also the case for several other neurological and psychiatric disorders, such as depression and schizophrenia (Fitzgerald



and Watson, 2018; Li et al., 2013; Uhlhaas and Singer, 2013). Transcranial Magnetic Stimulation (rTMS) is a common therapeutic approach involving the application of electric currents in order to modulate neural activity in specific regions or, more commonly, to the entire brain for therapeutic purposes, using both non-invasive and invasive techniques (Camacho-Conde et al., 2022). This therapeutic approach is used for psychiatric conditions like depression and has shown positive results (Figuee et al., 2022; Tsai et al., 2023). A meta-analysis of 23 studies using rTMS applied on the entire brain to treat core ASD symptoms or cognitive deficits showed a significant, albeit moderate, effect on social behavior (Barahona-Corrêa et al., 2018). However, only five studies reported sustained improvements lasting up to six months. TMS holds promise for treating certain aspects of ASD, yet optimal stimulation parameters, targets, and duration remain unclear. Research and clinical applications hinge on the idea that brain network dynamics play a causal role in pathological behavior and could reverse these phenomena. Presently, results offer promising treatment options for a wide range of neurobiological and psychiatric diseases (Chang et al., 2018; Figuee et al., 2022; Malvea et al., 2022; Tsai et al., 2023). Advancements in understanding how neuronal rhythms emerge and contribute to highly flexible and complex physiological behaviors, coordinating activities across distant brain regions, would greatly aid in selecting appropriate protocols. By identifying recurring patterns, neuronal populations, functional networks, important signaling pathways, and other crucial features, as proposed in this review and illustrated in Fig. 2, we can better understand how activity in different brain areas emerges as a network to produce complex cognitive functions.

## 9. Conclusion

In this review, we have delved into the intricate nature of social behavior, underscoring the imperative to perceive the social brain as comprising multiple partially overlapping neuronal networks and investigate brain-wide oscillations. At the heart of our investigation lies a key question: how do the many different brain processes happening simultaneously in different parts of the brain integrate to create decisions, memories, and actions during social behavior? While social neuroscience literature has predominantly focused on the mesoscale level, by examining specific brain areas, we posit that a crucial piece of the puzzle lies at the macro-scale level. Brain-wide networks appear to play a pivotal role in the emergence of complex and adaptive behaviors, such as social behavior. Yet, the mechanisms underlying the development and emergence of brain-wide networks in a manner conducive to complex and nuanced behavior remain enigmatic. How do various sensory modalities integrate across multiple brain areas? What influence do internal states exert on social behavior outputs? How can a single brain region be implicated in several distinct, sometimes contradictory, social behaviors? How do dispersed neuronal populations defined at the cellular and molecular levels contribute to network dynamics? We propose an integrative approach that combines multiple methods and tools, operating at diverse spatial and temporal resolutions, to tackle these questions, striving to transcend or compensate for technological limitations that preclude recording the entire brain during social behaviors.

## Declaration of Competing Interest

The authors declare no competing interests.

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## Declaration of Generative artificial intelligence (AI) and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT 3.5 for language editing. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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