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Harmonics of the social brain: How diverse brain regions coordinate appetitive social behavior

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Socioemotional behaviors rely on the integration of information across multiple systems in the brain. In this issue of *Neuron*, Mague et al. (2022) characterize a multi-regional functional network that coordinates positively valenced social interactions in mice.

Identifying the brain-wide neural networks underlying motivated social behavior is a challenging task. Seemingly simple behaviors such as approach and engagement with another individual rely on a complex set of collaborating brain structures (Anderson, 2016; Chen and Hong, 2018). Multimodal sensory streams carrying information about oneself, other individuals, and the wider physical and social context, are continuously surveyed by dynamically interacting systems that support emotional, social, and cognitive processes. Those, in turn, must compress and consolidate the signal into a unified course of action for the organism. Understanding this process will take more than an in-depth understanding of the structure and function of single information-processing hubs scattered around the brain. Neuroscientists will need detailed, temporally resolved maps of how disparate parts of the brain communicate and what aspects of that communication ultimately determine behavioral outcomes.

Most efforts to tackle this set of problems focus on one or two brain regions,

seeking mechanistic insight into the neural systems that causally determine the expression of social behaviors (Anderson, 2016). However, with the advancement of technologies that simultaneously listen in on multiple brain areas (e.g., functional magnetic and ultrasound imaging, multi-electrode recordings; Jun et al., 2017; Macé et al., 2011), it is becoming increasingly feasible to collect highly temporally and spatially precise information from multiple brain regions as individuals engage in social behaviors.

In this issue of *Neuron*, Mague et al. (2022) took a broad, multi-region look at the mouse brain during social interactions. To make the problem more tractable, the researchers focused on appetitive social interactions, defined as occasions when a mouse voluntarily approached and engaged with an unfamiliar conspecific. Those interactions were contrasted against exploration of a novel object (mice reliably show greater interest in engaging with other mice than with objects, Figure 1A). During this test, the scientists recorded electrical activity from

eight carefully selected brain regions with known or suspected involvement in socioemotional behavior (Figure 1B).

Armed with multiple characteristics of local field potentials alongside measures of coherence and directionality of signals between regions, the authors trained a machine-learning algorithm to identify functional networks that capture the information related to social versus object interactions. This resulted in a network with activity patterns corresponding strongly to social interaction events. In addition, Mague et al. (2022) introduced a way to incorporate trait-level differences between individuals by deliberately weighing each mouse's signal by its individual tendency to prefer social interactions. This unusual addition meant that Mague et al. (2022) could predict the social preference and differentiate individuals based on the activity of the inferred network.

The described network relied heavily on neural activity in the theta frequency band (4–11 Hz) and showed prominent directionality in its signaling structure, with

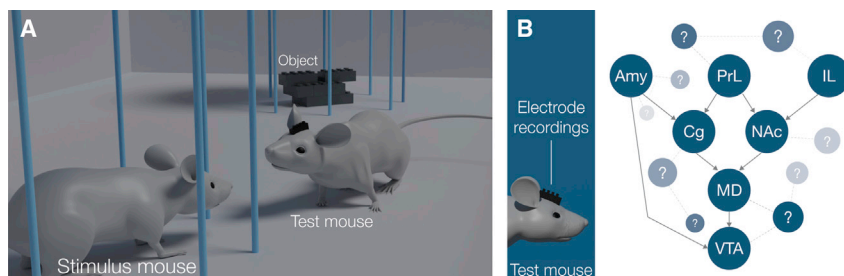


Figure 1. Multi-region brain networks for appetitive social interactions

Mague et al. (2022) employed a simple social versus novel object interaction paradigm and recorded neuronal activity simultaneously from multiple candidate brain regions previously implicated in motivational and social behaviors. They then used machine learning to identify functional networks within this framework that capture the information related to social versus object interactions. Abbreviations: Amy, amygdala; PrL, prelimbic cortex; IL, infralimbic cortex; Cg, cingulate; NAc, nucleus accumbens; MD, medial thalamus; VTA, ventral tegmental area.

cortical brain regions (e.g., prelimbic, cingulate) and the amygdala (AMY) passing information to the medial thalamus and terminating in the ventral tegmental area (VTA, Figure 1B). An extensive set of validation experiments demonstrated that their network also discriminated between non-social appetitive states or stimuli (sucrose versus water, safe area versus dangerous area) and between different appetitive and aversive social encounters.

As is commonly the case in behavioral neuroscience, the design of a behavioral paradigm determines what aspects of neural functioning are under scrutiny. Accordingly, the circumstances under which this network was constructed are crucial to its interpretation. The starting point for Mague et al. (2022) is the hypothetical existence of functional neural networks that specifically underpin voluntary, socio-positive interactions. Their task contrasts a novel object and a novel conspecific, directing the resulting network toward targeting the social aspect of the stimulus more than the valence of the interaction, as engagement with the novel object is also likely to be appetitive (mice prefer a novel object to a familiar object or to an empty cage). An alternative approach might have been to search for networks that isolate the social aspect of the interaction, networks that reflect the valence of the stimulus (both social and non-social) and to seek out points of communication between these two sets. Here, the result is a network that is mostly “social” (sensitive to both positive and negative social

interactions) but, in the absence of a social stimulus, also reactive to the overall valence of a stimulus or situation.

An important benefit of this type of multi-region investigation of neural activity during a task is that networks identified in this manner can inspire concrete hypotheses for mechanistic experiments. Recently, Murugan et al. (2017) identified several distinct neural populations in the prelimbic cortex (PrL) that projected to the nucleus accumbens (NAc), AMY, and VTA. They discovered that hyperactivation of the PrL→NAc projection disrupted social preference in a social interaction task. Accordingly, Mague et al. (2022) found a PrL→NAc circuit element in their functional network; however, their approach had an important additional benefit. They were able to isolate the theta band as a likely endogenous set of activation frequencies in the context of social approach. They went on to demonstrate that optogenetic activation at 10 Hz, but not 20 Hz, increased the time mice interacted with conspecifics, but not objects, alongside an overall increase in the accumulated signal from across their network. Importantly, echoing the findings of Murugan et al. (2017), activation of a circuit element that did not appear prominently in their network, PrL→AMY, had no impact on overall network activity or social behavior. These findings hint at the possibility that other, previously untested elements in this network may also be causally involved in social approach behavior.

However, the promise of new circuit-level discoveries should be approached

with caution. Given the technical challenges and expense involved in collecting high-quality electrical activity recordings, researchers may be tempted to focus preferentially on regions with known involvement in the behavior under investigation. This approach is valid and may generate new insights, as it does in the current work, but it necessarily limits the potential for novel discoveries. Recordings from other brain regions may reveal unusual suspects that contribute in unexpected ways. Another limitation, as Mague et al. (2022) are careful to indicate, is that functional links between brain structures are not proof of direct communication. The presence of directed functional connectivity may be due to one or more unknown players mediating or even supervising the information transfer. Conversely, the absence of apparent functional connections between regions also does not preclude their existence. For example, Gu-naydin et al. (2014) demonstrated that the activity of NAc-projecting VTA neurons could be used to differentiate between social and novel object interactions. This circuit element did not reveal itself in the current work. Together, these caveats highlight the need for careful selection of target regions and mechanistic follow-up experiments grounded in the underlying neuroanatomy.

A final experiment by Mague et al. (2022) hints at a way in which approaches like the one they employ have the potential to deliver translationally relevant findings. The authors test a transgenic mouse with a mutation in a gene associated with autism spectrum disorder in humans (*Ank2*, which codes for the ankyrin-B protein). Transgenic mice showed similar social preference and overall activity in the network under investigation as wild-type control mice. Surprisingly, however, network activity could not be used to infer individual social preference levels in the transgenic mice. In other words, although the same brain regions were at play in seemingly similar ways, activity patterns across this network did not appear to explain interindividual differences in socio-positive behavior in the mutants. What, then, explains differences in social preference in the mutant mice? Perhaps aspects of this network subtly differ in the mutants and an alternative, more informative network would emerge if

trained on mutant data. Or perhaps stable trait-level differences in social preference are more limited or altogether absent in the transgenic mice, making these difficult or impossible to detect. Future research with network-level insight can help address these questions.

The work by Mague et al. represents a valuable step in the direction of considering brain-wide networks when addressing the neurobiological underpinnings of social behavior. Such efforts may help to bridge the large divide between the single-cell, circuit, and whole-brain levels of investigation. That, in turn, has the potential to inspire better theoretical models of the relationship between the brain and behavior. Ultimately, approaches like this may hold the key to the identification of novel, translationally relevant targets for clinical psychiatry.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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