CellPress

Current Biology
Dispatches

Neuroscience: The sting of social isolation

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https://doi.org/10.1016/j.cub.2022.05.036

Social isolation produces deleterious effects on the brain and behavior in many species. A new study on bumblebees uses a multimodal approach to further our understanding of the state produced by prolonged social isolation.

Social connection is vital to everyday life[1]. When humans or other animals are deprived of social contact for an extended period, the effects can negatively impact quality of life and successful survival. Indeed, social isolation can produce profound physiological and emotional deficits, which increase the risk for mortality, dementia, heart disease, stroke and mental health disorders[1,2]. However, perhaps one of the most overlooked impacts of social isolation is its propensity to negatively influence subsequent social behavior. While this effect has often been eclipsed by the direct health risks posed by isolation, there is a growing focus on understanding the broader impacts of social isolation on social behaviors. This newfound focus of research couldn't be more timely as we find ourselves amidst a growing 'loneliness epidemic'[3] — born from changes to social structures, technological advancements and an aging population — that has only been accelerated by the COVID-19 pandemic and its subsequent restriction of social contact. Indeed, the presence and perception of social isolation (or 'loneliness') has never been higher[4]. In this issue of *Current Biology*, a new study by Z. Yan Wang, Grace McKenzie-Smith, Sarah Kocher and colleagues[5] uses cutting-edge, high-throughput computational tools to comprehensively assess the effects of social isolation in the bumblebee, *Bombus impatiens* (Figure 1). By identifying isolation-induced disruptions to social behavior, neurogenetics and brain development, this study reveals a novel underlying theme of behavioral and brain dysregulation induced by prolonged social isolation.

Social isolation affects a wide range of social behaviors across species (Figure 2). In humans, examples include increased aggression, social withdrawal, negative perception of social situations and reduced social aptitude[6,7]. Similarly, social isolation in a variety of animals has been shown to produce decreased social interaction[8,9], increased aggression[10–12] and disruptions in mating and courtship behavior[13–15] (Figure 2). The profound effect of isolation on multiple social behaviors highlights the need to fully understand the internal brain state produced by prolonged isolation, as well as its ability to alter multiple behaviors simultaneously.

Advances in automated multi-animal pose tracking and behavioral classification have revolutionized animal behavior research, allowing scientists to move beyond traditional behavioral scoring and gain a deeper understanding of an animal's internal state[16]. In their study, Wang, McKenzie-Smith and colleagues[5] harness the power of these tools to assess the effects of isolation on social behaviors in bumblebees, enriching our perspective of how social isolation is encoded by the brain. Using automated tracking software[17], the authors identify and extract the movements of individual limbs, wings and antennas of bumblebees behaving in pairs. These postural data are then used to compare stereotyped behavioral profiles for pairs

Figure 1. ***Bombus impatiens*.**
A model organism for studying complex group dynamics and social behavior using a multi-modal approach. (Photo: © Cambridge University Press.)

of interacting bumblebees that were either colony-raised, group-housed or isolated during early life stages.

Using these behavioral profiles to compare social and nonsocial behaviors in bumblebees, Wang, McKenzie-Smith and colleagues[5] identify an increase in 'social affiliation' — as indicated by physical proximity — among animals reared in isolation. Interestingly, this increase is only present when an isolated bee is interacting with another isolated conspecific, but not when an isolated bee is interacting with a socially experienced partner. This suggests that the disruption in social interaction following isolation only emerges when aberrations are present in the behavior of both partners. Changes in behavioral dynamics as a consequence of the combined social experience of multiple partners (e.g. isolated or group-housed) is a novel emergence in the field and should be further investigated.

To further assess social behavior in more detail, Wang, McKenzie-Smith and colleagues[5] extracted stereotyped behaviors from their mapped behavioral profiles. Across a range of behaviors, the authors show that isolation produces significant changes when comparing affiliative versus non-affiliative behaviors. These behaviors include increased idling, decreased locomotive behaviors, increased antennal motion and diminished increases in grooming behavior. These changes highlight the widespread disruptions to the social repertoire of isolated bumblebees and reveal a general theme of isolation-induced alterations of stereotyped behaviors or "social dysregulation". Importantly, the authors' high-throughput, computational approach towards investigating changes in behavior provides a powerful, general framework through which the mechanisms of an internal state, such as social isolation, can be decoded.

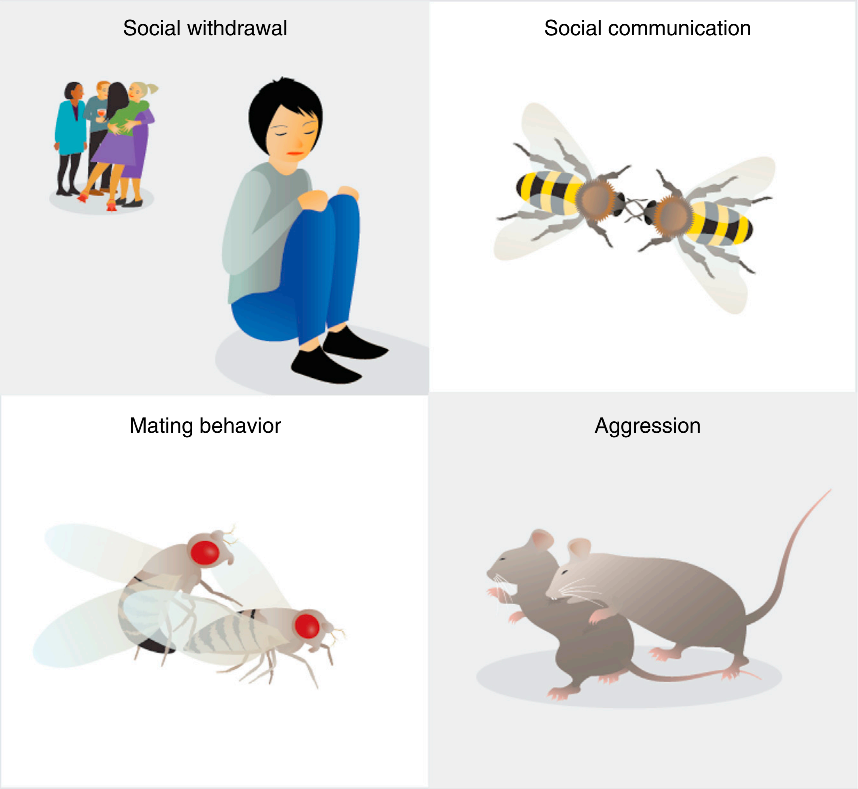

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Figure 2. Prolonged social isolation negatively impacts social behavior across species.
Social isolation can promote social withdrawal, disrupt mating and courtship song, increase aggression and dysregulate social communication in bumblebees (as indexed by altered antennae interaction). (Artwork: Julia Kuhl.)

Lastly, Wang, McKenzie-Smith and colleagues[5] provide evidence of the bidirectional effect of isolation on social behavior. As antennal behaviors are a primary mode of communication in bees[18] and may be central for social recognition, Wang, McKenzie-Smith and colleagues[5] assess how isolation affects antennal contact between social conspecifics. Intriguingly, while isolated, group-housed and colony-reared groups all engage in antenna–antenna contact, isolation results in increased variability of this behavior. This increased variability in social communication provides further evidence that isolation produces dysregulated social behavior, as the prolonged lack of social experience is sufficient to cause behaviors to go awry — sometimes without specific directionality of the effect. Such dysregulation is paralleled by the authors' neurobiological findings, such as their discovery that isolation rearing significantly increases the variability of brain volume at maturation and remodels gene expression brain-wide, with over one hundred differentially expressed genes compared to their socially-reared counterparts. Together, these findings provide strong evidence that isolation creates an internal state that is governed by systematic dysregulation from gene expression to neurodevelopment to behavior.

Bumblebees are a powerful model system for researching the impact of reduced social contact on behavior, as they live in the well-characterized, hierarchical social structure of a colony. Such colonies allow for the investigation of changes to housing conditions which vary along the social continuum (e.g. solitary living vs. living in a small group, a large colony, or in overcrowding conditions). In addition, bees in general allow for the direct assessment of how rearing conditions interact with one's fixed role in the nest (e.g. queen bee vs. worker bee). In addition to such highly organized social roles, the formation of the colony and continued shared habitat takes considerable social coordination by members of the colony, creating a rich social environment[19]. The ability to systematically manipulate housing conditions in a species with dedicated social functions and an intricate social environment provides a unique opportunity to interrogate the effects of social deprivation. Ultimately, this study highlights new avenues for the field using a unique model organism, emphasizes the critical role of social relationships in development and behavior and reveals the powerful ability of computational approaches to shed light on complex mechanisms underlying internal states.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Autophagy: Identification of MTMR5 as a neuron-enriched suppressor

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https://doi.org/10.1016/j.cub.2022.04.075

A puzzle of autophagy in neurons is that, unlike in other cells, it is not robustly induced by inhibition of mammalian target of rapamycin (mTOR). A new study now solves this conundrum and establishes that myotubularin-related phosphatase 5 limits the induction of neuronal autophagy by mTOR inhibitors.

Macroautophagy (hereafter referred to as autophagy) captures cytoplasmic cargo into autophagosomes for clearance in lysosomes[1]. This pathway is critically important for neuronal function and survival. In fact, knockout of key autophagy genes causes neurodegeneration in mice, and mutations in autophagy genes are linked to neurodegenerative disorders in humans[2,3]. Moreover, proteins that are prone to aggregation in neurodegenerative diseases are substrates for autophagy, sparking strong interest in autophagy as a therapeutic target[2]. Thus, a key question in the field is: how can autophagy in neurons be manipulated to enhance clearance of protein aggregates and promote neuronal viability in neurodegenerative disease? Conventional methods of inducing autophagy have limited effects in neurons compared with non-neuronal cells such as astrocytes[4–7]. However, the factors that confer resistance to these autophagy inducers in neurons have remained unknown. In a new study published in this issue of *Current Biology*, Chua *et al.*[8] solve this conundrum and identify myotubularin-related phosphatase 5