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PERSPECTIVE

For neuroscience, social history matters

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Neuropsychopharmacology (2023) 48:979–980; https://doi.org/10.1038/s41386-023-01566-8

INTRODUCTION

Humans and many animal models used in neuroscience are social species. For these species, social experience across the lifespan has lasting impacts on the brain and behavior. However, behavioral neuroscientists not studying social behavior rarely consider their subjects' social history. Factors such as social rank, history of isolation, and early care environment can have profound implications for neural and behavioral data interpretation. We argue this social history-informed approach may be critical for reconciling disparate findings across behavioral neuroscience research.

SOCIAL RANK

Group-living species, including humans, readily establish and maintain social dominance hierarchies. These social hierarchies are adaptive for community survival, allowing for resource allocation, supporting offspring survival, and reducing energy expenditure. Hierarchies are formed naturally in the wild for many species and can be modeled in the lab [1]. Studies across species have shown that at the individual level, social rank is a major determinant of long-term outcomes on nearly every level of neurobehavioral analysis, including hormones, brain structure, and social decision-making [1, 2]. As such, these baseline social rankings are a key consideration in interpreting experimental results.

In rodents, changes in social hierarchy formation induce changes in plasma hormones [2]. Once stable hierarchies are formed, their maintenance requires individuals use optimal behavioral strategies for their position. For example, in rodents, it is adaptive for subordinate animals to avoid the dominant and wait for access to food and receptive mates, otherwise risking injurious fighting. This may result in differences across several neural and behavioral outputs, including risk aversion and social approach [3–5]. Recent research has highlighted how social rank information is encoded in the medial prefrontal cortex and its subregion, the anterior cingulate cortex [6]. Following repeated winning during agonistic encounters, dominant mice show increased synaptic strength and neuronal activity in these regions [7]. On the other hand, subordinate rank can increase anxiety-like behaviors and influence vulnerability to chronic stress-associated metabolic changes and diseases [3, 8]. A recent study in mice shows that social dominance explains a large portion of non-social behavioral differences and genetic expression differences [9].

Given the importance of rank on behavior, plasticity and stress reactivity, researchers not expressly studying hierarchies should consider rank information when interpreting neurobehavioral results. Filming home-cage interactions can help provide rank information via observations of agonistic interactions like fights and chases [10]. Territorial urine marking tests and the tube test are two easy assays to address social ranks in rodents [11, 12]. In addition, physiological indices of rank, including circulating testosterone and the size of adrenal glands [2, 13], may be useful in interpreting variable experimental outcomes.

SOCIAL ISOLATION

Across social ranks, access to partners for interaction is crucial. Social isolation (SI) is inherently aversive for social species, triggering motivated behaviors to engage in social contact [14]. While a rich literature details the effects of SI through studies specifically manipulating this variable, SI can occur outside of these experiments. Indeed, most systems neuroscience studies include a built-in period of social isolation when animals are in recovery from an invasive surgical procedure.

These experiences are critical to consider when interpreting neurobehavioral data, as they have myriad impacts on brain function [6, 14]. In humans and rodents, acute social isolation is associated with changes in dopamine signaling in the substantia nigra pars compacta, ventral tegmentum, and dorsal raphe nucleus [15, 16]. Furthermore, chronic isolation causes heightened emotional reactivity to stress, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, aggression, and persistent defensive responses [17–20]. Given these impacts, we urge researchers to include details about any isolation periods experienced by test subjects in their experimental methods.

EARLY CARE QUALITY

One of the most robust predictors of lifelong psychiatric outcomes is the quality of early caregiving [21]. Research across species has detailed how specific aspects of the early care environment produce immediate and lasting impacts on nearly every level of brain function [22, 23]. For instance, typical caregiving buffers the infants' HPA axis—a key regulatory system for healthy development of the stress response. Conversely, these protective effects are weakened or absent with stressed and/or maltreating caregivers, resulting in dysfunction of emotional regulation circuits. Even nurturing behaviors fail to produce expected brain impacts when caregivers are stressed, or when the quality of caregiver-infant attachment is poor [24]. Researchers studying these processes use numerous experimental paradigms to model

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Received: 22 November 2022 Revised: 6 February 2023 Accepted: 1 March 2023
Published online: 15 March 2023

early life stress, including limiting the mother's nest resources and separating infants from the mothers [23].

However, numerous additional factors can increase the stress of the caregiver, and thereby impact the neurobehavioral development of the infant. For researchers breeding rodents in-house, these variables can include litter size, litter composition (male/female), and factors such as handling and the sex of experimenters/husbandry staff. On the other hand, shipping female rats during pregnancy or immediately post-partum is massively stressful and can induce atypical treatment of pups [25]. As any of these variables can alter maternal behavior towards the entire litter, it is critical to account for litter effects when assigning animals to experimental conditions.

While it is beyond the capabilities of basic researchers to consider every possible environmental feature of early life (e.g., maternal diet, housing type, ventilation), evaluating the stress of the mother can capture these collective impacts. A non-disruptive, relatively straightforward approach for researchers with access to pregnant or post-partum dams is to monitor their behavior and identify signs of distress, including trampling of pups and failure to retrieve scattered pups. As these behaviors have been robustly linked with neurobehavioral outcomes [22–24], they merit reporting in all neurobehavioral rodent studies, not just those focused on development.

CONCLUSION

The impact of previous social experience is known to be of paramount importance for cognition, development, and motivated behavior. These myriad factors can include social stability, paternal care, prior mating/sexual experience, conditioned social defeat, cage overcrowding, and many others. Here, we have turned our focus to three very specific social history factors: rank, isolation, and early caregiving quality. Although these variables are the subjects of intense study in experiments designed to manipulate them, they can introduce variability into any experiment using social species for animal models. We thus urge all researchers using social species to consider and report on these social factors.

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AUTHOR CONTRIBUTIONS

AG, NPC, and MO wrote the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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