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Book Forum

Are there model behaviors for model organism research? Commentary on Nicole Nelson's *Model Behavior* (Chicago 2018)

One might be inclined to assume, given the mouse donning its cover, that the behavior of interest in Nicole Nelson's book *Model Behavior* (2018) is that of organisms like mice that are widely used as “stand-ins” for investigating the causes of human behavior. Instead, Nelson's ethnographic study focuses on the strategies adopted by a community of rodent behavioral researchers to identify and respond to epistemic challenges they face in using mice as models to understand the causes of disordered human behaviors associated with mental illness. Although Nelson never explicitly describes the knowledge production activities in which her behavioral geneticist research subjects engage as “exemplary”, the question of whether or not these activities constitute “model behavior(s)”—generalizable norms for engaging in scientific research—is one of the many thought-provoking questions raised by her book. As a philosopher of science interested in this question, I take it up here.

According to Nelson, rodent behavioral researchers at pseudonymous *Coast University* and their close collaborators aim to identify the genes, brain regions and/or neural circuits involved in mental illnesses like addiction, anxiety and depression. To achieve this aim, they combine invasive intervention techniques such as gene knockouts, brain lesions and drug interventions (e.g., anxiolytics) with behavioral paradigms that allow them to determine the impact of such manipulations on a mouse's behavior.

Nelson presents a representative example of the basic structure of research in this field in Chapter 3 (see also Nelson, 2013). As she explains, one behavioral apparatus, the *elevated plus maze*, is used by Coast researchers to assess *anxiety* in mice. This maze, which looks roughly like a plus sign, “is elevated about a half a meter off the floor” (Nelson, 2018, p. 82) and is comprised of four arms. Two arms have walls on the sides and at the end and are thus described as “closed”, the other two have no walls and are designated “open”. An experiment begins when a mouse is placed in the center of the maze where the four arms meet and allowed to freely explore. Anxiety is operationally defined in terms of the amount of time a mouse spends in the closed compared to the open arms of the maze. The more anxious a mouse is, the more time it will spend in the closed compared to the open arms. This maze has and continues to be widely used as a tool for assessing anxiety in knockout mice and determining the efficacy of certain pharmacological agents for treating anxiety. It is also used in conjunction with other experimental apparatuses (e.g., the Morris water maze, fear conditioning chambers) to assess behavioral traits in mutant mice (e.g., Crawley, 2003).

This basic methodological approach of combining behavioral tools with intervention techniques is commonplace in neuroscience. Yet, in describing her interactions with Coast primary investigators, postdoctoral fellows, and graduate students in the contexts of courses, laboratory experiments, formal gatherings and informal discussions, Nelson indicates that she regards what she is observing as unexpected and surprising. What sets Coast researchers apart, from her perspective, is that they openly express skepticism about the very investigative strategies they are using to advance an understanding of the genetic and/or neural bases of mental illness. Before providing a complementary philosophy of science perspective on what I regard as extraordinary and exemplary about Coast's researchers' knowledge production activities, I want to consider how Nelson understands these activities from the standpoint of her own discipline, social science and technology studies.

Early in the book, Nelson describes a number of examples that indicate that Coast researchers are privy to some of the “kinds of barriers” that “might lie between them” and mechanistic explanations of mental illness (Nelson, 2018, p. 23). In fact, she claims they liberally use the term “complexity” to denote an array of epistemic hurdles they believe they face (Nelson, 2018, p. 23). For example, they recognize that because it is unclear whether current psychiatric classification systems like the *Diagnostic and Statistical Manual of Mental Disorders* individuate mental illnesses in ways amenable to discovering their causes, it remains an open question whether these categories should inform their research. However, given that the categories are (or were at the time that Nelson was writing) the only ones available to inform rodent research, an additional problem arises in using them: at least some symptoms associated with each mental disorder category seem uniquely human (e.g., suicide ideation, delusions). Rodents may not have such symptoms and even if they do, detecting them in behavior is not straightforward. Researchers thus select from a given mental disorder category those symptoms they believe can reliably be detected in mice. It is common for them to focus on a purportedly single behavioral symptom like anxiety that is associated with one or more mental disorder categories and develop experimental apparatuses like the elevated plus maze that allow them to detect if that symptom is present or absent in mice (e.g., Nestler & Hyman, 2010; Arguello & Gorgos, 2006).

These epistemic challenges that arise in the earliest stages of empirical inquiry are only just the beginning, however. As Nelson explains, “complexity talk” is also used to characterize problems that emerge while running rodent behavioral experiments. While the aim of such research is to establish causal connections between genes or circuits and observable measurable behaviors, Coast researchers recognize a number of potential confounding variables that may prevent the establishment of such connections. For example, a mouse's behavior in an elevated plus maze might be attributable to factors other than being placed in the maze including: the temperature of the colony room in which it is housed, the disposition and/or scent of an experimenter and ambient noise during the experiment. When concerns about potential confounds arise, work to identify the culprit(s) begins, often resulting in revisions to the experimental design and protocol. While researchers aim to control for such factors, they acknowledge their inability to identify and control for all potential confounds.

Coast researchers and their collaborators also explicitly worry whether the behavioral apparatuses they use actually measure what they are designed to measure. It remains an open question, for example,

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whether the elevated plus maze actually measures mouse anxiety. Additionally, even if they are able to establish that specific tasks measure those psychological traits they are intended to measure, they recognize that it is an open question what results from mouse anxiety experiments actually indicate about the causes of human anxiety.

Nelson uses the concept of an "*epistemic scaffold"* in Chapter 3 (See also Nelson, 2013) to characterize an array of strategies Coast researchers use to respond to these epistemic hurdles and "negotiot[e] the epistemic foundations of the field" (2018, 85). On one interpretation of this concept, the behavioral apparatuses that Coast researchers use, like the elevated plus maze, and the arguments put forward to justify their use, function as a kind of "support structure" (Nelson, 2018, p. 85), enabling inquiry into the causes of behaviors like anxiety to get off the ground. Yet, whereas in building construction a scaffold is a temporary structure used as a basis for erecting a building that is supposed to be stable enough to one day stand on its own, in rodent behavioral research, knowledge about the genetic or neural causes of behavior produced by means of these apparatuses lacks this kind of stability. Investigators, insofar as they are skeptical of the usefulness of these tools for producing stable causal knowledge, persist in probing them for potential confounds or errors with an eye towards revising or replacing them. Moreover, they carefully qualify the kinds of causal claims they are willing to make on the basis of their data and tailor the terms they use to refer to those behaviors in ways that reflect their lack of certainty about what the experimental apparatuses they use actually measure. For these reasons, Nelson contends that scaffolds in this research context "end up becoming permanently provisional structures: they are built for particular pragmatic purposes, but the work that they are needed for takes longer and is more complicated than expected, turning these supposedly transient structures into semi-permanent features of the scientific landscape" (Nelson, 2018, p. 85).

The overall structure of research at Coast is *surprising* especially given recent claims that science sometimes fails to be knowledge-producing because researchers fail to adhere to good standards of scientific practice. I want to make the case, appealing to the history of the philosophy of science, that it is remarkable in another sense. Philosopher of science Sir Karl Popper (1962) famously contended that what demarcated science from other areas of inquiry was that practitioners routinely questioned and tested foundational assumptions and rigorously attempted to experimentally disprove or "falsify" currently accepted theory. Philosopher of science Thomas Kuhn, using case studies from the history of physics, sought to demonstrate instead that "normal science" was characterized by uncritical commitment to foundational assumptions and the mere solving of theoretical puzzles. He argued that "it is precisely the abandonment of critical discourse that marks the transition" of an area of inquiry "to a science", and "once a field has made that transition, critical discourse recurs only at moments of crisis when the bases of the field are again in jeopardy" (Kuhn, 1970, pp. 6–7). If Popper is correct, science will likely never move past the point of questioning its foundational assumptions; if Kuhn is right, we should worry that science may not be sufficiently critical in ways that facilitate cumulative knowledge production. Research at Coast is suggestive, however, that Kuhn and Popper are both right. Rather than "revolutions" in science marking periods of "extraordinary research", as Kuhn claimed, perhaps truly remarkable science is that in which critical discourse and research to probe disciplinary foundations à la Popper runs in parallel with a Kuhnian program of hypothesis-driven research.

This directly relates to the question I raised at the outset of this commentary, namely, are the knowledge-production activities of Coast researchers *exemplary*? As philosopher of science Deborah Mayo argues, scientists not only need to test their hypotheses (Kuhn's project), they also require tools for criticizing the very tests that they use (Popper's project (Mayo, 1996, p. 37)). These two projects typically cannot be undertaken simultaneously (e.g., Schickore, 2018). Concerns that uncontrolled environmental stimuli may be disrupting their ability to establish causal links between genes, circuits and behavior prompts Coast researchers to undertake novel exploratory research (e.g., Steinle, 1997) designed to determine the presence of potential confounds and improve their experiments. Recognition that their experimental tools are insufficient for individuating discrete kinds of behaviors (i.e., anxiety) initiates a different complementary line of exploratory inquiry directed at improving or replacing these tools.

Positive conclusions aside, could current standards across the extended Coast research community be improved? Possibly. An important feature of such research is interdisciplinarity: it involves a toolbox of behavioral and intervention techniques that has greatly expanded in recent years (e.g., new behavioral techniques include rodent touchscreens (Bussey, Saksida, & Rothblat, 2001) and intervention techniques like optogenetics and knock-in mice). Although interdisciplinary training is increasingly more common in neuroscience, it is difficult for a single researcher to anticipate the entire range of potential errors to which a methodologically integrative experiment like those being undertaken at Coast may be subject. For example, a researcher who is an expert in rodent behavior may recognize potential problems with a mouse intervention experiment (e.g., environmental confounds) that are not on the immediate radar of an investigator trained in how to manipulate brain activity. Similarly, an expert in brain circuit manipulation may recognize potential problems with implementing a brain intervention that experts in mouse behavior may not have considered. If this is correct, in order for "error-probing" in this research area to be sufficiently thorough, it seems reasonable to advocate for what I previously dubbed "perspectival" or "coordinated pluralism" (Sullivan, 2014, 2017, 2018). The basic idea is that individual research groups should be comprised of researchers with diverse educational and training backgrounds who can together engage in critical analysis of behavioral and intervention techniques when experiments are designed, implemented and experimental results interpreted. From my recent experience as a participant-observer in a translational cognitive neuroscience laboratory at Western University, I believe that such coordinated pluralism is becoming a prominent feature of the landscape in this research area.

In conclusion, Nelson's book injects a much-needed optimism into recent debates about knowledge production in science and demonstrates the importance of the participant-observer perspective for identifying "model behaviors" most likely to improve scientific inquiry going forward.

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