Possible challenges in behavioral phenotyping of rodents following COVID-19 lockdown

To the Editor — Transgenic and knockout mouse models have proven to be useful in understanding the functional outcome of the brain in many neuropathological states and diseases. Preclinical behavioral analysis in rodents is an integral part of neuroscience research, but the reproducibility and repeatability of behavioral phenotyping greatly depend on state, trait, and technical factors¹ (Table 1). Subtle changes in animal handling, human interference, or the animals' environment may perturb the outcomes of behavioral analysis.

Recently, preventive lockdown and self-quarantine measures taken around the globe in response to COVID-19 have reduced numerous human activities, including transportation. Such a global shutdown has reportedly reduced the vibrations in earth's crust², which may be sufficient to modulate neurobehavioral functions in rodents. Earlier studies have reported that mice are highly sensitive to vibration—particularly at a resonance frequency range of 30 to 110 Hz^{3,4}; vibration-induced changes in behavior have been reported in C57BL/6 mice⁴. Acoustic noise can also affect the physiology and behavior of experimental rodents⁵. However, the effect of potential changes in acoustic noise due to COVID-19 lockdown may vary depending on the sound attenuation measures of different vivaria. In the present scenario of COVID-19 lockdown, laboratory rodents are potentially continuously exposed to an altered noise and vibration environment.

Massive austerity due to COVID-19 has also impacted resource availability, such as technical staff, animal feed, protective gear, and periodic maintenance of air handling units. Such measures might have affected routine animal care and relevant

Table 1 | Various factors that may affect the behavioral response of rodents

State Factors	Trait Factors	Technical Factors
<ul style="list-style-type: none"> • Technical skills and experience of the experimenter • Circadian timing • Setup and arrangements in the animal room • Nesting and bedding surface 	<ul style="list-style-type: none"> • Animal handling • Stress level of the animal • Health and age of the animal • Strain and sex of the animal 	<ul style="list-style-type: none"> • Automation in vivarium maintenance • Record keeping of health data • Control and monitoring of animal room environment • Standard operating procedure

husbandry practices. Additionally, any reduced demand for experimental animals by researchers might have shifted animal breeding schedules. Altered periodicity and changes in human interference, dietary regime, odour cues, and animal handling have all been reported to strongly influence rodent behavior^{5–8}. Moreover, environmental factors can operate a neurodevelopmental reprogramming of offspring and induce subsequent intergenerational and transgenerational changes in behavioral functions^{9,10}. The influence of environmental changes on the behavior of offspring may vary depending on the time and duration of exposure at a specific developmental stage¹⁰.

Therefore, post-pandemic behavioral analysis must carefully plan for an animal acclimatisation period. Since it is not yet clear how many generations will be affected, the use of immediate F1 progeny is not recommended for behavioral analysis of preclinical disease models. Behavioral changes caused by COVID-19 lockdown may further be characterized via comparison with the baseline data collected before the lockdown. Nevertheless, such potential changes in behavioral phenotype may not necessarily affect equally all models or endpoints. Therefore, intra-laboratory comparison of behavioral phenotypes in

post-lockdown batches may help future experimental planning. The present lockdown situation is also a reminder of the need for technological robustness in animal care and husbandry practice, such as automation in cage changes, autoclaving and cleaning, and the maintenance of environmentally stable vivaria with precise acoustic and seismic attenuation. □

Kailash Manda

Division of Behavioral Neuroscience, Institute of Nuclear Medicine & Allied Science, Delhi, India.

✉ e-mail: kailashmanda@gmail.com

Published online: 12 May 2020

<https://doi.org/10.1038/s41684-020-0559-4>

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