Small animal imaging presents an opportunity for improving translational research in biological psychiatry

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Recent efforts in biological psychiatry have made a significant push toward examining both psychopathology and brain circuitry on a continuum across the spectrum of healthy individuals to those suffering from chronic and unremitting neuropsychiatric disorders.[1] Neuroimaging methods have provided a critical tool through which to examine this continuum,[2,3] given their noninvasive, repeatable nature. Additionally, they provide a scaffold through which one can relate sources of neurobiological heterogeneity (in the form of brain anatomy and function) to clinical and behavioural heterogeneity.[4–6] In particular, magnetic resonance imaging (MRI) methods have been important in this regard, given the public availability of data and the multiple analysis streams that leverage different tissue properties to make inferences on brain topology and circuitry.[7,8] Arguably, this sustained strategy contributed to recent significant advances in using knowledge of brain circuitry to target novel brain stimulation approaches as treatments for neuropsychiatric disorders[9,10] and for improving our understanding of the mechanism of action of pharmacological agents (like ketamine) being repurposed for use in different clinical contexts.[11] In aggregate, these developments are highly suggestive of how significant gains in novel therapeutics can be obtained using reliable investigations of well-characterized brain circuits.

Despite these important advancements, there is still much work to do in understanding how neuropsychiatric disorders emerge over time. Human neuroimaging experiments, MRI in particular, lack the important ability to achieve detailed mechanistic insights that involve cellular- or molecular-level information. There are notable exceptions, such as the use of positron emission tomography or magnetic resonance spectroscopy (and related techniques), for obtaining data on specific molecular phenotypes.[12,13] Alternatively, one can relate neural phenotypes[14–16] to gene expression data from public resources like the Allen Human Brain Atlas;[17] however, these relationships are generally derived neuroinformatically and preclude the investigation of cellular and molecular phenotypes. There are limited means to perform detailed investigations across architectural scales (molecular, cellular, structural and functional connectivity, and morphology) in humans as one could perform using animal models of the central nervous system disorders. To this end, small animal imaging may provide meaningful opportunities in the context of biological psychiatry for bridging between macro- and microanatomic scales of brain circuitry. In this editorial, we describe both the utility of MRI research (with an emphasis on the use of rodent models) for gaining mechanistic insight into neuropsychiatric illness and how dimensional approaches that have provided important advances in the clinical/neuroimaging literature can be translated into experimental design.

Opportunities to use small animal imaging for discovery in biological psychiatry

Small animal neuroimaging is one of the few techniques in neuroscience where investigations in human and clinical populations preceded the detailed work that is beginning to emerge in experimental models. Thus, there remains a methodological barrier to the initiation of experiments using small animals. While there are important logistical and technical challenges that must be overcome in order to achieve a reliable signal that can be used for analyses,[18–21] these will not be addressed in this editorial; however, we suggest designing experiments with these challenges in mind. Nonetheless, there are considerable advantages to using small-animal neuroimaging that include the controlled experimental manipulations that can be done both in and out of the scanner; postmortem assessments for achieving translational insight; and the relatively short gestational, developmental, and aging periods that are ideal for longitudinal experiments.

In its infancy, the field of small animal neuroimaging leveraged MRI-based techniques to examine the structural and functional phenotypes related to genetically modified animal

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Cite as: *J Psychiatry Neurosci* 2021 October 20;46(5). doi: 10.1503/jpn.210172

models[22–24] or environmental exposures[25] typically in cross-sectional settings. This type of study design provides an important and useful starting point in the investigation of altered brain circuitry; however, it only scratches the surface of opportunities that animal MRI provides. One of the challenges in the use of experimental models is appropriately capturing and investigating the heterogeneity that is typically observed in neuropsychiatric diagnoses. This is especially important, given the dynamic nature of brain changes in response to environmental risk factors and treatments[5] and the neurodevelopmental underpinnings of many disorders,[26,27] which likely contribute to the variability observed[3] (e.g., several risk genotypes may map onto a single clinical diagnosis, or vice versa). This variability may also be a source of important information and potentially a key feature that needs to be better understood in order to make advances in our understanding of neuropsychiatric illness. In many animal models of neurodevelopmental or psychiatric disorders, the differences in effect sizes of treatment outcomes between experimental and control groups can be difficult to ascertain. However, leveraging this variability by harnessing clustering techniques from data science[28] or examining susceptibility or resilience[29] to a specific environmental risk factor (e.g., maternal immune activation [MIA][30]) are important strategies that allow for a more nuanced understanding of the spectrum of phenotypes. While these approaches are critical to examining the heterogeneous nature of the model organisms and, ultimately, the disorders experimenters are seeking to model, they still segregate or use specific, discrete categorizations rather than examine a dimension of brain and behaviour phenotypes. Despite these issues of intersubject variability, the availability of rodent models in biological psychiatry research has led to useful and important discoveries, such as identifying therapeutic strategies related to antidepressant action[31] (among other key findings).

Recent work from our group has provided a window into how this dimensional approach could be achieved. We examined multiple behaviours across different developmental stages in the same animal and demonstrated how they may be related to brain development using longitudinal structural neuroimaging in MIA-exposed mice.[32] Rather than using a single behavioural phenotype, we chose to use partial least squares[33] analysis that generated, in a data-driven fashion, linked dimensions of MIA-exposure-related variation in behaviour and brain development, where each mouse could be examined within a space of latent variables derived from within the data set. This analysis approach has proven successful in the human neuroimaging literature and provides an example of successful translation across species using comparable modalities. In order to harness this variability to the benefit of the scientific investigations, researchers may need to use new methodological approaches and statistical analyses that allow for the identification of differences along dimensions rather than discrete categories. This strategy could be augmented further by using other more "naturalistic" behaviours, such as variability in spontaneous home cage activity,[34] complementing the more standard tests we used previously.

Furthermore, in order to fully appreciate these subtle differences within the models related to neuropsychiatric disorders, it is critical to take a more integrative approach.[32] Some groups have started to do this; for example, recent work by Mueller and colleagues[29] used clustering approaches on a large sample of behaviourally phenotyped MIA offspring and identified subgroups of MIA offspring that were more or less behaviourally impaired. These subgroups were further found to differ based on transcriptional profiles and structural covariance, possibly linked to differences in inflammatory cytokine profiles.[29] Similarly, we have demonstrated[32] that using the linked brain–behaviour dimensions that we described above, we can identify transcriptional profiles related to autistic behaviours, inflammatory pathways and microRNA regulation. These critical integrative approaches start parsing the large set of biological factors that may be at play for any neuropsychiatric disorder. We believe that neuroimaging approaches may provide a useful scaffold through which to link biological data across different systems and varying scales of resolution.

Considering rodent models in a neurodevelopmental context using neuroimaging

In addition to the possibility of using multi-dimensional techniques, MRI-based studies of rodent models allow for the unique ability to investigate neural phenotypes at the whole-brain level and longitudinally. Given that the onset of many neuropsychiatric disorders occurs in childhood and adolescence,[26,27] it is imperative that studies of rodent models aimed at investigating the neurobiology of these disorders leverage the unique ability of MRI to generate spatiotemporal maps of brain variation. Recent important work has gone into leveraging the availability of longitudinal methodologies in rodent models[32,35–37] in both acquisition and statistical analysis. This type of work provides an important advance in our ability to characterize animal models and provides homology to human longitudinal neuroimaging studies that seek to examine neuropsychiatric disorders as deviations from normative developmental processes — a strategy that has provided critical insight into a range of neuropsychiatric disorders with neurodevelopmental underpinnings.[38–40] However, special care should be taken to assess and carefully understand limitations that may be caused by repeat assessments. Previous studies that examined the impact of repeated imaging and anesthesia found limited effects on behavioural and neuroanatomical phenotypes, but more work would be useful to examine these confounds.[35]

Using animal models has many advantages and is an essential tool for testing causality and identifying molecular mechanisms.[41] However, the utility of this strategy needs to be considered in the context of a few limitations. The use of any animal model to study human neuropsychiatric disorders or associated risk factors is extremely challenging because of the subjective nature of many core symptoms currently used to diagnose the disorders. To further complicate the problem, there are no objective biomarkers that

map onto specific symptoms used for diagnosis.[42] Therefore, examining risk factors or genotypes is critical to future studies using neuroimaging and small-animal models. Nonetheless, there are considerable benefits conferred by longitudinal MRI, such as whole-brain assays that may provide insight on where one should and could investigate further. While MRI lacks specificity to individual molecular and cellular mechanisms,[43] it is a critical spotlight that can help integrate brain structure and function in the context of biological psychiatry.

Taken together, we offer the following recommendations as a means of developing methods that can help improve our understanding of mechanistic and phenotypic signatures related to neuropsychiatric disorders. Chiefly, we suggest that improving longitudinal methodologies such that they integrate more translationally relevant behaviour (e.g., behavioural tests performed in humans and adapted to work in touchscreens for rodents[44]) is critical to creating more robust models of neuropsychiatric disorders. We further suggest that integration of transcriptomics, neurochemical and deeper cellular-level phenotypes (derived using advanced microscopy techniques) may allow individual-level phenotyping that may provide a more nuanced and detailed understanding of genetics, environmental risk factors and heterogeneity in treatment response. This will, in turn, require the back-propagation of advanced data science and machine learning techniques[2,3,30] that may enable the ability to make sense of "big data" at the level of the individual subject.

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Competing interests: E. Guma declares trainee funding from Fonds du Recherche du Quebec en Sante. No other competing interests declared.

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