



# Charting the path in rodent functional neuroimaging

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## ABSTRACT

Driven by a period of accelerated progress and recent technical breakthroughs, whole-brain functional neuroimaging in rodents offers exciting new possibilities for addressing basic questions about brain function and its alterations. In response to lessons learned from the human neuroimaging community, leading scientists and researchers in the field convened to address existing barriers and outline ambitious goals for the future. This article captures these discussions, highlighting a shared vision to advance rodent functional neuroimaging into an era of increased impact.

**Keywords:** mouse, fMRI, awake, fUSI, anesthesia, rat

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## 1. INTRODUCTION

Over the past decade, rodent whole-brain functional neuroimaging, particularly through functional magnetic resonance imaging (fMRI), has made significant progress in addressing both basic and applied research questions on brain function. Much of this progress has been driven by the expansion of rodent fMRI's reach to include large-scale mapping of intrinsic brain activity, often referred to as “functional connectivity”, or “fMRI connectivity” (Gozzi & Schwarz, 2016). As part of this research, the combined use of rodent fMRI with genetic modeling (Gozzi & Zerbi, 2023), chemo-optogenetics (Kim et al., 2023; Mandino et al., 2022; Menon et al., 2023; Oyarzabal et al., 2022; Rocchi et al., 2022; Wang et al., 2023; Yu et al., 2016; Zerbi et al., 2019), or advanced multimodal recordings (Cabral et al., 2023; Jung et al., 2021) has enabled the exploration of the neural mechanisms underlying brain network activity, fMRI connectivity, and behavior (Gil et al., 2024) with remarkable precision. Importantly, the discovery of plausible rodent precursors of human fMRI connectivity networks (Pagani et al., 2023; Sforazzini et al., 2014) has made it possible to directly translate pre-clinical findings to human research, revealing very encouraging cross-species correspondences (Bertero et al., 2018; Gutierrez-Barragan et al., 2024; Mandino et al., 2022; Pagani et al., 2023). Overall, rodent functional neuroimaging is strategically positioned to address several long-standing questions in modern systems neuroscience, while also facilitating the direct cross-species translation of results in biomedicine. However, despite the rapid growth and success of this approach, its implementation is not without inherent challenges. Recently, leaders in the field of rodent fMRI gathered in Rovereto, Italy, to address the unique challenges facing this area of research and to identify collaborative solutions aimed at accelerating progress over the next 5–10 years. Three macro areas of key intervention were identified that could benefit from community-fostered solutions: the adoption of awake functional brain mapping, the implementation of multimodal neuroimaging, and the standardization of data acquisition and analysis.

## 2. TOWARDS AWAKE RODENT NEUROIMAGING

Rodent functional neuroimaging relies overwhelmingly on controlled sedation. This approach has become the gold standard in rodent fMRI owing to its ease of implementation as well as the possibility of tightly controlling restraint-induced stress and imaging artifacts caused by head and/or body motion. However, a wide array of anesthetic protocols have been adopted across small-animal fMRI labs, hindering cross-lab comparisons. Moreover, seda-

tives can unpredictably interact with ongoing neural and hemodynamic activity, thus biasing the distribution and organization of resting and evoked fMRI activity (Hamada et al., 2024). The use of sedatives also restricts brain states and prevents the investigation of task-activated networks.

Recent attempts to avoid the use of anesthesia have shown promise, documenting the possibility to reliably detect fMRI activity in non-anesthetized animals habituated to the scanner (Desai et al., 2011; Gutierrez-Barragan et al., 2019; Liang et al., 2011). However, despite this initial progress, technical and interpretive challenges greatly complicate the implementation of awake rodent imaging (discussed below). For this reason, the use of controlled sedation remains a valuable experimental option that can crucially integrate and complement ongoing efforts toward the implementation of awake functional neuroimaging.

### 2.1. Controlled sedation is here to stay

There is a general agreement that controlled sedation continues to hold significance and utility due to several unique advantages. These include, for example, tight control of arousal levels and brain state, an essential requisite in chemo/optomodulation studies (Giorgi et al., 2017; Grimm et al., 2024), or in the use of peripheral sensory stimulation, in which a prolonged modulation of brain activity under quasi-stable states is highly advantageous. The use of anesthesia also plays a critical role in minimizing motion and related artifacts, resulting in higher quality data and a considerably faster and less resource intensive turnout. While sedation may influence the functional organization of certain brain networks and their relation to behavior, it also effectively eliminates the need for prolonged immobilization, and avoids potential functional impacts from repeated acclimation training. Moreover, the functional organization of brain networks appears to be largely preserved by multiple sedation regimens, resulting in functional networks that are broadly comparable to those obtained from awake animals. Furthermore, neuroimaging with anesthesia preparation in rodents remains a key avenue of investigating systems-level mechanisms underlying anesthesia-induced unconsciousness (X. Chen et al., 2024).

Notwithstanding its convenience, the use of anesthesia has its challenges. Conducting neuroimaging experiments under controlled sedation requires extremely careful consideration of the specific anesthetic mechanism employed, the desired anesthesia depth, and experimenters should be mindful of possible unpredictable interactions between anesthesia and the stimulation employed (Hamada et al., 2024) or the (patho)physiology being investigated. For example, the anesthetic states

produced by light or deep isoflurane anesthesia are very different, and commonly used gaseous halogenated anesthesia tends to accumulate in fat tissue, potentially altering anesthetic state (Gozzi et al., 2008; Sirmipilatz et al., 2022). Similarly, injectable anesthetics are also characterized by evolving pharmacological efficacy over time (Nasrallah et al., 2014). Thus, tight control and standardization of anesthesia depth are crucial in experiments comparing groups or conditions. Without this, large spurious changes in resting or evoked fMRI activity due to variations in anesthesia depth may obscure or worse, be misinterpreted as, biologically plausible effects.

In the case of experiments encompassing transgenic lines (for example, mutant versus wildtype animals), genotype-dependent differences in sensitivity to anesthesia can be probed via measurements of minimal alveolar concentration (Sonner et al., 2000). However, if differences in anesthetic susceptibility between models arise, it remains unclear how these should be dealt with. More broadly, the implementation of measurements allowing for a standardization of anesthesia depth in individual animals is of crucial importance. Anecdotally, intubation and artificial ventilation provide tighter control of anesthesia depth compared to standard nose cones and allow a more stable control of blood gas levels, although this procedure significantly increases experimental complexity (Ferrari et al., 2012). Alternatively, adjustment of anesthesia levels to reach a target respiratory frequency, or a detectable response to exogenous visual or sensory stimulation, can be used to harmonize anesthesia depth across animals (Oyarzabal et al., 2022). We, however, note that, at present, no universal quality control measure for anesthesia depth is available. Future efforts are required to establish these metrics and compile a set of best sedation practices, validated across different research sites.

To complicate matters, peripheral measurements of physiological parameters that can directly or indirectly fMRI BOLD activity, like arterial blood gas levels, or blood pressure, are technically challenging, and present species-specific constraints. For example, arterial pCO<sub>2</sub> can be non-invasively recorded in rats through the use of transcutaneous monitors (Ramos-Cabrer et al., 2005). However, this method does not appear to be reliable in mice. Similarly, arterial blood pressure requires surgical femoral artery cannulation, a procedure that is technically challenging in mice, where it requires specialized skills (Ferrari et al., 2012). To mitigate physiological variability and improve data quality, laboratories have so far employed non-invasive monitoring tools for heart rate, respiratory rate, and oxygen saturation via pulse-oxymetry. However, newcomers to the field should be aware that the implementation of these measurements is more challenging and less reliable in smaller animal species.

Researchers should also be aware that anesthetic agents may produce largely different brain states as a function of their pharmacological profile. For example, medetomidine produces waves and spindles reminiscent of NREM sleep, low-level halothane anesthesia mostly consists of high-frequency power (similar to REM sleep), while ketamine produces wake-like EEG (Gent & Adamantidis, 2017; Reimann & Niendorf, 2020). In this respect, the widespread reliance on a medetomidine-isoflurane combination in rodent studies, while useful for comparing conditions across laboratories, has the drawback of limiting fMRI investigations to a single, stereotypical electrophysiological state. Efforts should, thus be directed at widening the current repertoire of sedative regimen. More importantly, given the varying interactions that different anesthetic mechanisms can exert with different neuromanipulations, it is of paramount importance to assess how the resulting functional effects may generalize across different anesthetic regimens, and potentially to awake conditions via proof-of-concept awake studies (Gutierrez-Barragan et al., 2022; Rocchi et al., 2022).

While the possibility of reliably mapping functional connectivity networks with fMRI represents one of the most notable recent extensions of functional neuroimaging in rodents, the translational impact of this approach is not limited to resting paradigms. Sensory and opto-chemogenetic stimulations are increasingly used to uncover the neural basis of neurovascular coupling and to visualize central pathways implicated in sensory processing, with important implications for our understanding of how neural activity is translated into hemodynamic signals (Cerri et al., 2024; Gil et al., 2024). As with studies conducted at rest, a number of unresolved technical questions accompany functional stimulation studies in rodents. Key among them is the unclear influence of various anesthetic mixtures on sensory-evoked responses (Rungta et al., 2017), as well as the yet undetermined contribution of local versus nonspecific hemodynamic responses to sensory stimuli (Pisauro et al., 2016). Additionally, the confounding role of peripheral cardiovascular factors, such as stimulus-induced blood pressure changes, remains under-investigated (Gozzi et al., 2007; Reimann et al., 2018). Community efforts toward paradigm standardization and benchmarking are critically required also in this area of investigation, with initial results showing promise (Grandjean et al., 2020, 2023).

## 2.2. Navigating the complexity of awake functional neuroimaging

Despite the convenience of anesthesia, a transition to awake imaging is a desired evolution of functional brain mapping in small animals. The opportunities offered by

reliable awake functional interactions between anesthesia and different kinds of neuromanipulations, to the lack of unwanted interferences with neurovascular coupling, up to a more direct translation of fMRI findings to neuroscience methods used in awake rodents, such as calcium imaging or electrophysiology.

While convincing examples of fMRI mapping in awake rodents have been demonstrated in the past few years (Bergmann et al., 2016; Gutierrez-Barragan et al., 2022; Liang et al., 2012), the implementation of awake imaging comes with a number of foundational challenges. One of the main hurdles is animal immobilization, which is typically achieved through head-fixation or tight body restraint procedures. This process often requires surgical apposition of custom implants and time-consuming habituation to reduce stress from prolonged immobility. Additionally, the scanner environment presents its own set of stressors, including noise and vibrations from gradient operations, the novelty of the scanner, and the presence of odors left by other stressed conspecifics, predators, or reagents due to the shared use of the scanner by multiple research teams.

To date, the effect of different habituation procedures on image quality and arousal state of animals remains unclear (reviewed in Mandino et al. (2024)). The duration of habituation protocols varies widely across studies, typically ranging from 6 to 14 days. A conservative guideline suggests a period of 10–14 days for robust acclimation in a conventional fMRI setting (Mandino et al., 2024). However, shorter durations (6 to 8 days) may still be effective, particularly when key elements, such as exposure to the real scanner, are incorporated (Dinh et al., 2021; Zou et al., 2024). A critical challenge in evaluating acclimation efficacy is the inconsistent use of stress hormone measurements. These measurements are difficult to obtain using non-invasive approaches, and are further complicated by methodological discrepancies in sample collection and the absence of established reference levels in the literature. Notwithstanding these issues, acclimation procedures have been convincingly shown to substantially reduce corticosterone levels across different laboratories (Mandino et al., 2024)). This suggests that acclimation may be effective in reducing stress. However, the extent to which this reduction compares to non-restrained or freely behaving conditions remains unclear. Moreover, while habituation can effectively reduce stress, the demands of high-throughput environments where efficiency is key (such as in pharmaceutical research) can present logistical challenges. Strategies such as exposure to mock scanners and batch training can improve the feasibility of awake fMRI in these settings, but acclimation procedures remain labor-intensive and difficult to implement on a large scale.

To address these challenges, we propose three complementary approaches. First, benchmark cross-laboratory studies are required to foster standardization and to more rigorously assess the effectiveness of habituation procedures on stress and image quality. This could follow the model of a recent initiative that established a community protocol for anesthetized rat fMRI (Grandjean et al., 2023). Second, the development and optimization of free induction decay (FID)-based MRI sequences (Idiyatullin et al., 2015; Ljungberg et al., 2021; Madio & Lowe, 1995; Weiger & Pruessmann, 2019) for fMRI applications should be prioritized. Initial evidence of the convenience of this approach has been demonstrated using multi-band sweep imaging with Fourier transformation (MB-SWIFT) (Dvořáková et al., 2024; Lehto et al., 2017; Paasonen et al., 2020), followed by zero echo time (ZTE), and Steady-state On-the-Ramp Detection of INduction-decay with Oversampling (SORDINO, (MacKinnon et al., 2025) sequences. These techniques offer promising alternatives to conventional Echo-planar imaging (EPI)-based BOLD fMRI, addressing key challenges such as acoustic noise, susceptibility artifacts, and motion-related confounds, which are critical factors in awake rodent fMRI. We anticipate broader adoption of these techniques in the coming years. However, these alternative fMRI sequences face their own challenges, including less-well understood contrast mechanisms compared to BOLD, limitations in sequence and reconstruction generalizability, and constraints in imaging resolution and sensitivity. Moreover, because EPI remains the most widely used fMRI method in humans, understanding the physiological basis of EPI-based fMRI signals will remain a focus of rodent functional neuroimaging. Finally, precise in-scanner control of rodent behavior and physiology is essential. This may involve the development, temporal alignment, and standardization of sensors to monitor a range of behaviorally and physiologically relevant variables, including head motion, breathing, facial expressions, and pupil size (Hike et al., 2024).

A more fundamental challenge related to awake whole-brain functional neuroimaging lies in determining the significance of the actual brain states achieved in non-compliant, scanner-habituated animals like rodents, which are known for engaging in almost continuous behavioral activity (like sniffing, whisking, etc. (Winder et al., 2017)). When applied to the implementation of resting-state fMRI, the question that arises is thus whether rodents are ever truly “at rest”. This problem does not pertain to fMRI specifically. A number of influential electrophysiological or optical imaging studies have, indeed, shown that awake head-fixed mice continually engage in overt (for example, locomotor activity), as well as more nuanced volitional behaviors and motion outputs



(like whisking, or facial movements, etc.) (Stringer et al., 2019; Winder et al., 2017). The issue at hand does not solely pertain to the adverse effects of motion on signal quality. Rather, it encompasses the broader possibility that the resulting functional signals may significantly, or even primarily, reflect ongoing behavioral or motor outputs. To address this issue, recent investigations of “resting brain activity” in awake head-fixed mice have encompassed the concatenation of calm periods among motile bouts (Bertolo et al., 2023). However, this approach limits usable recordings to only a small fraction of the acquired time series. Complicating matters further, behavioral and motion outputs in head-fixed mice tightly covary with peripheral indexes of arousal such as pupil diameter and explain infraslow dynamics in neural signals relevant to the interpretation of resting-state fMRI (Stringer et al., 2019). Moreover, neurovascular coupling appears to evolve as a function of arousal state (Meyer-Baese et al., 2024).

A pressing question that the field of awake neuroimaging must address is whether and how the ever-evolving arousal state of awake head fixed rodents, including activity recorded in movement-free bouts, compare to the “quiet wakefulness” that characterizes most human fMRI studies. In this respect, the possibility that scanner habituated animals are in a higher arousal state than human counterparts should always be considered when interpreting the results of rodent neuroimaging studies in the context of translational research. Furthermore, high-arousal states may confound stimulation studies (like those using optogenetics) by eliciting unintended motor or interoceptive signals that might mask or confound those generated at the primary stimulation site. Overall, a trans-disciplinary understanding of the impact of arousal and volitional movement on recordings of “resting” brain activity is a key priority of functional neuroimaging in small animals. While we await to obtain a deeper understanding of this phenomenon, researchers transitioning to awake imaging should recognize and account for this central problem.

The implementation of sensory stimulations or task-based fMRI in awake, behaving rodents is at present highly problematic, mostly a consequence of high susceptibility of fMRI to apparent (B0-related) motion-induced artifacts, and the constraints related to the limited available space within the scanner bore. We expect advances in FID-based, center-out encoding fMRI techniques (Dvořáková et al., 2024; Paasonen et al., 2020) to facilitate this endeavor by minimizing acoustic noise interference and susceptibility to motion artifacts, thus enabling the implementation of more complex tasks (MacKinnon et al., 2025). There is consensus in the field that stimulation- and task-based

functional neuroimaging are highly complementary to resting-state mapping, and both should be pursued to enhance the translational impact of small-animal functional neuroimaging. Prompted by the limitations of stimulation or task-based fMRI in awake animals, a growing portion of the imaging community is now considering alternative neuroimaging methods to relate large-scale activity to behavior. In this context, functional ultrasound imaging (fUSI) has shown the greatest promise, owing to its excellent portability and its ability to record whole-brain patterns of functional activity during complex behavioral tasks (El Hady et al., 2024). Although still in its infancy, fUSI also offers a notable advantage over fMRI: its substantially lower cost. This is particularly relevant in the context of preclinical MRI systems, where a monopolized market (Freeman & Morris, 2015) has led to steadily rising operational costs over the past two decades. As a result, there is a genuine concern that preclinical MRI may become economically unsustainable, even for well-funded laboratories and institutions. The preclinical community, with the support of their hosting institutions, should unite in lobbying leading MRI scanner manufacturers to make them aware of these concerns, and to ensure that this technology remains broadly accessible and economically sustainable.

## 2.3. Towards multimodal functional neuroimaging

### 2.3.1. Chemo- and optogenetic-fMRI

One of the most important contributions of rodent functional neuroimaging to the broader neuroscience community is the ability to probe how cell-type specific manipulations can affect large-scale patterns of brain activity. The combination of fMRI with chemogenetics or optogenetics (chemo-fMRI (Giorgi et al., 2017), opto-fMRI (Kahn et al., 2013; J. H. Lee et al., 2010)) represents an investigational platform that is unique in its ability to probe causality between neural events at different investigational scales. Importantly, the causal nature of these approaches serves as a key mechanistic complement to the inherently correlational neuroimaging approaches available in humans (Pagani et al., 2023; Rocchi et al., 2022; Siddiqi et al., 2022).

Chemo- and optogenetic-fMRI in rodents have become increasingly prominent over the past few years (Bernal-Casas et al., 2017; Cerri et al., 2024; Chan et al., 2017; X. Chen et al., 2019; Y. Chen et al., 2020; Choe et al., 2018; Christie et al., 2013; Cover et al., 2021; Decot et al., 2017; Desai et al., 2011; Ferenczi et al., 2016; Giorgi et al., 2017; Gozzi et al., 2010; Grandjean et al., 2019; Grimm et al., 2021; Hamada et al., 2024; Han et al.,

2022; Helbing et al., 2024; Ioannas et al., 2022; Iordanova et al., 2015; Jung et al., 2021, 2022; Kahn et al., 2011, 2013; Kargl et al., 2020; Kim et al., 2023; J.H. Lee et al., 2010, H. J. Lee et al., 2016; J. Y. Lee et al., 2022; Leong et al., 2016, 2021; N. Li et al., 2011; Z. Li et al., 2023; Y. Li et al., 2024; Liang et al., 2015; Mandino et al., 2024; Markicevic et al., 2023; Menon et al., 2023; Moon et al., 2021; Nakamura et al., 2020; Oyarzabal et al., 2022; Peeters et al., 2020; Rocchi et al., 2022; Roelofs et al., 2017; Ryali et al., 2016; Salvan et al., 2021; Sanda et al., 2024; Schmid et al., 2017; Takata et al., 2018; Tu & Zhang, 2022; Vo et al., 2023; Wang et al., 2023; Wei et al., 2021; Weitz et al., 2015; Yu et al., 2016; Zerbi et al., 2019; Zou et al., 2024). Notable examples of the application of these methods include the possibility of non-invasively dissecting large-scale networks and circuits via targeted optogenetic stimulations and inhibitions (Jung et al., 2022; J. Y. Lee et al., 2022). The application of this paradigm to sensory stimulations can help identify dysfunctional circuits and determine potential therapeutic targets in disease models (J. Y. Lee et al., 2022; Lee et al., 2024). The growing utilization of these methods has enhanced our ability to identify and control for technical limitations and confounding artifacts related to their implementation, including heat- or visually-induced artifacts from light stimulation (Schmid et al., 2017), as well as off-target hemodynamic effects produced by commonly used chemogenetic ligands (Giorgi et al., 2017; Zerbi et al., 2019). As these approaches become more accessible, future research needs to be directed at determining how these manipulations affect and interact with different brain states, both in anesthetized and awake conditions, and how these are impacted by peripheral confounds produced by these manipulations. In this respect, the implementation of surrogate measures of arousal, such as pupillometry, represents a key extension to chemo- and opto-fMRI recordings. Opportunities also exist for introducing standardized protocols and experimental designs such that the physiological signals and peripheral effects elicited by the chemo- and optogenetic manipulations can be benchmarked across laboratories. These investigations should include measurements of respiratory and peripheral cardiovascular parameters such as heart rate. We also note here that in both chemo- and opto-fMRI studies, the role of stimulus-evoked arterial blood pressure changes has been for the most part neglected, despite its established confounding contribution to central hemodynamic measures of brain activity (Ferrari et al., 2012). More importantly, it is also crucial that the field comes to a general agreement about the proper design and validation of chemogenetic-fMRI. A major confounding factor is the lack of electrophysiological validation of target chemogenetic manipulations in the spe-

cific brain area, and under the specific experimental conditions of the fMRI experiment. Such validation is a necessary prerequisite for interpreting chemo-fMRI results, given the highly variable effects chemogenetic effectors can produce across brain regions, species, and promoters (Kovács et al., 2024; Rocchi et al., 2022). We also note that opto-fMRI cannot be straightforwardly implemented with standard radiofrequency cryorefrigerated coils, because of limited space. There is, thus, a need for advanced customized setups and/or fiber designs that can be used in conjunction with cryocoil technology (Grimm et al., 2022; Zou et al., 2024).

### 2.3.2. Multimodal recordings of brain activity

Multimodal recordings of both spontaneous and stimulus-evoked fMRI activity can critically advance our elusive understanding of these phenomena both at the mesoscopic (Rungta et al., 2017) and large-scale level. This area of investigation is of strategic importance given the widespread use of fMRI to indirectly infer neural activity in human cognitive neuroscience both in task-evoked and in task-free settings.

Notable examples of the use of small-animal fMRI to uncover the neurovascular cascade underlying the BOLD response have been reported in recent years via the combination of multimodal optical and/or electrophysiological recordings (Ceri et al., 2024; Vo et al., 2023). The initial extension of these approaches to investigate the underpinnings of large-scale fMRI coupling has also been recently described (Rocchi et al., 2022; Tu & Zhang, 2022). In this respect, emerging hybrid imaging technologies such as PET/fMRI hold great promise, as they offer the unique capability to enhance fMRI with metabolic and molecular insight (Wehrl et al., 2013). While PET/MRI has not yet been extensively applied to investigate the bases of fMRI connectivity in rodents, this approach could help clarify the relationship between neuronal activity and specific metabolic or molecular processes, including the contribution of intrinsic neurotransmitter activity (Haas et al., 2024; Ionescu et al., 2025; Millevert et al., 2023). Similarly, multimodal fMRI may now uniquely leverage progress in the miniaturization of electrophysiological probes, and the rapidly increasing repertoire of fluorescent encoders (Sabatini & Tian, 2020) to provide an unprecedented multifaceted dissection of the neural and hemodynamic processes underlying fMRI. Recent technological advancements also include the combination of fMRI with widefield optical imaging, an approach that may uniquely cross-link neural and hemodynamic signals at the meso- and macroscale (Lake et al., 2020).

As promising as these approaches are, the entrance barrier for these methods in terms of cost, equipment, and

technical skills required for data integration is still substantial. While the level of complexity of electrophysiological and optical setup differs significantly, the implementation of multimodal fMRI still relies on the use of customized parts and apparatuses that required dedicated know-how, and that only the best-equipped labs are in a position to implement via dedicated personnel or workshop units. The analysis of the ensuing signals and their denoising (like gradient filtering in electrophysiology, hemodynamic correction in calcium imaging, co-registration in widefield imaging) are also a complex endeavor that at present does not seem to be readily exportable across labs. Given the pioneering stage of this research area and the lack of standardized solutions, the preclinical community should aim to promptly share relevant information (including design blueprints, guidelines, code, and procedures) in open repositories to facilitate replication by capable laboratories. The organization of theoretical and hands-on training courses, possibly covering other areas of functional neuroimaging, would also greatly boost the adoption of these methods. To drive this forward, we need to establish a growing community base that includes all major contributors in the field (including the many who were not part of this initial impromptu working group), to create a larger and more authoritative network to guide progress and standardization.

## 2.4. Unifying standards for data acquisition and analysis

### 2.4.1. Data acquisition protocols

As emphasized throughout this manuscript, advancing rodent functional neuroimaging requires a concerted effort toward the standardization of procedures. The recent adoption of common data curation and sharing standards (for example, Brain Imaging Data Structure – BIDS (Gorgolewski et al., 2016)) paves the way for similar standardization efforts at the data acquisition and experimental design stage.

All the participants in this working group are familiar with multiple instances of inadequately labeled datasets and scantily described experimental methods. To address this, we propose establishing a consensus on minimal data and metadata descriptors (including MRI coils, sequences, animal cradle design) and developing software tools to automate data curation, including parsing metadata to organize datasets into the BIDS format. We also advocate strict adherence to ARRIVE guidelines for animal experiment reporting (Percie du Sert et al., 2020). By improving reporting practices and identifying a rational set of optimal parameters through cross-laboratory initiatives (Grandjean et al., 2020), we anticipate that the

field will naturally transition toward consensus on a set of benchmarked experimental procedures.

The advantages of a transition toward the use of standardized data acquisition protocols are substantial. Firstly, standardization can greatly facilitate transfer of know-how, and comparison of results via a cross-laboratory data benchmarking based on existing literature. Standardized protocols also allow for published datasets to be aggregated into multi-center studies to increase statistical power (Zerbi et al., 2021). By minimizing the need for extensive piloting, standardized data acquisition procedures can also significantly reduce the workload for experimenters. Furthermore, consensus protocols can help increase confidence in reported findings, as reviewers and readers can compare baseline metrics with previously reported values to verify data quality. Finally, standardized data acquisitions may facilitate the development of relevant software and robust exploratory pipelines.

Notwithstanding the virtues of standardized protocols, this workgroup acknowledges that “standardization is a tool, not a policy”. As such, the application of consensus protocols is not meant to be dogmatic, nor should it constrain the experimental needs or creativity of researchers. Standardization guidelines should rather be viewed as recommendations, particularly in instances where no rational basis favors one particular set of parameters. They may also serve as helpful directives during the initial stages of projects. Additionally, standards should not supplant pilot studies, the outcomes of which are encouraged to be published as supplementary materials.

### 2.4.2. Analysis pipelines

There is wide consensus among investigators of this working group on the importance of developing end-to-end, user-friendly, and open-source preprocessing pipelines tailored for rodent functional neuroimaging analysis. So far, the field has mostly relied on in-house implementations built on processing tools developed for human neuroimaging (like AFNI, FSL, etc.). However, these analytic tools are not always directly back translatable to rodent fMRI data and, as such, require workarounds to be used.

While most investigators agree that a minimal processing approach might be sufficient for rodent functional neuroimaging data (Grandjean et al., 2020, 2023), establishing empirical, data-driven quality metrics could significantly enhance the reliability of data quality assessments across laboratories. Standardizing pipelines and quality assurance metrics will not only improve the rigor and reproducibility of findings, but also encourage researchers from other fields to explore rodent neuroimaging.

Recently, progress has been made toward the development of pipelines tailored to the requirements of rodent neuroimagers (Desrosiers-Grégoire et al., 2024; Zerbi et al., 2015). One notable example is the RABIES (Desrosiers-Grégoire et al., 2024) suite, which stands out for its customizability and extensive reporting of quality metrics. However, the maintenance and curation of such open-source consensus pipelines will critically depend on cross-laboratory initiatives aimed at funding and supporting these efforts. Additionally, the impact of commonly used site-harmonization methods employed in human neuroimaging (for example, COMBAT (Orlhac et al., 2022)) has yet to be evaluated within the rodent community. This family of methods needs to be tested and benchmarked against current preprocessing pipelines in rodents.

Furthermore, defining agreed-upon processing and quality assessment guidelines is particularly challenging in the field of fMRI connectivity, where the absence of a ground truth for distinguishing specific from spurious functional connectivity complicates pipeline benchmarking in both humans and rodents. Initial efforts to define empirical data quality metrics have been proposed (Desrosiers-Grégoire et al., 2024), but further benchmarking of pipelines against physiological and anatomical data is needed. To this end, previous studies have compared the topography of functional connectivity networks to the Allen Brain Institute's mesoscale connectome (Coletta et al., 2020; Grandjean et al., 2017; Whitesell et al., 2021), offering potential anatomical validation for fMRI connectivity networks mapped in conditions of low arousal or anesthesia, where the overlap between structure and function is maximal (Gutierrez-Barragan et al., 2022). As our understanding of the physiological basis of fMRI continues to grow, the extension of cross-validation methods to include complementary readouts, such as multi-site electrophysiology readouts, may help differentiate bona fide functional activity from artifactual or spurious signals (Lake et al., 2020; Rocchi et al., 2022).

### 3. CONCLUSIONS

We outlined the exciting potential of rodent whole-brain functional imaging as well as the critical need to address key challenges on the path to a more impactful contribution of this emerging field of research. By fostering collaboration and open science practices, the field can overcome hurdles related to data acquisition consistency, awake imaging complexities, and the extrapolation of results across species (Gutierrez-Barragan et al., 2024; Pagani et al., 2023). Standardization efforts and the development of robust, user-friendly data acquisition and data analysis pipelines will be instrumental in ensuring

data quality and reproducibility. Furthermore, adopting multimodal approaches that combine fMRI with other techniques offers great promise for advancing our understanding of brain function. Looking ahead, sustained investment from neuroscience initiatives and funding bodies is crucial to propel this emerging field of translational research forward. Through collaboration and resource sharing, the rodent functional neuroimaging community can unlock the full potential of this powerful tool, significantly advancing our understanding of how brain activity unfolds at the macroscopic level.

### ETHICS

This perspective article does not present any new data or experimental findings; therefore, no ethical approval or informed consent is required.

### DATA AND CODE AVAILABILITY

This perspective article does not report original data or findings, nor was any bespoke code written or used in its preparation.

### AUTHOR CONTRIBUTIONS

A.G. and A.S. wrote the first draft of the manuscript. All authors contributed to subsequent manuscript editing and revision.

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## DECLARATION OF COMPETING INTEREST

The authors declare no conflict of interest.

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