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Toward next-generation primate neuroscience: A collaboration-based strategic plan for integrative neuroimaging

The PRIMatE Data and Resource Exchange (PRIME-DRE) Global Collaboration Workshop and Consortium*,*
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Open science initiatives are creating opportunities to increase research coordination and impact in nonhuman primate (NHP) imaging. The PRIMatE Data and Resource Exchange community recently developed a collaboration-based strategic plan to advance NHP imaging as an integrative approach for multiscale neuroscience.

BACKGROUND

Nonhuman primate (NHP) neuroimaging can address critical barriers in characterizing brain organization, function, development, and variability (Milham et al., 2018a; PRIMatE Data Exchange (PRIME-DE) Global Collaboration Workshop and Consortium, 2020). Interfacing with complementary approaches, it can (1) contribute to an integrative, multiscale understanding of neural circuitry and mechanisms underlying behavior, cognition, and mental health; (2) bridge gaps between "ground truths" (e.g., neuronal tract tracing and neural recordings) and MRI-based estimates of structural and functional connectivity; and (3) benchmark circuit-level perturbation techniques that provide causal insights and bases for novel neurotherapeutics (Klink et al., 2021). When combined with neuroimaging of other species, NHP imaging can improve our understanding of brain evolution and translate neuroscientific advances between rodents and humans.

Recognizing the value of data sharing and open science practices in human neuroimaging (Milham et al., 2018b), recent efforts now extend to NHP imaging. The PRIMatE Data (Milham et al., 2018a) and Resource (Milham et al., 2018a; Messinger et al., 2021) Exchanges (PRIME-DREs), along with the accompanying biannual Global Collaboration Workshops (GCWs), were launched to accelerate progress in NHP neuroimaging and promote a culture of collaboration. The inaugural GCW brought together global investigators to assess needs (Milham et al., 2018a; PRIMatE Data Exchange (PRIME-DE) Global Collaboration Workshop and Consortium, 2020; Messinger et al., 2021) on topics including data collection protocols; animal welfare and ethics; intellectual property; data standards, quality assessment, and analytic pipelines; and paradigm design. It also seeded collaborations focused on common challenges and solutions to key technological, procedural, and analytic issues (*NeuroImage* special issue).

We report on a strategic plan of broad neuroscientific relevance formulated by the PRIME-DRE community during the second GCW (April 2021), attended virtually by 200+ investigators. It includes both short-term and long-term missions, organized around three strategic objectives and several cross-cutting priorities (Figure 1).

PRIME-DRE STRATEGIC PLAN

- Vision: obtain an evolutionarily informed, multimodal, multiscale understanding of the primate brain to guide next-generation scientific advances and therapeutics.
- Mission: accelerate translation between NHP and human neuroscience by transforming NHP neuroimaging into a more collaborative and reproducible field. This involves widespread sharing of (1) data linked to digital, multimodal, three-dimensional (3D) atlases for the broader range of NHP species; (2) methods and tools for mapping among species, including humans; and (3) visualization and analysis tools that can facilitate comparison between rodent, NHP, and human data.

Strategic objective #1: Improving NHP neuroimaging data quality, consistency, and interpretability

Relevance

NHP neuroimaging has achieved many methodological advances, but these sometimes propagate slowly. Greater awareness and openness of methods and tools will accelerate propagation. This can be achieved through robust benchmarking, establishing best practices, advancing user-friendly tools, and generating training materials and opportunities.

Program of work

1. Improve data quality and consistency. Challenges in standardizing NHP scanning include differences in hardware, brain sizes, and physiological state. MRIs are acquired on both human 3T and preclinical (>3T) (Autio et al., 2021) scanners depending on availability and species size. Scanning NHPs requires custom hardware (e.g., special RF coils, species-specific head holders), particularly when combined with electrophysiological, pharmacological, and neurovascular manipulations. Anesthesia and awake scanning protocols would benefit from sharing experiences and benchmarking to establish evidence-based best practices. The same applies to signal-enhancing contrast agents, which require species- and agent-specific procedures, dosing, and scanning parameters.

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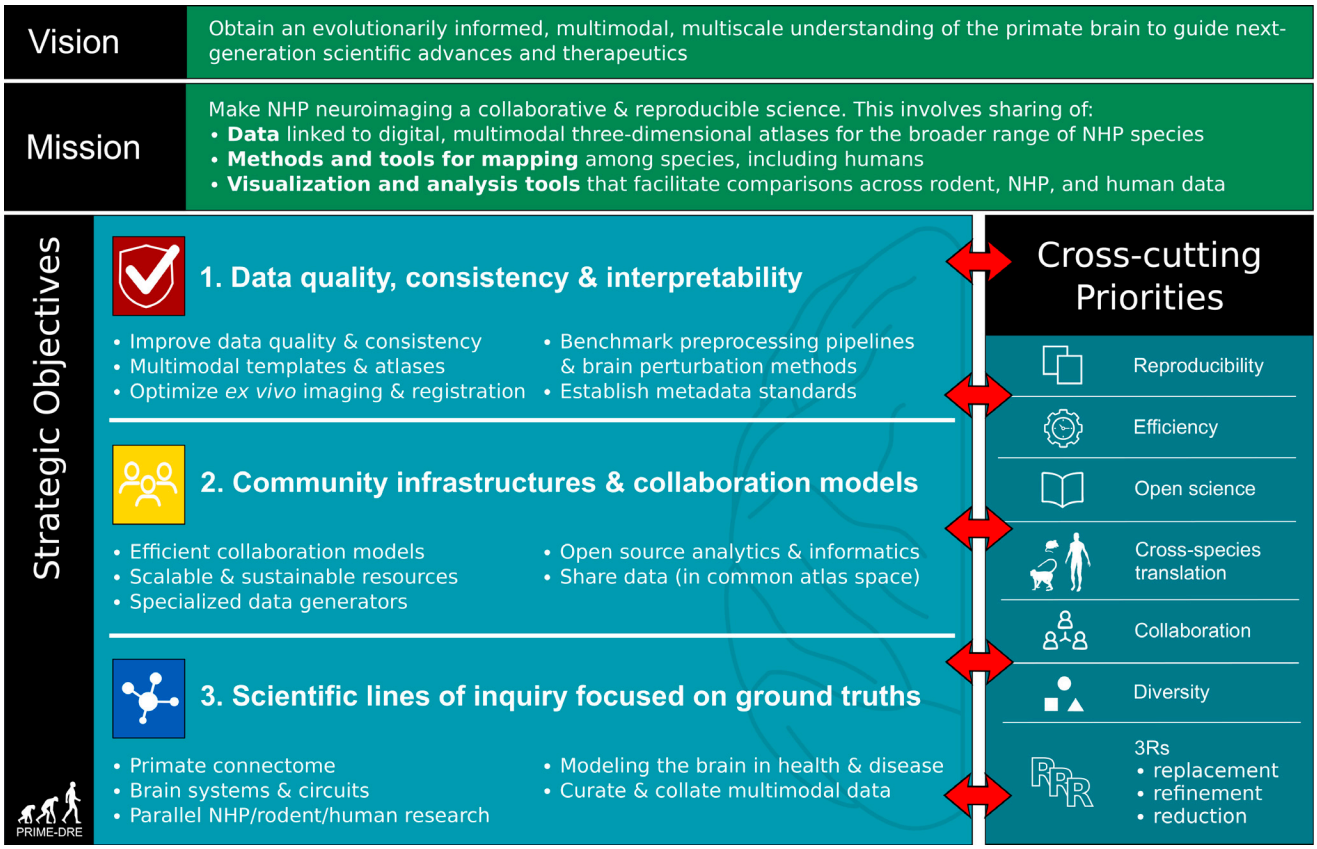

Figure 1. Strategic plan for nonhuman primate neuroimaging

The PRIME-DRE community here stipulates its vision, mission, and three strategic objectives, along with the plan of work and cross-cutting priorities required to achieve the objectives. See the main text.

Efforts to harmonize human data collection across sites, hardware, and scanning protocols will also benefit NHP imaging (Autio et al., 2021). NHP neuroimaging would benefit from broader adoption of slice-accelerated imaging (for higher-resolution fMRI and diffusion MRI [dMRI]) and high-resolution structural MRI (T1w, T2w) to align multimodal data (e.g., electrophysiological recordings, tracer injections, neurovascular, and activity perturbations) to state-of-the-art brain atlases. Rather than a "one-size-fits-all" approach, the community can collaboratively develop evidence-based standards for data collection and reporting (including animal preparation) (Autio et al., 2021; Basso et al., 2021; Messinger et al., 2021). Benchmarking acquisition protocols and procedures will help account for site-based inter-animal and cross-species variation, accelerating standardization. Evaluation of data reproducibility and bias across protocols should be improved by optimizing anesthesia or behavioral training regimes and by using RF coils with more homogeneous coverage and high signal/noise (Autio et al., 2021).

2. Improve and benchmark preprocessing pipelines. Preprocessing methods in human MRI have dramatically improved to (1) enhance signals; (2) reduce noise, artifacts, bias, and distortions; (3) improve alignment across modalities and subjects; and (4) augment the fidelity of data representations and metadata relative to brain geometry. Increasingly, toolmakers are developing end-to-end pipelines for preprocessing (Messinger et al., 2021) (e.g., HCP toolboxes, among others).

However, species-specific pipelines require customization rather than "off-the-shelf" application of pipelines originally optimized for human data. Various solutions have been developed for preprocessing steps (Messinger et al., 2021) (e.g., brain extraction, co-registration), although often in isolation and with insufficient benchmarking. Minimum standards for NHP preprocessing pipelines are progressing, including surface segmentation, subcortical extraction, and analytics (Milham et al., 2018a; Autio et al., 2021). Further, benchmarking of existing preprocessing step(s) can minimize duplicated effort and increase reproducibility. Standardized "benchmarking datasets" should be identified for straightforward comparison across analytical methods. Pipelines that work across species (e.g., by swapping brain templates [Messinger et al., 2021] and size parameters) will enable fair comparisons using similar preprocessing workflows.

3. Improve NHP multimodal templates and atlases. Brain templates are "average" or representative brains that provide a common spatial framework for combining individual subject data. They can be expressed in 3D stereotaxic coordinates, cortical surface-based coordinates, and hybrids—"grayordinates" (Autio et al., 2021; Hayashi et al., 2021). Brain atlases are often linked to a particular spatial reference frame and provide maps of

neuroanatomical subdivisions, serving to link NHP neuroimaging with other modalities. Currently, atlases differ by parcellation, nomenclature, coordinates, and representation of individual variability (Messinger et al., 2021). Recent progress in marmoset neuroinformatics has achieved a common parcellation scheme (Messinger et al., 2021; Majka et al., 2021), which will benefit from further validation and extension to other species.

Our goals include (1) advancing robust parcellations that take into account different sources of variation (e.g., inter-individual, methodological); (2) developing multimodal parcellations based on neuroimaging, as well as histology, and establishing robust evaluation methods and criteria; (3) improving individual alignment to atlas(es) by developing transformations between different atlases, coordinates, methods, developmental stages, and species (RheMAP; https://prime-re.github.io/templates_and_atlases/rhemap.html); and (4) creating probabilistic, multimodal ''supra-atlases'' by integrating information across atlases and parcellations, leading to neuroanatomically registered knowledge libraries for interpreting data and generating novel hypotheses.

4. Optimize ex vivo imaging and registration methods. *Ex vivo* imaging includes postmortem MRI or optical tomography scans and histological microscopy. Accurate co-registration of *ex vivo* MRI and histology with *in vivo* MRI is needed to link macroscale and microscale features (e.g., cytoarchitecture, gene/receptor expression, tracing) and to compensate for deformations occurring during brain removal and fixation. A systematic examination of brain deformation across large, globally shared samples could help refine *ex* to *in vivo* registration algorithms, decrease manual effort, and help align histological section stacks to native and template MRI (Hayashi et al., 2021; Majka et al., 2021).

5. Establish metadata standards. Effective communication of sample composition (e.g., demographics, behavior, genetics, histology, rearing history), data acquisition (e.g., imaging acquisition parameters/protocols), and organization procedures are critical to data sharing, transparency, and reproducibility. A blueprint for adoption of the BIDS (Brain Imaging Data Structure) metadata standard to NHP imaging was generated (Poirier et al., 2021). Refinement of this standard and generation of tools to support its use and validation will facilitate broad adoption, especially if guided by the FAIR principles for data management (https://www.go-fair.org/fair-principles/).

6. Benchmarking brain perturbation methods. A growing array of methods has emerged for system- and circuit-level brain perturbation, including activation or deactivation by transcranial (e.g., electrical, magnetic, focused ultrasound), invasive (e.g., deep brain microstimulation, near-infrared optical stimulation, chemical), physiological (e.g., hypercapnia, anesthesia), and/or genetic (e.g., chemogenetics, optogenetics) (Klink et al., 2021; Poirier et al., 2021) approaches. Collaborative benchmark studies will be crucial to rigorously compare methods, preferably in the same animals and across laboratories. Additionally, computational modeling can predict effects with untested parameters and guide refinement of perturbation techniques and parameters (Klink et al., 2021). Complementary methods should be used to evaluate and benchmark perturbation effects (e.g., fMRI, laminar and ultrahigh-density neurophysiological recordings).

Strategic objective #2: Build community infrastructures and collaboration models

Relevance

Widespread collaboration with increased transparency, greater efficiency, and reduced redundancy may dramatically accelerate delivery on the proposed scientific vision and mission. New collaborative models should be established, aided by a robust infrastructure for standardized data acquisition and analysis.

Program of work

1. Efficient collaboration models. The GCW community agreed to (1) promote the parallelization of resource-intensive experiments, which can accelerate progress by distributing time and expense of behavioral training and data collection across labs; (2) improve coordination and awareness of efforts across laboratories to reduce redundancy and harmonize data acquisition; (3) incentivize and credit researchers for collaborative data generation and analysis, currently underappreciated by promotion committees. Software- and informatics-based solutions that promote communication, collaboration, and recognition will be particularly important.

2. Scalable and sustainable resources. PRIME-DE and PRIME-RE (Messinger et al., 2021) are grassroots initiatives that demonstrate the feasibility and value of community resources for sharing data (raw and processed), tools, and knowledge. However, they are not yet sustainable, scalable platforms. Future efforts will benefit from (1) adopting existing informatics infrastructure for data sharing, (2) generating best practices for sharing, (3) decentralizing and incentivizing data sharing, (4) obtaining funding agency support for global community infrastructures (including development, maintenance, and use), and (5) implementing ethical structures to guide institutional exchanges of animals (when appropriate) or tissue (e.g., for histology, slice physiology) and the reuse of data.

3. Specialized data resources. Some types of data would be broadly useful but are most efficiently collected at a limited number of sites because of specialized equipment or skills (e.g., ultrahigh field magnets, cutting-edge brain perturbation techniques, multimodal/multiscale recording capabilities, histological/anatomical expertise), high-throughput data acquisition, rare species, or specific age ranges. Investment in community resource datasets and coordination of activities among sites with specialized resources will collectively increase data access and scientific yield.

4. Open-source analytic and informatics software. The complexity of NHP imaging analysis necessitates investing in sharing of analytic tools to promote transparency, reproducibility, and scalability to avoid redundancy and entry barriers for new investigators (Messinger et al., 2021). To further break down research silos, the development of open-source end-to-end analysis software solutions that embody best practices (e.g., quality control steps) and necessitate standards (e.g., metadata) is essential. When possible, solutions developed in human and rodent imaging should be leveraged to avoid duplication and support cross-species linkage. Greater focus on software applications that facilitate integration and visualization of multimodal data is essential to achieve multiscale brain perspectives.

5. Share existing datasets registered to a common atlas. Existing NHP datasets acquired over decades provide uniquely valuable resources. However, such data are typically available only in summary or descriptive form in individual reports (e.g., lesion, recording sites, histology, tracing); in some cases, raw data have been shared (e.g., histological collections or paper records). Preserving, curating, and sharing such data is needed, particularly immunostaining and tract tracing. Once aligned to modern atlases, these will be valuable comparative resources that advance the 3Rs (replacement, reduction, and refinement in animal experimentation).

Strategic objective #3: Advance scientific lines of inquiry focused on achieving ground truths

Relevance

NHP research offers access to ground truths regarding brain structure and function using techniques unavailable in humans and/or for which rodents may be suboptimal evolutionary models. Such data are critical to inform multiscale, mechanistic, and/or biophysical models that can facilitate translation to future neurology and psychiatry applications. Central will be mechanistic lines of inquiry for key domains of brain function (e.g., sensation, perception, movement, cognition) that incorporate evolutionary change, development, aging, behavioral adaptability, and neural plasticity. Elucidation of robust multiscale models will require leveraging multimodal data and a growing array of tools for establishing and evaluating correlational and causal relationships.

Program of work

1. Primate connectome advances. Obtaining a multiscale perspective on the wiring diagram of the brain and its functional interactions remains a central goal in neuroscience. In humans, MRI-based estimates of structural connectivity (from dMRI) and functional connectivity (from fMRI) deviate markedly from ground truth anatomical connectivity, owing to their spatial resolution, artifacts, noise, and bias. A promising strategy here is to estimate connectivity from high-quality fMRI and dMRI data in NHPs and to relate these to anatomical connectivity derived from tract-tracing studies (Autio et al., 2021; Majka et al., 2021), which provide gold-standard graded and directional connectivity data. Systematic retrograde tract-tracing efforts in macaques and marmosets are on course to map their mesoscale connectomes (Hayashi et al., 2021; Majka et al., 2021). While anatomical studies provide a type of ground truth, they do not portray the functional efficacy (weights), prominence of activation or the complexities in circuit activation, such as the push-pull of opposing circuits. In this regard, functional tract tracing at laminar resolution, such as fMRI connectomes based on focal stimulation, could provide a complementary view of circuit function dynamics (Klink et al., 2021). Importantly, elucidating the principles of allometric scaling of connectivity and parcellation will aid translation between NHPs and humans.

2. Brain systems and circuits. There is tremendous scientific interest in modeling brain networks across cells, circuits, and systems. A coordinated effort around fundamental questions within systems neuroscience may provide answers at different scales and derive unprecedented insights on general principles. Examples include feedforward and feedback interactions, layer- and cell-specific approaches, and perturbation studies. Such principles have been described as connectivity motifs that reflect common modes of information distribution and integration. Identification of such motifs might lead to a systematic and mathematical construct for representing information in biology, a prospect that would impact the fields of artificial intelligence and neuromorphics. Cross-species data will shed light on whether such principles are evolutionarily conserved. Development and aging will crosscut evolutionary insights.

3. Coordinated experiments bridging NHP, rodents, and humans. Integrating NHP data and analytics with rodent and human open data initiatives will allow us to break through currently untestable scientific questions and identify which aspects of the human brain can be best modeled in different species. Coordinating analysis and experimentation will lead to new hypotheses and scientific questions—particularly for efforts to understand how genetics and environmental factors influence brain mechanisms underlying complex behavior. For example, coordinated acquisition of multimodal longitudinal imaging data in rodents and NHPs, together with controlled behavioral, pharmacological, and genetic manipulations, would facilitate exploration of brain processes underlying healthy aging and resilience.

4. Modeling the brain in health and disease. Computational modeling generates formal, falsifiable hypotheses. Connectome-based models can be integrated with neuroimaging and other metadata and causally tested with brain perturbation. It is critical to obtain increasingly detailed multimodal data in typical and perturbed conditions. One aspect of brain organization yet to be incorporated in neurological, neurosurgical, and psychiatric treatment is the underlying mesoscale specificity of brain circuits. The advent of multiscale mapping methods, combined with focal scale perturbation, may enable intervention in a highly precise and patient-specific manner (Klink et al., 2021). Such improved precision would substantially impact models of circuit perturbation. Additionally, biophysical modeling of neuroimaging data will improve and benefit from increased validation testing. The development of biophysically realistic models of cognitive functions parallels efforts to advance fMRI in NHPs performing cognitive tasks. Future efforts to uncover the distributed mechanisms underlying cognitive functions *in vivo* and *in silico* will benefit from cross-community interaction and collaboration.

Cross-cutting priorities

Several guiding principles emerged during formulation of this strategic plan, which should be maintained as priorities across all strategic objectives to ensure their success. They include: reproducibility, efficiency, open science, cross-species translation (toward both humans and rodents), interdisciplinary collaboration, expanded participation and diversity among investigators, and attention to the 3Rs.

How will success be measured?

Defining specific metrics of success is premature. However, we can identify changes that would signify major progress. For example, strategic objective #1 will provide a growing armamentarium of standardized, high-quality data and processing and analysis tools that are well characterized with respect to validity, reliability, utility, and accessibility and their relative positioning. Strategic objective #2 will yield a research culture that

increasingly values collaboration and has the data, informatics, and analytic platforms required for its implementation, including tools for ensuring recognition of contributions. Strategic objective #3 will resolve key questions about the primate connectome, establish more powerful translational pipelines to rodents and humans, advance mechanistic system- and circuit-level information, and lay a foundation for future secondary data analysis and next-generation innovations. Progress will be evaluated during (1) triannual PRIME-DRE video conference calls, each focused on a specific strategic objective and maintaining broader community input via surveys/discussion, and (2) biennial GCWs. PRIME-DRE will also establish a registry of projects relevant to each strategic objective and program of work, which theme leaders from the GCW will help maintain. There will be an emphasis on operationalizing concepts, such as benchmarking, and developing collaborative projects, work, and follow through.

Funding strategies and models

Achieving this plan will depend upon major investments by funding agencies and financial stakeholders. Traditional funding awards, focused on individual investigators or small collaborations, can support the various programs, although in a piecemeal fashion. Their efficiency and collective impact will depend on the mutual coordination of awards (e.g., planning of designs, standardized protocols) and commitments to rapidly and openly sharing the data and resources generated in standardized ways. The latter is crucial for minimizing redundancy and promoting transparency and reproducibility. While funding agencies can provide such coordination and impose sharing mandates, the human imaging community's experiences emphasize the need for investigator buy-in. To this end, the growth and enthusiasm surrounding PRIME-DRE signals an increasing readiness of investigators to (1) work more collectively with existing data, methods, and analytical tools; (2) collect (meta)data and develop tools with a mindset toward sharing; (3) generate and adopt standards for future data collection; and (4) collaborate to increase the scope, speed, generalizability, and impact of research.

A complementary model, exemplified in human neuroimaging, is that of large-scale resource-generation projects (e.g., HCP, UK Biobank). These projects provided investigators with high-quality data and accelerated the maturation of research methods (e.g., data collection, quality control, image processing/analysis), infrastructure (e.g., informatics, tools), and paradigms (e.g., high-throughput data collection). Nearly every investigator in human imaging has benefited from these efforts regardless of whether they were directly involved. Creation of large-scale resource-generation projects in the NHP neuroimaging community would have similar effects if designed to leverage global collaboration. Mechanisms that bring together funding from multiple international agencies, inspired by the present strategic plan, will be particularly well suited for scaling and achieving the ambitions stated here.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.neuron.2021.10.015.

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DECLARATION OF INTERESTS

Stephen Frey is an employee and shareholder of Rogue Research Inc. Pierre Pouget is the cofounder of P3LAB, a company developing eye-tracking systems for human and non-human primates.

REFERENCES

Autio, J.A., Zhu, Q., Li, X., Glasser, M.F., Schwiedrzik, C.M., Fair, D.A., Zimmermann, J., Yacoub, E., Menon, R.S., Van Essen, D.C., et al. (2021). Minimal specifications for non-human primate MRI: Challenges in standardizing and harmonizing data collection. Neuroimage *236*, 118082. https://doi.org/10.1016/j.neuroimage.2021.118082.

Basso, M.A., Frey, S., Guerriero, K.A., Jarraya, B., Kastner, S., Koyano, K.W., Leopold, D.A., Murphy, K., Poirier, C., Pope, W., et al. (2021). Using non-invasive neuroimaging to enhance the care, well-being and experimental outcomes of laboratory non-human primates (monkeys). Neuroimage *228*, 117667.

Hayashi, T., Hou, Y., Glasser, M.F., Autio, J.A., Knoblauch, K., Inoue-Murayama, M., Coalson, T., Yacoub, E., Smith, S., Kennedy, H., and Van Essen, D.C. (2021). The nonhuman primate neuroimaging and neuroanatomy project. Neuroimage *229*, 117726.

Klink, P.C., Aubry, J.F., Ferrera, V.P., Fox, A.S., Froudist-Walsh, S., Jarraya, B., Konofagou, E.E., Krauzlis, R.J., Messinger, A., Mitchell, A.S., et al. (2021). Combining brain perturbation and neuroimaging in non-human primates. Neuroimage *235*, 118017.

Majka, P., Bednarek, S., Chan, J.M., Jermakow, N., Liu, C., Saworska, G., Worthy, K.H., Silva, A.C., Wójcik, D.K., and Rosa, M.G.P. (2021). Histology-Based Average Template of the Marmoset Cortex With Probabilistic Localization of Cytoarchitectural Areas. Neuroimage *226*, 117625.

Messinger, A., Sirmpilatze, N., Heuer, K., Loh, K.K., Mars, R.B., Sein, J., Xu, T., Glen, D., Jung, B., Seidlitz, J., et al. (2021). A collaborative resource platform for non-human primate neuroimaging. Neuroimage *226*, 117519.

Milham, M.P., Ai, L., Koo, B., Xu, T., Amiez, C., Balezeau, F., Baxter, M.G., Blezer, E.L.A., Brochier, T., Chen, A., et al. (2018a). An Open Resource for Non-human Primate Imaging. Neuron *100*, 61–74.e2.

Milham, M.P., Craddock, R.C., Son, J.J., Fleischmann, M., Clucas, J., Xu, H., Koo, B., Krishnakumar, A., Biswal, B.B., Castellanos, F.X., et al. (2018b). Assessment of the impact of shared brain imaging data on the scientific literature. Nat. Commun. *9*, 2818.

Poirier, C., Hamed, S.B., Garcia-Saldivar, P., Kwok, S.C., Meguerditchian, A., Merchant, H., Rogers, J., Wells, S., and Fox, A.S. (2021). Beyond MRI: on the scientific value of combining non-human primate neuroimaging with metadata. Neuroimage *228*, 117679.

PRIMatE Data Exchange (PRIME-DE) Global Collaboration Workshop and Consortium (2020). Accelerating the Evolution of Nonhuman Primate Neuroimaging. Neuron *105*, 600–603.