stress resilience and vulnerability that may underlie the variability seen in the behaviors of rewilded mice. Further research will be necessary to parse out the different effects of microbiota and peripheral immune changes, unpredictable stress, physical activity, and environmental enrichment on the microglial response, as well as its consequences in terms of neuronal circuitry remodeling. Manipulating any one of these variables individually, in laboratory settings, has caused variations in microglial immunological and physiological functions [4,7,8].

It is conceivable that exposure to increased physical activity in the outdoor settings, given that the mice must dig their own burrows and search for food, causes stress relief and beneficial microglial changes similar to those seen during voluntary exercise in other mouse studies [8]. In humans, experiences with nature have been shown to be strongly linked to stress relief and improved cognition [9,10].

Rewilding mice, as elegantly exemplified by Cope and colleagues in their study, may create more nuanced animal models and take environmental effects into account. Such models are instrumental in studying a wide range of pathologies driven by interplay between genetic and environmental risk factors. They may provide a window to dissect the mechanisms driving stress resilience – whether mediated by increased physical activity, sensory stimulation, or relaxation techniques – and provide better targets for effective therapies in combination with treatments aimed at modulating microglial function and stimulating neuronal plasticity.

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[1]Neurosciences Axis, Centre de recherche du CHU de Québec, 2705 Boulevard Laurier, Québec, G1V 4G2, Canada

*Correspondence:
tremblay.marie-eve@crchudequebec.ulaval.ca (M.-È. Tremblay).

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References

1. Cope, E.C. *et al.* (2019) The effects of living in an outdoor enclosure on hippocampal plasticity and anxiety-like behavior in response to nematode infection. *Hippocampus* 29, 366–377
2. Leung, J.M. *et al.* (2018) Rapid environmental effects on gut nematode susceptibility in rewilded mice. *PLoS Biol.* 16, e2004108
3. Anacker, C. and Hen, R. (2017) Adult hippocampal neurogenesis and cognitive flexibility – linking memory and mood. *Nat. Rev. Neurosci.* 18, 335–346
4. Tay, T.L. *et al.* (2017) Microglia across the lifespan: from origin to function in brain development, plasticity and cognition. *J. Physiol.* 595, 1929–1945
5. Abdel-Haq, R. *et al.* (2019) Microbiome–microglia connections via the gut–brain axis. *J. Exp. Med.* 216, 41–59
6. Masopust, D. *et al.* (2017) Of mice, dirty mice, and men: using mice to understand immunology. *J. Immunol.* 199, 383–388
7. Tay, T.L. *et al.* (2018) Microglia gone rogue: impacts on psychiatric disorders across the lifespan. *Front. Mol. Neurosci.* 10, 421
8. Jensen, S.K. and Yong, V.W. (2014) Microglial modulation as a mechanism behind the promotion of central nervous system well-being by physical activity. *Clin. Exp. Neuroimmunol.* 4, 188–201
9. Bowler, D.E. *et al.* (2010) A systemic review of evidence for the added benefits to health of exposure to natural environments. *BMC Public Health* 10, 456
10. Kuo, M. *et al.* (2019) Do experiences with nature promote learning? Converging evidence of a cause-and-effect relationship. *Front. Psychol.* 10, 305

Forum

Practical Considerations for Navigating Registered Reports

Anastasia Kiyonaga [1,*] and Jason M. Scimeca [1,*]

Recent open science efforts to improve rigor and reliability have sparked great enthusiasm. Among these, the Registered Report publication format integrates best practices in hypothesis-driven research with peer review that occurs before the research is conducted. Here, we detail practical recommendations to help researchers negotiate the mechanics of this developing format.

Preregistering study plans and predictions (i.e., recording them before knowing the results) is a promising way to align research practices with the ideals of the scientific method [1–3]. The Registered Report publication route escalates and incentivizes the commitment to this practice: detailed study protocols and analysis procedures are peer-reviewed and accepted in principle before the research is conducted [4,5]. Reviewers provide input that can modify the experimental design before data collection and the research must then adhere to the approved protocol.

A growing list of neuroscience journals offer Registered Reports (https://cos.io/rr/) [4,6,7]. These journals provide standardized basic requirements for the format, but these can underplay the true practical demands of meeting stringent Registered Report criteria. For instance, it is clear from the guidelines that sample size estimates are required; yet it is unclear how to thoroughly meet this requirement. There is little concrete instruction available to guide the nuts and bolts of executing the Registered Report process and researchers may wonder whether the approach would be suitable for their work (or whether the payoff will be worth the effort) [8]. This uncertainty may unnecessarily prolong the process or deter researchers from undertaking it in the first place. Here, we offer recommendations to demystify and accelerate the Registered Report pipeline for researchers in any field of neuroscience; if one can make hypotheses and describe how they will be tested, then this is a fitting

Hypotheses, predictions, and interpretations

GOAL: limit space of potential post-hoc interpretation

Delineate testable hypotheses

- Is the scientific premise justified and sound?
- Remember: One does not need to endorse a particular outcome, as long as the results can inform theory

Make concrete predictions

- Include directional descriptions of possible outcomes (e.g., 'condition A greater than condition B')

Describe how predictions will be tested

- What specific measures? What statistical tests?

Link hypotheses and tests to interpretations

- How would you interpret possible outcomes? Which results would support which theories?

Ask whether the design can generate diagnostic results which clearly inform the predictions

- Will possible data patterns clearly support proposed interpretations? Will results make a valuable contribution to the field regardless of outcome?

Power analyses and sample size

GOAL: minimize false positives and negatives

Identify critical tests

- What specific statistics will be used to test predictions? (e.g. t-test, correlation, ANOVA interaction, etc.)

Estimate expected effect size

- Scour the literature for studies using similar methods, designs, and statistical tests to find the likely range of effect sizes for your tests
- Consider the lower end of this range and account for publication bias to attain a conservative effect size estimate
- Assess the smallest effect size that would be theoretically meaningful for what you are studying
- Pilot data are encouraged to show feasibility of experiment and plausibility of effect size, but are insufficient on their own

Determine required sample size with power analysis

- For your power analysis input, use effect size estimated from statistical test that is comparable to proposed test
- Conduct a priori power analysis for your proposed test (e.g., via statistical toolbox or software package) to calculate required sample size

Reproducible methods and exclusion criteria plan

GOAL: control experimenter degrees of freedom

Explicitly define dependent variables

- Explain **any** calculation that will be applied to raw data before the data are submitted to statistical tests
- Define basic terms (e.g., does 'average' describe mean or median?) as well as transformations (e.g., z-scores)

Exhaustively describe inclusion criteria that will be applied before collecting any critical data

- What conditions must participants meet to be enrolled? What criteria will preclude a participant from enrolling?
- Include standard criteria (e.g. safety) along with specific conditions that must be met to test hypotheses (e.g., baseline screening performance)

Exhaustively describe exclusion criteria that will be applied after collecting any critical data

- Specify every plausible circumstance that would justify removal of **data or participants** after data has been collected
- Include technical issues and quality assurance steps, outlier removal, and any specific data conditions that preclude (or must exist prior to) testing your hypothesis

Define outcome-neutral controls

- How can one be certain the manipulation was successful? Will these controls convince a reader that neither positive nor negative results are spurious?

Ask whether the methods are truly transparent

- If someone were to repeat the study and found a different result, are there any degrees of freedom that might explain the difference?

Is the proposed protocol doable?

Check for unnecessary methodological constraints

- Is every criterion well-motivated? Are you confident all methods are feasible? Is there a contingency plan if some constraints are unmet? Can a simpler design address the same question?

Assess required sample size and effect size estimate

- If required sample size is impractical, or no comparable effects exist in the literature, consider an alternative sample size estimation approach (e.g., step-wise peeking procedure, Bayesian stopping rule, hard cap on sample size)
- Seek out resources, staff, or collaborations that can help

Extend your timeline for unforeseen circumstances, then submit!

Trends in Neurosciences

Figure 1. Practical Steps for a Thorough Registered Report. Workflow delineating the underlying steps to address three of the primary criteria on which Registered Reports are evaluated. Additional practical resources are aggregated at https://osf.io/5gazv/wiki/.

format (Figure 1) (a collection of practical resources, including tools for addressing the criteria described here and examples of Registered Reports that have been accepted-in-principle, is available at: https://osf.io/5gazv/wiki/).

Negotiating the Registered Report Process

Registered Report submissions must convince reviewers that the study will be valuable, regardless of how the results turn out, and many of the criteria to accomplish this are more multifaceted than they appear. However, it is precisely these efforts on the front end that promise more robust and reliable research. While it will likely be labor intensive to achieve these benefits, the Registered Report process can be handled efficiently if one is equipped to address the requirements from the start.

Delineate Confirmatory Hypotheses

Because Registered Reports are intended to constrain the space of potential *post hoc* interpretation, the proposal must be grounded in concrete, testable predictions. While this may seem like a straightforward and familiar criterion, it takes several steps to do this well (Figure 1). Nonetheless, Registered Reports can be an empowering venue for testing new theories or arbitrating between competing theories, because predictions are documented at the outset. Even when researchers are agnostic about the outcome, a set of feasible predictions can be proposed, as long as the associated tests and interpretations are clearly delineated. Moreover, serendipitous discoveries can be included (given they are marked as exploratory) to lay the groundwork for new hypotheses [2,7].

When specifying confirmatory hypotheses, it is insufficient to merely sketch the expected (or possible) findings. Instead, a strong Registered Report should systematically detail the motivation for the hypotheses (i.e., justify the scientific premise), how predictions will be tested (i.e., with statistical tests of particular measures), and what the results would mean (i.e., informing particular theories). For instance, directional hypotheses may take the form of: 'We will use a *t*-test to compare mean firing rates between condition 1 and condition 2. If condition 1 is greater than condition 2, it would support theory A; if condition 2 is greater than condition 1, it would support theory B'.

This hypothesis-driven framework also demands that the design can generate discriminatory data patterns, which clearly inform the predictions. An inadequately specified hypothesis might take the form of: 'We will enter firing rates into an ANOVA with three factors. If there is a three-way interaction, it would support theory A; if there is no three-way interaction, it would support theory B'. Those potential data patterns could manifest or be interpreted any number of ways, therefore, that space must be narrowed. At each step of study development, researchers should critically assess whether the design is: (i) truly diagnostic, so that positive findings will strongly support the proposed interpretation; and (ii) optimized to prevent false negatives, so that null results will be credible [7].

Demonstrate Sufficient Statistical Power

Registered Reports hinge on providing sufficient statistical power to minimize false positives and negatives [9]. While many journals and funders now require *a priori* sample size justification, this is often done *ad hoc* ('previous studies used this') or even *post hoc* ('we stopped when we reached $P < 0.05$'). Such perfunctory justification is insufficient for a Registered Report (as for any rigorous scientific inference), and the considerations for a robust power analysis can be surprisingly extensive (Figure 1).

Registered Reports using frequentist statistics should be powered to detect the smallest effect that is both plausible and theoretically meaningful (but see https://osf.io/pukzy/ for alternatives). Yet, there is no one-size-fits-all procedure for estimating this value. Despite the temptation to rely on a single previous study or promising pilot data, this can produce misleading estimates [7,10]. Instead, one should incorporate a range of values from the relevant literature [11] and take into account that these may be inflated by publication bias. Depending on the research question at hand, one should also consider what would constitute a meaningful effect for the field (which may be smaller or larger than significant effects in the literature) (cf. [12]). This can be a nebulous requirement, and there is no universal definition of the 'right' effect size. However, a successful Registered Report will ultimately require a thorough and compelling argument for the proposed approach.

Finally, the mechanics of the power analysis will depend on the proposed study design and statistical test. First, the input effect size should be based on comparable tests from the literature. Next, the sample size calculation should be conducted for the proposed tests and design. For instance, if the proposal tests an interaction in a repeated-measures ANOVA, the estimate should be calculated specifically for this test (e.g., rather than a main effect or between-subjects design). This necessary consideration can be onerous, however, because few power analysis tools are equipped for complex statistical tests. Therefore, Registered Reports favor straightforward analysis plans for which hypotheses can be clearly defined. Importantly, sophisticated scientific questions and complex datasets are still well-suited for Registered Reports; predictions should just be expressed as the simplest comparison between conditions.

Ensure Reproducibility and Replicability

Because the purpose of Registered Reports is to limit experimenter degrees of freedom and ensure methodological rigor [2,3,5], the methods should be described exhaustively enough that a conscientious researcher in a different lab could recreate the study. Achieving this goal requires a thoughtful assessment of the many routine procedures or seemingly inconsequential details that are often omitted from manuscripts. These include experimental technicalities, inclusion/exclusion criteria, quality checks, and analytic choices, all of which must be described beforehand, rather than be determined during or after data collection (Figure 1). However, in neuroscience research, certain variables may be unknown or indefinable beforehand. Accordingly, decisions can be based on observation of the data, provided the rules guiding those decisions are clearly described (Box 1).

With standard preregistration (or a study conducted without preregistration), deviations from the planned design/methods carry no practical repercussions. In contrast, such deviations in a Registered Report could ultimately be grounds for article rejection. Accordingly, researchers should think carefully about how they define procedures and whether they can adhere to them. The most vexing aspect of the entire Registered Report process may be anticipating potential complications, in order to choose parameters wisely. While it is important to be explicit, specifying inessential criteria (although well-intentioned) might disqualify much of the data or invoke counterproductive methodological rigidity. Instead, every criterion should be well-motivated to bolster confidence in the outcomes. Finally, researchers should consider adding cushioning for unexpected obstacles into their timeline, budget, and mind-set.

Concluding Remarks

While the Registered Report process shifts some of the 'heavy lifting' to the early stages of study design, data collection will entail ongoing monitoring for compliance with the proposed criteria, as well as troubleshooting of unforeseen issues. Thus, the Registered Report endeavor will likely require researchers to go above-and-beyond the typical study requirements. However, the preemptive review process and proactive planning should enhance the quality and credibility of the work, ultimately benefitting individual researchers and the field at large.

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Box 1. Registration Procedures for the Neurosciences

Although neuroscience study designs and data patterns are often complex, hypothesis-driven research in virtually all neuroscience disciplines is amenable to registration. Some likely challenges researchers might face, and suggested solutions, are highlighted below.

Cognitive and Systems Neuroscience

Decisions about which measures will best address hypotheses may depend on observations of the data (e.g., determining informative cells or electrodes, relevant frequency bands or epochs, functional magnetic resonance imaging regions of interest). Registered Reports can specify an algorithmic but noncircular approach to govern these decisions. For instance, an omnibus ANOVA can determine which electrodes show task-relevant signal and will ultimately be analyzed, or a leave-one-subject-out procedure can be used to construct a region of interest for each subject/animal.

Behavioral and Molecular Neuroscience

Experiments may comprise repetition over animals or samples with high variability and researchers must decide which data points are relevant to the proposed hypothesis tests (e.g., which individual animals to include/exclude? Which intervention parameters are effective?). Registered Reports can specify a set of criteria that each sample or manipulation must meet to confidently interpret outcomes (e.g., include only animals that display pattern X, advance to next stage using only intervention that shows X), or an algorithmic approach to identify relevant covariates for inclusion in final analysis (e.g., using step-wise linear regression). For all disciplines, an if-then decision tree can also help to define thresholds and constrain these analytical paths (Figure I) [2].

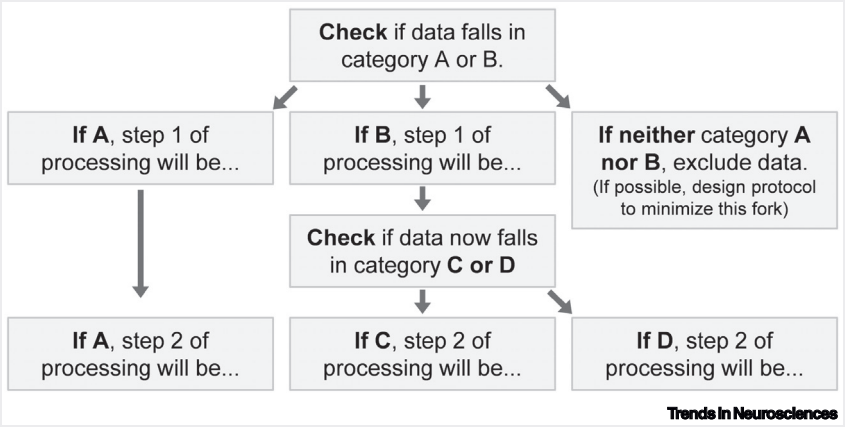

Figure I. Schematic Data-Processing Decision Tree.

[1]Helen Wills Neuroscience Institute, University of California, Berkeley, CA, USA

*Correspondence:
kiyonaga@berkeley.edu (A. Kiyonaga) and
jscimeca@berkeley.edu (J.M. Scimeca).

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References

1. Nosek, B.A. *et al.* (2015) Promoting an open research culture. *Science* 348, 1422–1425
2. Nosek, B.A. *et al.* (2018) The preregistration revolution. *Proc. Natl. Acad. Sci. U. S. A.* 2017, 201708274
3. Poldrack, R.A. *et al.* (2017) Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nat. Rev. Neurosci.* 18, 115–126
4. Chambers, C.D. (2013) Registered Reports: a new publishing initiative at Cortex. *Cortex* 49, 609–610
5. Munafò, M.R. *et al.* (2017) A manifesto for reproducible science. *Nat. Hum. Behav.* 1, 1–9
6. Baxter, M.G. and Burwell, R.D. (2017) Promoting transparency and reproducibility in behavioral neuroscience: publishing replications, registered reports, and null results. *Behav. Neurosci.* 131, 275–276
7. Chambers, C.D. *et al.* (2014) Instead of "playing the game" it is time to change the rules: Registered Reports at AIMS Neuroscience and beyond. *AIMS Neurosci.* 1, 4–17
8. Poldrack, R.A. (2019) The Costs of reproducibility. *Neuron* 101, 11–14
9. Button, K.S. *et al.* (2013) Power failure: why small sample size undermines the reliability of neuroscience. *Nat. Rev. Neurosci.* 14, 365–376
10. Albers, C. and Lakens, D. (2018) When power analyses based on pilot data are biased: inaccurate effect size estimators and follow-up bias. *J. Exp. Soc. Psychol.* 74, 187–195
11. Lakens, D. (2013) Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front. Psychol.* 4, 1–12
12. Keefe, R.S.E. *et al.* (2013) Defining a clinically meaningful effect for the design and interpretation of randomized controlled trials. *Innov. Clin. Neurosci.* 10, 4S–19S