

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

- | | |
|-------------------------------------|---|
| n/a | Confirmed |
| ☐ | ☒ The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ A description of all covariates tested |
| ☐ | ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☒ | ☐ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☒ | ☐ Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection	OpenCV in Python 3.7 was used to identify swimming tadpole positions in video recordings in Fig. 2. Otherwise no other custom software was used for data collection. Mouse behavior data were collected using iNoldus instrumentation using EthoVision XT 14 (Noldus, Leesburg, VA).
Data analysis	All transcriptomics data used for drug predictions can be accessed through the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) or Open Science Framework (https://osf.io/7nrd3/) using the identifiers indicated in Table 1. The NeMoCAD code is stored on Zenodo (https://doi.org/10.5281/zenodo.7692712) and access can be requested by submitting the S1 Form to the Data Manager, Wyss Institute for Biologically Inspired Engineering at Harvard University (email: Info@wyss.harvard.edu).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Supplementary Table 2 lists accession numbers for all datasets used, including the tadpole data generated in this work, which was deposited to the GEO database for public access

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	not applicable
Reporting on race, ethnicity, or other socially relevant groupings	not applicable
Population characteristics	not applicable
Recruitment	not applicable
Ethics oversight	not applicable

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Xenopus screens utilized 5-8 tadpoles per condition. Mouse studies utilized n=5 or more mice per treatment condition.
Data exclusions	No data were excluded from the analyses.
Replication	All Xenopus and mouse studies were repeated at least once, except the mouse study with oral dosing was conducted once.
Randomization	Xenopus and mice were randomly selected into treatment groups.
Blinding	Studies were not blinded. The Rett model animals were obviously different from controls, preventing full blinding. Drug administration and data collection was performed by the same researcher who prepared the reagents and so could not be blinded. Care was taken during data analysis to use objective metrics wherever possible to avoid bias.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

anti-MeCP2 (Rabbit) Invitrogen PA1-887
 anti-alpha acetylated tubulin (Mouse) Sigma-Aldrich T7451
 anti-beta tubulin (Mouse) DSHB E7
 Isolectin B4 (Griffonia simplicifolia) Sigma-Aldrich L2895
 alpha-acetylated tubulin (rabbit) Abclonal ab179484
 anti-beta III tubulin (chicken) Biolegend 801202
 Rabbit IgG Isotype Control Thermo Fisher 02-6102
 Mouse IgG Isotype Control Invitrogen 31903
 Goat anti-mouse IgG Alexa Fluor 594 Invitrogen T1271722
 Goat anti-rabbit Alexa Fluor 647 Abcam ab 150083
 Goat anti-mouse Alexa 546 Invitrogen A-11030
 Goat anti-rabbit Alexa 633 Invitrogen 2079350

Validation

Antibodies were used as provided by the manufacturer. Both isotype controls with secondary antibodies and secondary antibodies alone were used to control for nonspecific staining.

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals

Outbred wild-type *Xenopus laevis* embryos, undetermined sex but presumably included males and females, were obtained regularly from the Michael Levin Laboratory at Tufts University.
 MeCP2-null (MeCP2-/-) (strain 003890) mice and age-matched WT male littermates (MeCP2+/+), purchased by Jackson Laboratories (Bar Harbor, ME)

Wild animals

not applicable

Reporting on sex

We used male hemizygous null MeCP2 mice because it was the gold standard for Rett and MeCP2null females are difficult to generate due to the infertility of MeCP2 heterozygous female mice.

Field-collected samples

not applicable

Ethics oversight

All vertebrate research was conducted in compliance with a Harvard Medical School-approved IACUC protocol. Embryos were sourced from Tufts University in compliance with an IACUC protocol.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks

not applicable

Novel plant genotypes

not applicable

Authentication

not applicable