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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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 (*n*) 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 *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	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. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	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 *d*, Pearson's *r*), 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	MinKNOW (v1.15.1) for MinION DNA sequence data acquisition.
Data analysis	Bowtie 2 (v2.3.4), FASTX-Toolkit, MassHunter Quant Software package (vB.07.01), Albacore (v2.1.10), minimap2 (v2.10), nanopolish (v0.10.2), DNAscent (custom software; deposited at GitHub).

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Raw and processed Illumina and MinION data are available from NCBI GEO under accession number GSE121941.

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

Life sciences study design

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

Sample size	Where statistics have been done, samples sizes (N numbers) have been specified in figure legends and/or the main text.
Data exclusions	In all cases data exclusion criteria were pre-established and are described in the methods section. For model training, signal event outliers were excluded. For BrdU-seq, reads with poor alignment were excluded (we required reads to be uniquely mapped and without mismatches).
Replication	For proof-of-principle experiments (Fig. 1) and model training (Fig. 2) multiple experimental conditions were tested and in each case found to be consistent with our findings. For the cell cycle experiments (Fig. 3 & 4), data were compared to multiple independent tests (Illumina sequencing and Mass Spectrometry).
Randomization	N/A. All data shown in this study is of the measurement of DNA replication, where randomization is neither standard nor appropriate.
Blinding	N/A. Data shown in this study was on the experimental measurement of DNA replication, where blinding is neither standard nor appropriate.

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
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	BD Biosciences, Purified Mouse Anti-BrdU, Clone B44, LOT 7157935
Validation	From manufacturers website: "Anti-BrdU identifies BrdU (but not thymidine) in single-stranded DNA, free BrdU, or BrdU coupled to a protein carrier. The antibody also reacts with iodouridine.". Citations: Beisker W, Dolbeare F, Gray JW. An improved immunocytochemical procedure for high-sensitivity detection of incorporated bromodeoxyuridine. Cytometry. 1987;8:235. Dolbeare F, Beisker W, Pallavicini MG, Vanderlaan M, Gray JW. Cytochemistry for bromodeoxyuridine/DNA analysis: Stoichiometry and sensitivity. Cytometry. 1985;6:521-530. Dolbeare F, Gratzner HG, Pallavicini MG, Gray JW. Flow cytometric measurement of total DNA content and incorporated bromodeoxyuridine. Proc Natl Acad Sci USA. 1985;6:521-530. Gratzner HG. Monoclonal antibody to 5-bromo and 5-iododeoxyuridine: A new reagent for detection of DNA replication. Science. 1982;218:474. Gray JW. Monoclonal antibodies against bromodeoxyuridine (special issue). Science. 1985;6:501-673. Nagashima T, Hoshino T. Rapid detection of S-phase cells by anti-bromodeoxyuridine monoclonal antibody in 9L brain tumor cells in vitro and in situ. Acta Neuropathol (Berl). 1985;66:12. Pinkel D, Thompson LH, Gray JW, Vanderlaan M. Measurement of sister chromatid exchanges at very low bromodeoxyuridine substitution levels using a monoclonal antibody in Chinese hamster ovary cells. Cancer Res. 1985;45:5795.".