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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 <u>Authors & Referees</u> and the <u>Editorial Policy Checklist</u>.

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For	all statistical analyse	s, 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.						
\boxtimes	A description of all covariates tested						
\boxtimes	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 Give <i>P</i> values as exact values whenever suitable.						
\boxtimes	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings						
\boxtimes	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes						
\boxtimes	\square Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated						
	Our web collection on <u>statistics for biologists</u> contains articles on many of the points above.						
Software and code							
Policy information about <u>availability of computer code</u>							
Da		pemed.CUDA module of AMBER16 MD simulation engine on ANTON2 supercomputer Nikon NIS Element					

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

Data analysis

Policy information about availability of data

All manuscripts must include a <u>data availability statement</u>. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets $\,$

cpptraj program from the AMBER suite

MATLAB (script available as Supplementary Note 2)

- A list of figures that have associated raw data
- A description of any restrictions on data availability

VMD1.9.3 GraphPad Prism 7 Origin Pro 2018

Experimental and computational data are available upon reasonable request. Requests should be made to Jerome Lacroix (jlacroix@westernu.edu) or to Yun Luo (luoy@westernu.edu).

Field-spe	ecific re	porting			
Please select the or	ne below that is	the best fit for your research. If you are not sure, read the appropriate sections before making your selection.			
	В	ehavioural & social sciences Ecological, evolutionary & environmental sciences			
For a reference copy of t	For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf				
Life scier	nces stu	ıdy design			
All studies must dis	sclose on these	points even when the disclosure is negative.			
Sample size	No sample size	sample size calculation was performed.			
Data exclusions	No experimenta	ital data were excluded from analyzes.			
Replication	Most attempts	s to replicate experimental results were successful. No replication was attempted for our simulation data.			
Randomization	No randomization	ition of sample was performed.			
Blinding	Experimental ar collection.	tal and Simulation Data were acquired using softwares, not by human intervention, thus no blinding was necessary for data			
We require information	on from authors a	Decific materials, systems and methods about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, 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 Methods					
n/a Involved in th		n/a Involved in the study			
Antibodies	,	ChiP-seq			
☐ ☑ Eukaryotic cell lines ☐ Flow cytometry		Flow cytometry			
Palaeontology MRI-based neuroimaging					
Animals and other organisms					
Human research participants					
Clinical dat	ā				
Eukaryotic c	ell lines				
Policy information	about <u>cell lines</u>				
Cell line source(s	line source(s) HEK293T cells lacking Piezo1 (Delta PZ1) were created by and obtained from the Patapoutian Group at Scripps Research.				
Authentication None of the cell lines w		None of the cell lines were authenticated.			

None of the cell lines were tested for Mycoplasma contamination.

None of the cells are known to be commonly misidentified.

Mycoplasma contamination

Commonly misidentified lines (See <u>ICLAC</u> register)