

Comprehensive profiling of brain dynamics during anesthesia across phylogeny

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The behavioral effects of anesthetics are highly conserved across species, hinting at shared and fundamental underlying mechanisms. Here we compile a dataset of multiscale neural activity during wakefulness and anesthesia, encompassing human, macaque, marmoset, mouse, zebrafish and nematode. Applying massive feature extraction, we characterize local neural dynamics across >6,000 time-series features. This reveals a conserved dynamical profile of anesthesia across species, characterized by shorter intrinsic timescales of neural activity and dampened inter-regional synchrony. Deep-brain stimulation of the macaque centromedian thalamus reverses this profile and restores behavioral responsiveness. This conserved dynamical phenotype covaries with conserved transcriptional profiles of excitatory and inhibitory neurotransmission. Biophysical modeling provides a potential mechanistic link between the macroscale dynamical phenotype of anesthesia and microscale effects of key molecular targets on the timescales of synaptic excitation and inhibition. These analyses reveal a shared neural endpoint of anesthesia: across species and scales, anesthetics induce spatiotemporal isolation of local neural activity.

Mapping how neural dynamics support brain function across spatial and temporal scales is a key goal in the neurosciences^{1–4}. A prominent paradigm for understanding neural dynamics and their function is to manipulate them through general anesthesia. Anesthetic agents modulate neuronal signaling, altering local and global dynamics, reversibly suppressing the brain's ability to process information and respond to the external environment. Although different species have evolved unique ways to respond to their specific environments, the behavioral effects of anesthetics (namely, suppression of behavior and inability to interact with the environment) are highly conserved across species, from primates to nematode worms^{5–8}, hinting at

shared and fundamental underlying mechanisms. Neural changes observed at the macroscale can then be related to downstream effects on cognition and behavior, and to upstream cellular, molecular and synaptic mechanisms at the microscale. Thus, systematically and reversibly perturbing brain function with anesthesia while recording neural activity provides a unique opportunity to understand how the dynamics of local neural activity mediate the links among anatomy, chemoarchitecture and the organism's functional repertoire. Indeed, numerous imaging studies have reported evidence of changes in neural activity that accompany transitions between wakefulness and anesthesia^{9–20}.

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However, the current picture of how anesthetics influence neural dynamics remains fragmented and incomplete. On one hand, some reported effects may be specific to a particular species, or a particular anesthetic agent. On the other hand, despite some notable exceptions (for example, refs. 21–26), most studies tend to focus on a single species, a single anesthetic and specific hand-picked features of neural activity—such as spectral power, amplitude or temporal entropy. Yet, each time series can be characterized by thousands of different properties—from statistics of the distribution such as mean, variance and outliers, to periodicity and autocorrelation at different lags, stationarity and measures of signal complexity and self-similarity^{27–29}. Therefore, the currently prevalent approach of focusing on a handful of preselected properties leaves open the risk of missing key aspects of neural dynamics, potentially leaving large gaps in our understanding.

To go beyond these limitations of the current literature and triangulate on a potential ‘final common endpoint’ of anesthesia^{5,30,31}, here we conduct large-scale data-driven feature screening to systematically map how anesthetics perturb the entire dynamic profile of the brain—across multiple species and across multiple pharmacological agents. We first compile a unique multiscale dataset spanning single-neuron recordings in invertebrates (*Caenorhabditis elegans*), non-mammalian vertebrates (larval zebrafish), and functional magnetic resonance imaging (fMRI) in mouse and primate species (marmoset, macaque, human) undergoing imaging during loss and recovery of responsiveness induced by multiple volatile and intravenous anesthetics, as well as re-awakening from anesthesia induced by deep-brain stimulation (DBS) of the macaque centromedian thalamus (CT; Fig. 1a). Altogether, the species included here encompass key model organisms for neuroscience. We then apply state-of-the-art methods for massive feature extraction^{27,28} to systematically characterize the activity of every cortical region/neuron in this broad and diverse dataset, in terms of more than 6,000 univariate features from the vast modern literature on time-series analysis^{29,32,33} (Fig. 1b). The result is an exhaustive, data-driven characterization of how anesthesia reshapes the dynamics of neural activity—across dynamical features, across pharmacological agents, across species and across scales, from single neurons to entire brain regions.

This comprehensive characterization enables us to pursue one key hypothesis: that, across different species, anesthetics with divergent molecular targets exert their common effect of suppressing behavior^{5,8,30,31} by eliciting convergent changes in local neural dynamics. Crucially, our hypothesis is that some feature(s) will be consistently perturbed by anesthesia, but we do not restrict our investigation to features pre-specified a priori. On the contrary, our goal is to obtain an unbiased exploration of the landscape of anesthetic-induced changes in neural dynamics—across species, across drugs, across scales and across dynamical features. Once the landscape is mapped, we proceed to ask whether any feature changes consistently across anesthetics and species. It is far from trivial that any consistency will be found (as we confirm with null models), given the biological and methodological diversity of the datasets included here—spanning nine orders of magnitude from single-neuron calcium dynamics to hemodynamics of entire brain regions, with seven drug regimes in six species covering 700 million years of evolution (Supplementary Fig. 1).

Focusing on effects that are consistently shared across multiple anesthetics and species allows us to exclude physiological or methodological confounds specific to any one drug, species, or imaging modality, and instead triangulate on potential neural underpinnings of what they share: breakdown of responsiveness to the environment. In sum, our strategy is to combine comprehensive data-driven screening of thousands of dynamical features, with a stringent criterion for consistency across species and anesthetics demanded by our driving hypothesis (Fig. 1c).

To foreshadow our results, comprehensive and systematic phenotyping of dynamical features under anesthesia reveals a dynamical

regime of neural activity that is conserved across species, scales and drugs. DBS of the CT re-awakens the animal from anesthesia, and induces a change in dynamics in the opposite direction, demonstrating bidirectional control over brain dynamics and wakefulness. Finally, biophysical modeling provides a potential mechanistic link between the macroscale dynamical phenotype of anesthesia and microscale effects of key molecular targets on the timescales of synaptic excitation and inhibition.

Results

Here we perform comprehensive phenotyping of the changes in local neural dynamics induced by different anesthetic agents, across more than 6,000 dynamical features of univariate time series from across the scientific literature^{27–29}. We compile and systematically phenotype multiple datasets, each including at least one awake and one anesthetized condition (Fig. 1a). Please see Methods for specific details regarding acquisition and processing of each dataset; an overview of the key parameters is provided in Extended Data Table 1. Specifically, we include a dataset of resting-state fMRI (rfMRI) data obtained from $n = 15$ healthy humans (*Homo sapiens*) who were scanned at baseline and during deep anesthesia with the inhalational anesthetic sevoflurane, as well as during spontaneous recovery of consciousness³⁴; a dataset of $n = 5$ macaque monkeys (*Macaca mulatta*) scanned several times during wakefulness and anesthesia with sevoflurane, propofol or ketamine (keta)³⁵; a dataset of $n = 4$ marmoset monkeys (*Callithrix jacchus*) scanned during wakefulness and anesthesia with isoflurane (iso), sevoflurane (sevo) or propofol (propo)³⁶; a dataset of $n = 43$ mice (*Mus musculus*) scanned either during wakefulness ($n = 10$) or anesthesia with halothane (halo, $n = 19$) or combined medetomidine (med)-isoflurane ($n = 14$)¹². To broaden our investigation beyond mammalian species, we also include a new dataset of $n = 7$ larval zebrafish (*Danio rerio*) with neuronal calcium imaging acquired during wakefulness or in the presence of the anesthetic tricaine, having a comparable temporal resolution to our fMRI recordings (1,014 ms). Because the effects of anesthesia are shared even with invertebrates^{5–7}, we also include a dataset of $n = 10$ nematode worms (*C. elegans*) with calcium imaging acquired with or without isoflurane anesthesia, having a comparable temporal resolution to our fMRI recordings (500 ms)³⁷. For all the above datasets, we contrast every wakeful condition against every anesthetized condition. Finally, we also include an additional macaque dataset, comprising $n = 2$ macaque monkeys scanned several times with fMRI during wakefulness, propofol anesthesia and anesthesia combined with DBS of different thalamic nuclei—centromedian thalamus (CT), which induced awakening despite continuous anesthetic infusion; and ventral–lateral thalamus (VT) that did not induce awakening¹³. For this dataset, we contrast baseline wakefulness against propofol anesthesia. We also contrast awakening induced by CT DBS during anesthesia (that is, propofol is present but the animal is awake), against anesthesia without DBS, and against anesthesia with VT DBS (which does not induce awakening). The inclusion of this unique dataset enables to dissociate the mere presence of a high dose of propofol from its effect on wakefulness.

Starting from the preprocessed time series of each brain region's fMRI activity (respectively, each neuron/neuron group's calcium imaging activity in the nematode and zebrafish data), we use the highly comparative time-series analysis (hctsa) toolbox^{27,28} to extract its full dynamical profile across the most comprehensive available set of scientific time-series features (Fig. 1b). The hctsa features include methods from across the interdisciplinary scientific literature on time-series analysis, including not only biology but also physics, engineering and economics. Features range from basic statistics of the distribution of time points (for example, mean, variance), outliers, periodicity and stationarity, to linear and nonlinear autocorrelation at different lags, predictability of future activity from its past using models of various complexity, motifs of the discretized time series and their prevalence, and many more^{27,28}. Each time-series feature takes a univariate time

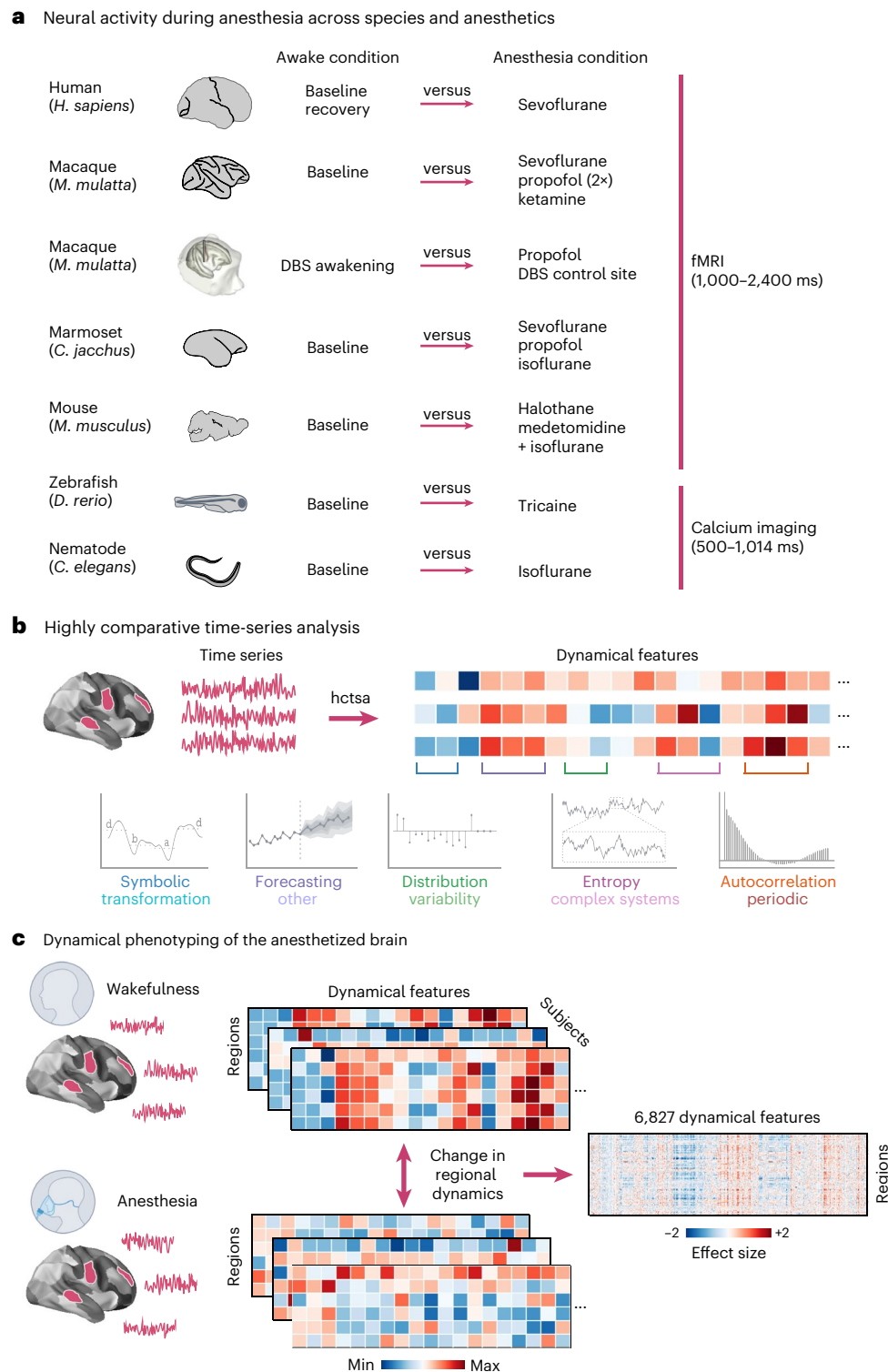


Fig. 1 | Systematic phenotyping of brain dynamics under anesthesia.

a, Overview of datasets and contrasts included in the present study. Human—awake versus vol 3% sevoflurane and recovery versus vol 3% sevoflurane³⁴. Macaque (two datasets)—awake versus sevoflurane; awake versus propofol; awake versus ketamine³⁵; awake versus propofol (no-DBS); CT DBS versus propofol (no-DBS); and CT DBS versus VT DBS¹³. Marmoset—awake versus sevoflurane; awake versus propofol; and awake versus isoflurane³⁶. Mouse—awake versus halothane; and awake versus medetomidine–isoflurane⁴². Zebrafish—awake versus tricaine anesthesia. Nematode—0% isoflurane versus 4% isoflurane³⁷. For the mammalian species, time series were acquired using fMRI. For the nematode and zebrafish,

time series were acquired from GCaMP calcium imaging. **b**, Using ‘hctsa’²⁷, we extract >6,000 dynamical features to characterize each time series of regional/neuronal brain activity. **c**, Analytic strategy—for each brain region, we compare dynamical features during wakefulness and anesthesia. We obtain a regions-by-features matrix of effect sizes for each contrast, which can be compared across datasets. See Extended Data Table 1 for full details on sample sizes, imaging techniques and acquisition parameters. Credit: wakefulness and anesthesia icons in **c** are adapted from ref. 8, Springer Nature Limited. Brain icons and DBS in **a** adapted from SciDraw under a Creative Commons license CC BY 4.0. Macaque DBS in **a** adapted with permission from ref. 13, AAAS.

series as input, and returns a single, real-valued summary statistic. Filtering for features that could not be computed for all regions/neurons yielded 6,827 features for further analysis. For each wakefulness–anesthesia contrast (for example, baseline versus isoflurane anesthesia in marmoset; recovery versus sevoflurane in human; DBS versus no stimulation in macaque), we perform a statistical test to compare the value of each feature during wakefulness and anesthesia. This is performed separately for each region (respectively, neuron). For each contrast, this procedure returns a matrix of size brain regions/neurons $\times$ 6,827 features (Fig. 1c). Please note that the features' raw values can vary widely across features, spanning several orders of magnitude and hindering comparison. However, here we are not interested in raw feature values, but rather in how they change under anesthesia. Rather than quantifying this anesthetic-induced difference in terms of the original feature units (for example, mean difference), which would incur the same problem, we can instead quantify it by its effect size. Being expressed in units of s.d., effect sizes are comparable across features and also across regions, species and datasets. We measure effect size using Hedges' g , which is interpreted in the same way as Cohen's d , but is more appropriate for small sample sizes. Because the same features are used across all species, this procedure ensures that our datasets can be meaningfully compared—same features and same units.

Systematic phenotyping of local neural dynamics under anesthesia

To test the hypothesis that diverse anesthetics exert their evolutionarily conserved effect of suppressing behavior by eliciting similar changes in local neural dynamics, we do not prespecify some dynamical features of putative interest. Rather, we systematically and comprehensively assess thousands of features from across the scientific literature on time-series analysis. Figure 2 shows the matrix of regions $\times$ dynamical features obtained by averaging across all contrasts and datasets belonging to the same species. Each regions-by-features matrix shows the overall effect size when contrasting the awake condition versus the anesthesia condition, such that positive (red) values indicate an increase during anesthesia. Within each species, the majority of features appear to be affected by anesthesia in the same way across regions/neurons (that is, most columns are either predominantly red or predominantly blue, indicating consistent increase/decrease). Nonetheless, this consistency does not imply uniformity—differences among regions can also be observed. Supplementary Fig. 5 shows the same data after z scoring each column and reordering the rows within each species, to further highlight patterns of regional heterogeneity. As expected, some differences among species are evident—some features show inconsistent patterns of increase and decrease in different species; and the mouse, zebrafish and nematode data display overall greater sensitivity (evidenced by overall greater effect sizes). Although interspecies differences and differences in the types and doses of anesthetics used may have a role, some of the observed differences may potentially be explained by the higher spatial and temporal resolution of their respective acquisitions. Namely, the mouse data have the fastest fMRI sampling and longest time series, while the nematode and zebrafish data use calcium imaging to measure activity of individual neurons at even greater spatial and temporal resolution (Extended Data Table 1).

Notably, despite differences in acquisition and spatial resolution, processing strategies, model organism and anesthetic agent and dose, we observe prominently aligned vertical bands of the same color (indicating consistent change) across datasets, suggesting that diverse anesthetics elicit similar increases and decreases in local dynamics across species (Fig. 2). A very similar profile of changes in brain dynamics is observed in the macaque, when instead of comparing anesthesia against baseline wakefulness, anesthesia is compared against re-awakening induced by DBS of the CT. Likewise, a similar profile of changes is observed when comparing DBS of the VT, which does not re-awaken the animal, against CT stimulation (Supplementary Fig. 2).

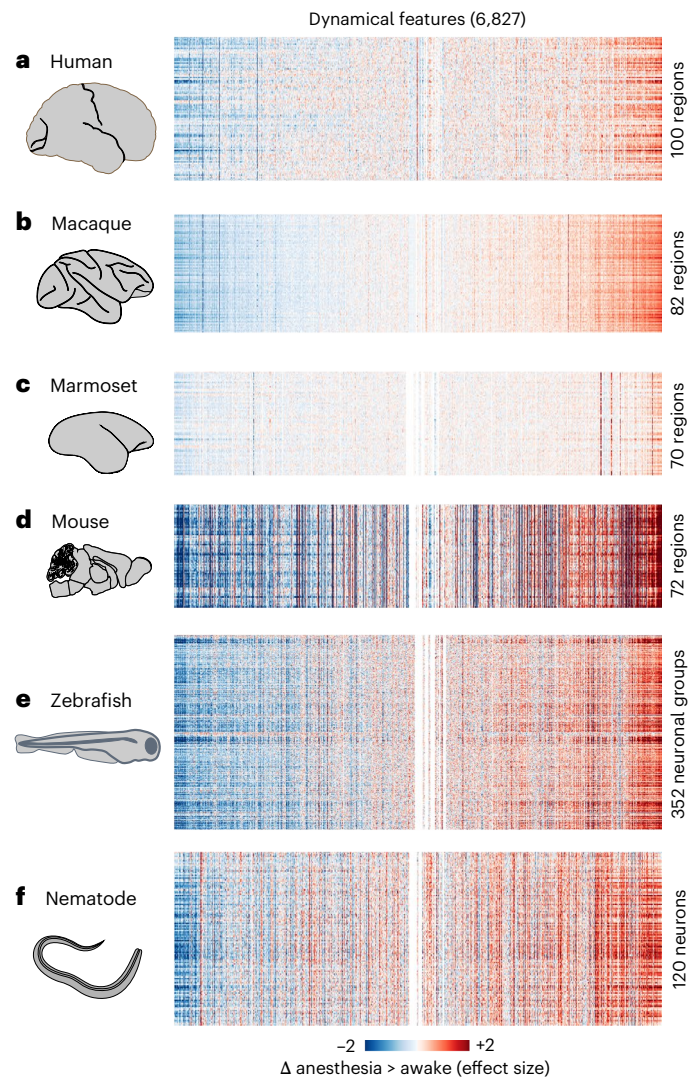


Fig. 2 | Anesthetic-induced changes in neural dynamics across species.

a, Human—mean effect sizes across awake versus vol 3% sevoflurane and recovery versus vol 3% sevoflurane. **b**, Macaque—mean effect sizes across awake versus sevoflurane; awake versus propofol; awake versus ketamine (for the multi-anesthesia dataset); awake versus propofol (no-DBS); re-awakening induced by CT DBS versus propofol anesthesia without DBS; and re-awakening induced by CT DBS versus VT DBS (which does not re-awaken the animal), both during propofol anesthesia (for the DBS dataset). Extended Data Fig. 2 shows the DBS contrasts separately. **c**, Marmoset—mean effect sizes across awake versus sevoflurane; awake versus propofol; and awake versus isoflurane. **d**, Mouse—mean effect sizes across awake versus halothane and awake versus medetomidine-isoflurane. **e**, Zebrafish—effect size for awake versus tricaine. **f**, Nematode—effect size for awake versus isoflurane. For all species, positive effect sizes indicate anesthesia > awake. The order of features (columns) is the same in each species, sorted to highlight common patterns. For visualization purposes, the color range is capped at $(-2, +2)$. Supplementary Fig. 5 shows the same data after column-wise z scoring and reordering the rows to highlight patterns of regional heterogeneity. Brain icons in **a**, **d**–**f** adapted from SciDraw under a Creative Commons license CC BY 4.0.

In other words, when DBS of the thalamus successfully reverses the behavioral effects of anesthesia, it also changes the profile of local fMRI signals in the opposite direction as the effects of anesthesia.

We then home in on the phylogenetically conserved dynamic profile associated with anesthesia. We proceed as follows. For each contrast (comparison between an awake condition and an anesthetized condition, using a particular anesthetic in a particular species), we first average the effect size of each feature across all regions/neurons to

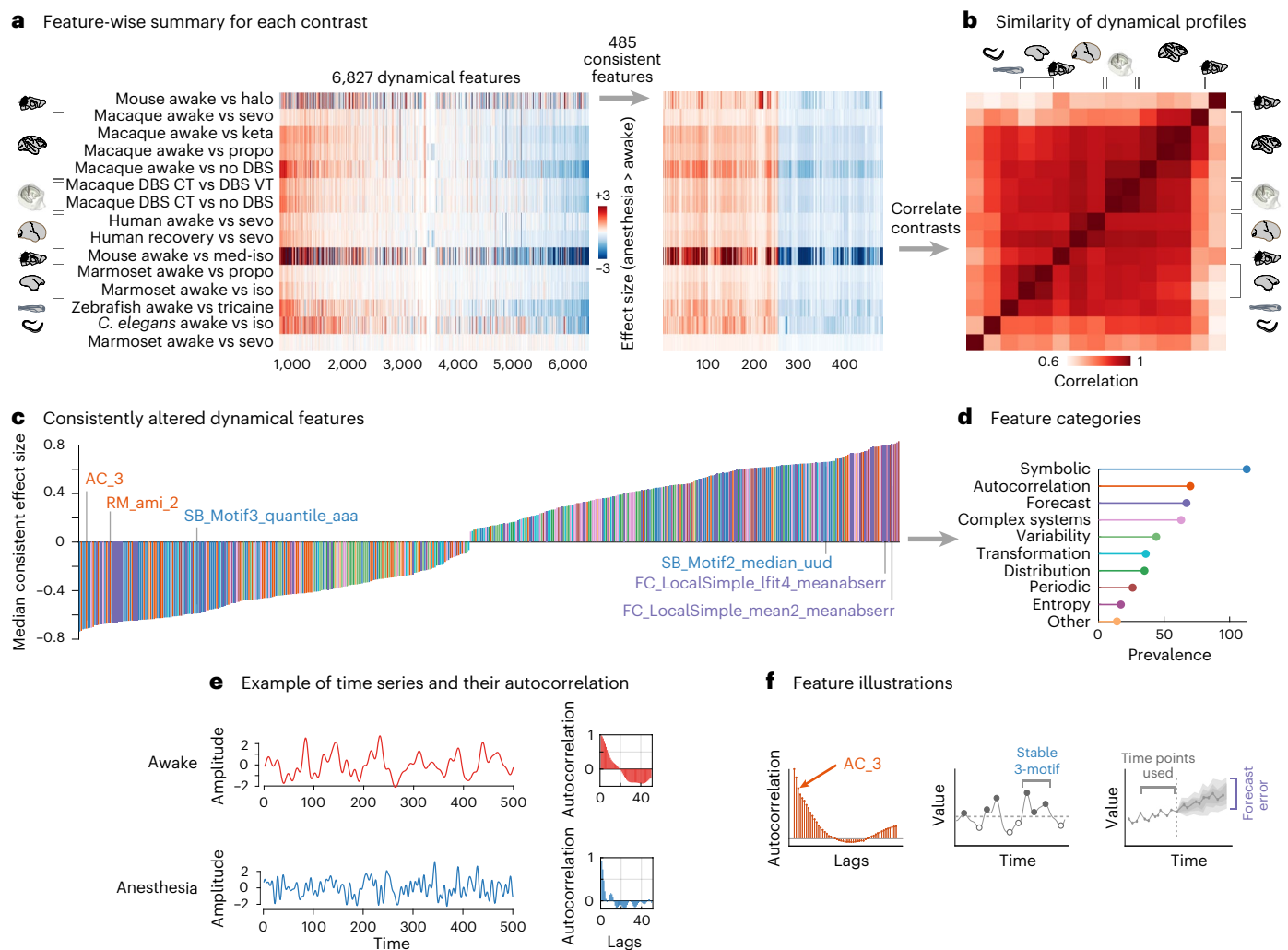


Fig. 3 | Consistent effects of anesthesia on neural dynamics. **a**, Summary of feature-wise dynamical changes for each contrast and each species. For each contrast, effect sizes are averaged across brain regions/neurons to obtain a single value for each feature, representing its overall change across the brain. To identify dynamical features that are consistently altered across species and anesthetics, features are filtered to retain only those whose direction of effect is the same in each species (all positive or all negative). The outcome of this procedure is a set of 485 dynamical features that are consistently altered across regions/neurons, across anesthetics and species. For visualization purposes, the color range is capped at $(-3, +3)$. **b**, The dynamical signatures of anesthesia are positively correlated across species and anesthetics (mean = 0.86). This value is significantly greater than the level of correlation that would be expected by chance purely based on the fact that features have the same sign, as quantified by a permutation-based null model generated by shuffling the features within each contrast while preserving their sign (one-sided $P < 0.0001$; Supplementary Fig. 10). **c**, The median effect sizes (Hedges' g) are shown for each of the 485 consistent features, color coded according to membership of ten broad categories of dynamics (feature types; Supplementary Table 2). Exemplary

features are highlighted. Extended Data Fig. 1 shows the full range of effect sizes across contrasts for each feature. Supplementary Fig. 9 shows that the mean effect size across features and contrasts is significantly greater in magnitude than the canonical threshold for a medium-sized effect (Hedges' $g = 0.5$)—mean = 0.58, $P < 0.001$, two sided, from bootstrap resampling. **d**, Prevalence of ten broad categories of features (Methods) among the consistent ones, revealing a predominance of features pertaining to autocorrelation, forecasting error and symbolic motifs. **e**, Examples of time series from an awake (red) and an anesthetized (blue) macaque, showing faster decay of autocorrelation under anesthesia. **f**, Cartoon illustrations of representative features from the most prevalent categories—autocorrelation; time series discretized into symbols above and below a cutoff value to produce motifs (symbol sequences); and error in forecasting the future of the time series from a model trained on past values. Additional example time series for each contrast and species, including the effects of DBS, are provided in Supplementary Fig. 6, and statistical comparisons for each contrast are provided for RM_AMI_2 in Supplementary Fig. 7. Brain icons in **a** and **b** adapted from SciDraw under a Creative Commons license CC BY 4.0; macaque DBS in **a** and **b** adapted from ref. 13, AAAS.

obtain a single overall value representing how each feature is affected by that anesthetic in that species. This generates one summary effect size per feature, per contrast (Fig. 3a and see Extended Data Fig. 1 for the full range of effect sizes across contrasts for each feature). Next, we compare the contrasts to identify time-series features that are consistently altered across species and across anesthetics. Please note that this analysis includes the contrast between CT DBS and no-DBS in the macaque, as well as between CT DBS and VT DBS, that is, when the animal is re-awakened despite the presence of propofol in the bloodstream—thereby ensuring that we only retain features

that track the anesthetic's effect on behavioral responsiveness, not its mere presence. Specifically, we filter the features to retain only those whose overall direction of change (increase or decrease) is the same across all awake–anesthesia contrasts, in every species considered here (that is, all positive or all negative). Please note that this is a stringent criterion—any feature would be excluded from this set if its direction of change were inconsistent in even just one contrast of one dataset. Indeed, neither motion nor temporal signal-to-noise (tSNR) proxy track anesthesia state in a way that would meet our criterion of consistency—each shows both increases and decreases across the various datasets,

unlike every one of our consistent features (Supplementary Fig. 3 and Supplementary Table 1). In other words, the features of neural dynamics that we identify are more consistent than either motion or tSNR proxy in their association with anesthesia. With 15 contrasts, the probability of a feature showing such a consistent change purely by chance is $1/(2^{14})$ or 0.00006; hence, we should expect a single consistent feature due to chance for every 16,384 (more than twice as many features as we include). Instead, we find 485 time-series features that are consistently altered across regions/neurons, across anesthetics and across species (Fig. 3a). These dynamical signatures of anesthesia are highly correlated across different anesthetics and different species (Fig. 3b).

The vastness and diversity of the scientific literature on time-series analysis come with a challenge—not all features are equally straightforward to interpret, nor is it feasible to interpret hundreds of features individually. Some features may come from more obscure pockets of the literature, or reflect more convoluted properties or transformations on the data. We used a range of approaches to address this issue. First, we used domain knowledge across the author group to identify meaningful and interpretable properties among the consistent ones (pointing to autocorrelation and forecasting error). We also stratified dynamical features into ten broad categories, based on associated keywords in hctsa^{27,28} and further inspection (Methods; Supplementary Table 2). Notably, this is not intended to be a formal taxonomy of dynamics—some features may plausibly belong to more than one category, and some categories are only loosely defined. Nonetheless, stratifying features can be helpful to narrow down what the consistent features returned by our comprehensive screening have in common. In particular, among the consistent features, we find categories pertaining to autocorrelation and forecasting (Fig. 3d).

Examining specific individual features from these broad categories, we find that, on one hand, features related to linear and nonlinear temporal autocorrelation of neural signals are reduced under anesthesia (Fig. 3c,d). For example, some of the features showing large reductions are AC_3 and RM_AMI_2, which index the autocorrelation at lag 3 and automutual information at lag 2 of the time series, respectively. On the other hand, anesthesia increases the error of forecasting the future of a time series based on its past (Fig. 3c,d). For example, FC_LocalSimple_lfit4_meanabserr quantifies the mean absolute error of a linear fit from the past four time points, and FC_LocalSimple_mean2_meanabserr reflects the mean absolute error of forecasting based on the mean of the last two time points. Figure 3e illustrates how these features capture changes in the underlying dynamics of neural time series, focusing on autocorrelation as a feature that is straightforward to compute and readily interpretable.

We also find a high prevalence of the symbolic category (Fig. 3d). Guided by this observation, we find that anesthesia reduces the prevalence of ‘stable’ or ‘uniform’ motifs, whereby the same symbol occurs multiple times in a row (for example, a motif SB_motif3_quantile_aaa, whereby the time-series value is in the top of three quantiles thrice in a row) and instead it increases the prevalence of ‘unstable’ or ‘mixed’ motifs (for example, SB_motif2_median_uud, whereby the time series mixes values higher and lower than a median split), which we can interpret as overall destabilization of local dynamics (we discuss this point in detail in the ‘Discussion’). Illustrations of the three most prevalent categories of dynamical features are provided in Fig. 3f. Altogether, we find that anesthesia appears to induce a breakdown in the relationship between past and future of neural activity, whereas a change in the opposite direction is consistently observed upon re-awakening induced by targeted thalamic DBS in the macaque.

Temporal autocorrelation of spontaneous neural activity has been interpreted as reflecting how long neural information persists in a local brain area to influence its future behavior—the ‘temporal receptive window’ over which inputs coming into that brain region are integrated^{1,3,38–40}. Our data-driven analysis suggests that this fundamental organizational property of the brain is compromised under

anesthesia. We therefore follow up this data-driven analysis in a targeted manner by explicitly quantifying the intrinsic timescale at which each region operates. We define intrinsic timescale as in ref. 41, as the product of repetition time (TR) and the sum of autocorrelation function values up to the point where autocorrelation drops to zero, such that the future of the time series becomes independent of its past (Fig. 4a). A larger value of this measure indicates a longer intrinsic timescale⁴¹. For each species (human, macaque, marmoset, mouse, zebrafish and nematode), we compare the distribution of regional intrinsic timescales between wakefulness and anesthesia. Within every single species, we find that on average across regions, intrinsic neural timescales are significantly reduced under anesthesia (Fig. 4b–g; results for each individual contrast are provided in Supplementary Fig. 8). This effect is neither uniform across regions nor random. Rather, anesthetic-induced reduction of intrinsic timescales is proportional to each region’s baseline level of intrinsic timescale, such that regions/neurons with longer intrinsic timescales face the most severe reductions, indicated by significant negative correlations across regions between baseline level and anesthetic-induced change (Fig. 4b–g). In contrast to the anesthetic-induced shortening of intrinsic local timescales, intrinsic timescales become longer upon DBS of the centromedian thalamus in macaques—both compared against anesthesia without stimulation, and compared against behaviorally ineffective stimulation of the control site in VT (Extended Data Fig. 2). Hence, the direction of change of intrinsic local timescale tracks behavioral responsiveness. Altogether, at the temporal resolution afforded by fMRI and GCaMP calcium imaging, we find that anesthesia consistently induces a compression of the brain’s intrinsic timescales, leading to reduced local persistence of information, and shorter temporal windows for integration.

From local dynamics to global networks

Up to this point, we have focused on local dynamics. However, individual neurons and regions are embedded in a larger synaptic network. In a complex network such as the brain, changes in regional dynamics may both shape and be shaped by changes in inter-regional functional interactions. For instance, if two populations begin to operate at faster or slower timescales, what effect does this have on their capacity to spontaneously synchronize with each other? To investigate the relationship between local dynamics and network-wide communication, we estimate two measures of inter-regional dependence (Fig. 5a). First, we compute the temporal synchrony of fluctuations in neural activity, operationalized as the magnitude of functional connectivity (FC; zero-lag Pearson’s correlation between blood-oxygen-level dependent (BOLD)/calcium imaging time series; Fig. 5a). Second, we compute the magnitude of pairwise similarity between regional dynamical features generated by our large set of time-series features²⁹, measuring the dynamical profile similarity (DPS) of two neuronal populations²⁹ (Fig. 5c). The two measurements allow to identify distributed regions that potentially display common local dynamics—suggesting common functional roles—without necessarily displaying time-locked activity.

We find that, across species and anesthetics, anesthesia desynchronizes the interactions between different regions (Fig. 5b). At the same time, we find that anesthesia does not only change the dynamical properties of individual regions, it also weakens the relationships between the dynamical profiles of different regions, significantly reducing their similarity (Fig. 5d). In addition, in the awake brain, regions (or neurons) with similar dynamics—suggesting similar computational properties—tend to display time-locked activity, suggesting that they also perform the same function (Fig. 5e). To provide an analogy, coworkers (regions) with similar job descriptions (dynamical profiles) may be likely to work similar hours (that is, be synchronized). However, in the anesthetized brain, regions with similar dynamics are less likely to show synchronous fluctuations, and lose their coordination (Fig. 5f and see also Supplementary Fig. 11 for statistical comparisons for each contrast and dataset). Notably, just like anesthesia’s effects on regional

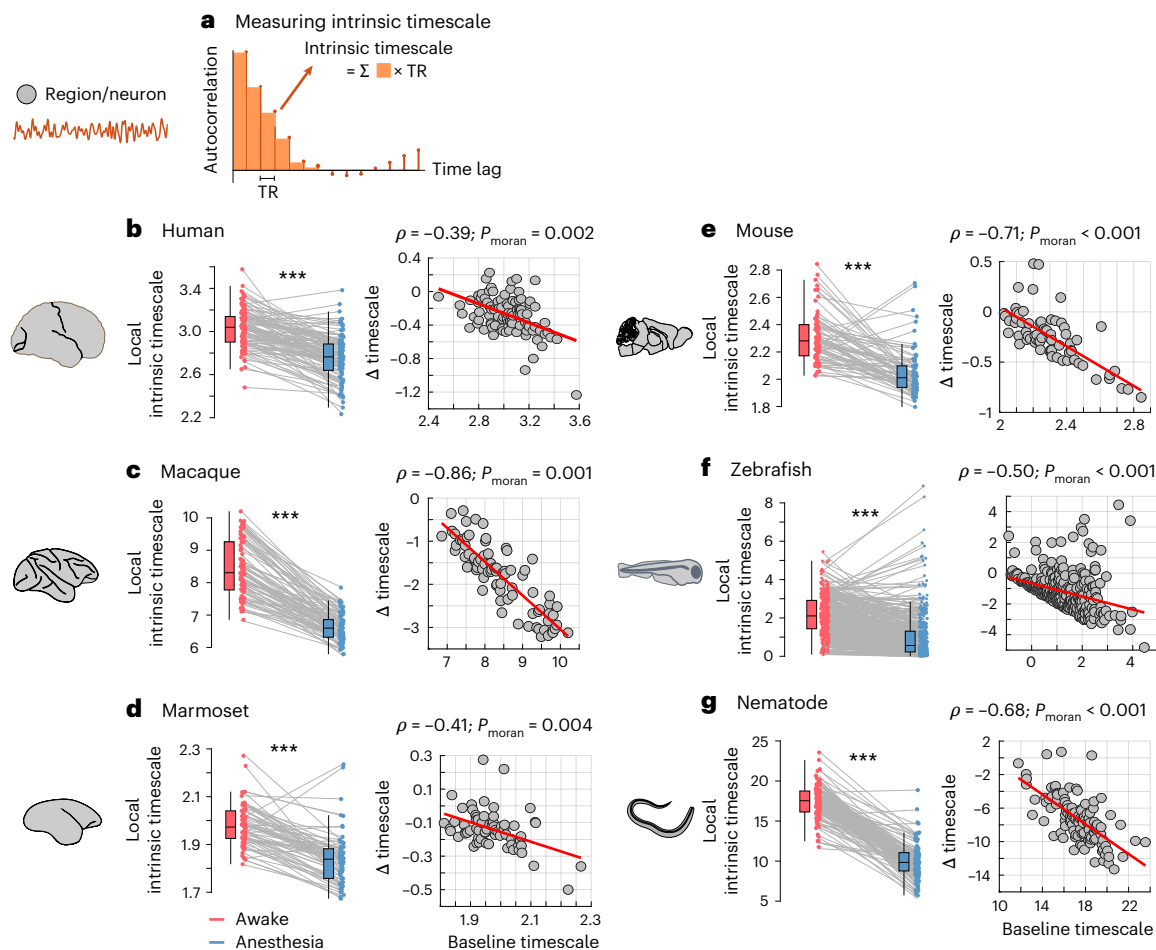


Fig. 4 | Anesthesia reduces intrinsic neural timescales across species.

a, Quantifying intrinsic neural timescales from spontaneous activity. For each region/neuron, the autocorrelation function is obtained by correlating the original time series with a time-lagged version of itself for increasing lags. Intrinsic neural timescale is computed by summing the values of the autocorrelation function (each multiplied by the TR) up to the point where autocorrelation drops to zero. A larger value of this measure therefore indicates a longer intrinsic timescale⁴¹. **b–g**, For each species (human (**b**), macaque including the DBS contrasts (**c**), marmoset (**d**), mouse (**e**), zebrafish (**f**) and nematode (**g**)), we obtain the mean intrinsic timescale of each region across wakefulness (red), and across anesthesia conditions (blue). Within each species,

we compare these distributions of regional intrinsic timescales. Each datapoint represents one region/neuron. Box plots indicate centerline and median; box limits indicate upper and lower quartiles; whiskers indicate $1.5 \times \text{IQR}$. *** $P < 0.001$, from nonparametric (permutation based) paired-samples two-sided t test. We also show the Spearman correlation between anesthetic-induced change in regional intrinsic timescale and each region's intrinsic neural timescale while awake. Significance of correlations (two sided) is assessed against null models generated with Moran spectral randomization (Methods). See Source Data for full statistical reporting. Brain icons in **b, c, e–g** adapted from SciDraw under a Creative Commons license [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/). IQR, interquartile range.

dynamics, these effects of anesthesia on inter-regional interactions reverse their direction of change upon re-awakening induced by DBS of the centromedian thalamus, whether contrasted with no stimulation, or with inefficacious stimulation (at the same intensity) of the control site in VT (Fig. 5b,d,f). Altogether, anesthesia changes both local neural dynamics and inter-regional interactions.

Mapping local neural dynamics to gene expression across species

So far, we have observed that diverse anesthetics induce consistent changes in local neural dynamics across species. Because anesthetics can perturb local biophysics by acting on various molecular targets and ion channels, for example, altering postsynaptic excitability in response to neurotransmitter release^{42–44}, we then ask whether these phylogenetically conserved changes in local dynamics might be underpinned by patterns of gene expression that are similarly conserved across species. To address this question, we use species-specific databases of cortical transcriptomics for human (microarray), macaque (spatiotemporal enhanced resolution omics sequencing (stereo-seq)),

mouse (in situ hybridization (ISH)) and marmoset (ISH; Fig. 6a; see Methods for details of each dataset). For each species, we map spatial patterns of cortical expression for a list of 23 orthologous brain-related genes that are available across all four species. This list is a subset at the intersection of the previously published lists of human–macaque⁴⁵ and human–mouse⁴⁶ orthologous brain-related genes, and genes for which quantitative data are also available throughout the cortex for the marmoset. It comprises genes pertaining to neurotransmitter and neuropeptide receptors, including key glutamate and GABA receptors (AMPA, NMDA, GABA_A) as well as the dopaminergic, serotonergic, noradrenergic and cholinergic systems; myelin; and interneuron cell-type markers (parvalbumin, somatostatin, calbindin, vasoactive intestinal polypeptide; see Supplementary Table 4 for the list of gene names).

We then use partial least squares (PLS) correlation to integrate cortical transcriptomics with dynamical features (each concatenated across species, after z scoring within species). PLS is a data-driven technique that identifies multivariate patterns of maximum covariance across datasets—in this case, regional gene expression and regional

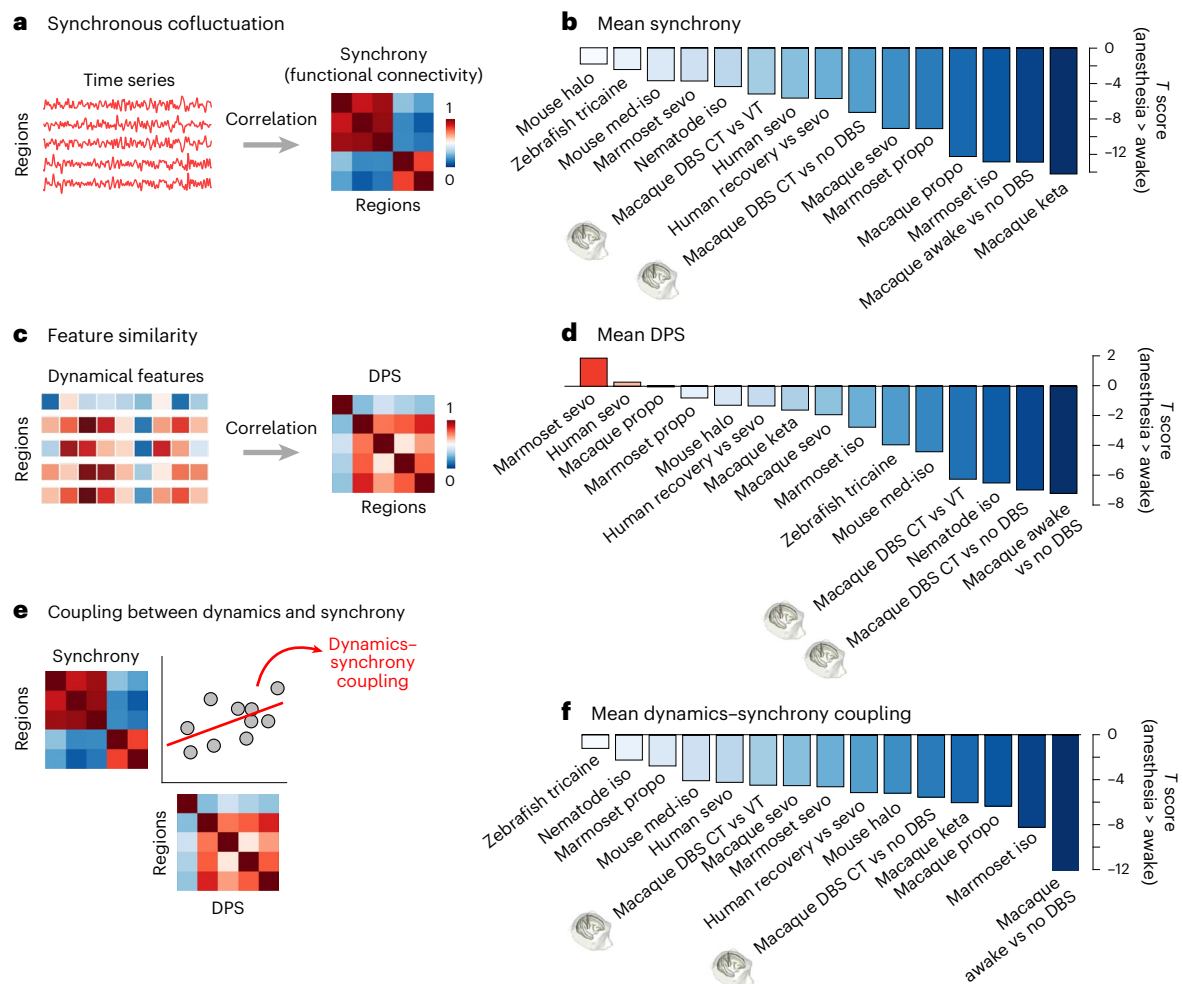


Fig. 5 | Anesthesia desynchronizes the brain and decouples synchrony from local dynamics. **a**, Synchrony is measured as the magnitude of correlation between two regions' time series over time, reflecting confluctuation. **b**, Across species and anesthetics, anesthesia significantly reduces the mean magnitude of synchronous confluctuations of neural activity. **c**, DPS is measured as the magnitude of correlation between the dynamical features of two regions' time series. For both synchrony and DPS, the result is a region-by-region matrix of pairwise similarities. **d**, Anesthesia significantly reduces the mean similarity

across regions' dynamical profiles. **e**, Coupling between synchrony and dynamics is obtained by correlating the matrix of inter-regional synchrony and the matrix of inter-regional DPS. It quantifies the extent to which regions characterized by similar time-series features also show similar temporal confluctuations. **f**, Across species and anesthetics, anesthesia reduces the coupling between synchrony and dynamics. *T* scores calculated from nonparametric permutation-based two-sided *t* test. Macaque DBS in **b**, **d** and **f** adapted from ref. 13, AAAS.

changes in dynamical features, each z scored within species and then concatenated across species (Methods). As a form of unbiased feature selection to aid interpretation, instead of the full set of consistent dynamical features we use a reduced set of representative time-series features (known as the canonical time-series characteristics or catch22 (ref. 47)). Because catch22 includes features pertaining to autocorrelation, forecasting and temporal frequency, capturing many dynamical properties that we found to be consistently perturbed by anesthesia, for our main PLS analysis we use the catch22 features to provide more interpretable results (Methods; Fig. 6, Supplementary Table 3 and Supplementary Figs. 12–15) for the list of 21 included features and their explanations. Crucially, the same latent variables (LVs) are recovered when using the full set of consistent dynamical features see Extended Data Fig. 3 and Supplementary Fig. 16).

PLS reveals a statistically significant LV (linear weighted combination of the original variables) relating anesthetic-induced changes in local dynamics and cortical patterns of gene expression across species. This LV2 explains significantly more covariance than explained by spatial autocorrelation alone (25%; by contrast, LV1 is not significant, after taking into account spatial autocorrelation). This significant LV is spatially associated with consistent cortical patterns in each

species, which can be broadly characterized as anterior–ventral to posterior–dorsal gradient (Fig. 6c). At one end, LV2 relates measures of time reversibility and forecasting error with the expression of a key marker gene for inhibitory interneurons (*PVALB*), and the α_1 subunit of the inhibitory GABA_A receptor, target of propofol and many volatile anesthetics^{43,44}, as well as the pacemaker channel *HCN1*, a shared target of both propofol and ketamine^{18,43}; myelin-related gene *MBP*; and the inhibitory M₂ muscarinic cholinergic receptor *CHRM2* (Fig. 6d,e). At the other end, LV2 relates changes in measures of autocorrelation with NMDA excitatory receptors *GRIN3A*, which are inhibited by anesthetics including ketamine⁴³, as well as other glutamatergic excitatory receptors, both ionotropic (*GRIA1* AMPA receptor) and metabotropic (*GRM5*, *GRM1*); excitatory nicotinic cholinergic receptors (*CHRNA2*), and cannabinoid and opioid neuromodulatory receptors (*CNR1*, *OPRK1*; Fig. 6d,e). Altogether, we find that conserved anesthetic-induced changes in local dynamics are subtended by a transcriptomic gradient that is likewise conserved (at least across rodent and primate species), encompassing genes pertaining to regulation of excitation, inhibition and neuronal rhythms—possibly indicating shared neurobiological circuitry on which anesthesia operates.

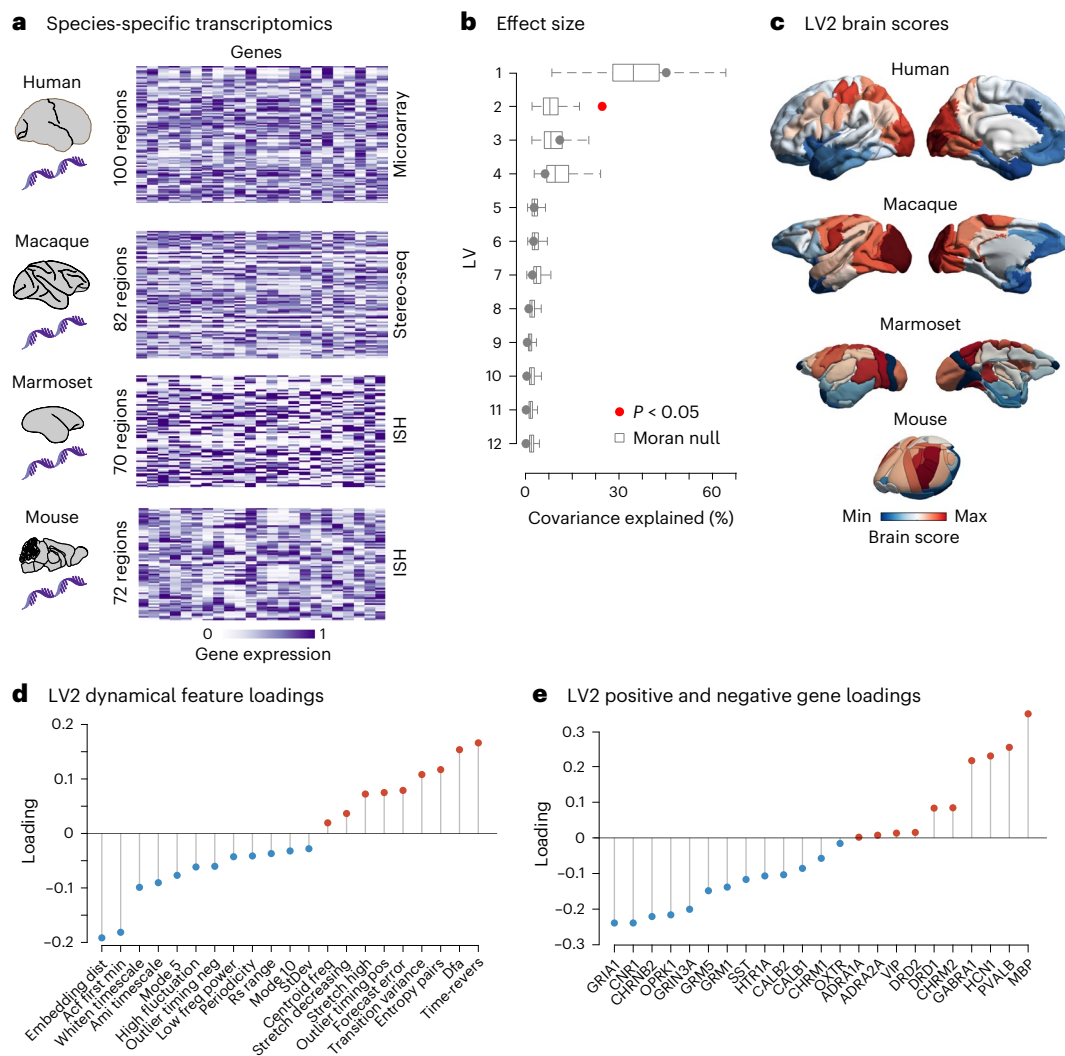


Fig. 6 | Anesthetic-induced changes in neural dynamics map onto phylogenetically conserved dimensions of cortical gene expression. **a**, Species-specific cortical expression of key brain-related genes from microarray (human), stereo-seq (macaque) and ISH (marmoset and mouse) was obtained. Expression of each gene is sigmoid normalized to lie in the interval between 0 and 1. RNA icon in **a** adapted from SciDraw under a Creative Commons license [CC BY 4.0](#). **b**, We find a statistically significant latent dimension of multivariate association between gene expression and anesthetic-induced feature change (LV2). The first latent dimension is not significant beyond the effect of spatial autocorrelation. We assess significance against a null distribution generated using Moran spectral randomization (Methods), whereby brain maps of each species are randomized, but their spatial autocorrelation is preserved, embodying the null hypothesis that local dynamics and gene expression are spatially correlated with each other purely because of inherent spatial autocorrelation. For each LV, a one-sided P value is computed as the proportion of null covariances explained (across 500 surrogate PLS analyses) that are greater in magnitude than the empirical covariance explained. No adjustment is

made for multiple comparisons. Box plots indicate centerline and median; box limits indicate upper and lower quartiles; whiskers indicate $1.5 \times \text{IQR}$; $n = 500$ surrogates from Moran spectral randomization. See Source Data for individual P values. **c**, Representation of the significant LV2 on the cortex of human, macaque, marmoset and mouse, delineating a conserved anterior–ventral to posterior–dorsal gradient. **d**, Loading of each representative dynamical feature onto the significant dimension of multivariate association with gene expression. **e**, Loading of each gene onto the significant dimension of multivariate association with dynamical features. Red indicates positive loading, blue indicates negative loading. Highly consistent LVs are recovered, when the analysis is repeated using all dynamical features that are consistently perturbed by anesthesia across species, instead of the reduced set from catch22 (Extended Data Fig. 3). We observe the same significant LV2, with the same anterior–ventral to posterior–dorsal cortical gradient across species, alongside correlated gene loadings (Supplementary Fig. 16; please note that sign of PLS LVs is arbitrary). RNA and brain icons in **a** adapted from SciDraw under a Creative Commons license [CC BY 4.0](#).

Computational modeling of anesthetized neural dynamics from microscale to macroscale

Finally, having identified a consistent dynamical signature of anesthesia across species and anesthetics, we seek to better understand its potential mechanistic origin through computational modeling. Computational models provide a way to link specific biophysical parameters to their functional consequences by simulating how brain activity changes upon changing the parameters^{48–50}. In this vein, recent work developed a computational approach to evaluate how molecular mechanisms impact large-scale brain activity, and

used it to model anesthesia⁵⁰. The modeling framework consists of a whole-brain model of biophysically grounded mean fields, which integrate cellular and molecular properties (membrane conductances and AMPA, NMDA and GABA_A synaptic receptors), thereby linking microscale properties to their macroscale consequences. At the microscale, the model simulates anesthesia as biologically realistic increase in the time constant of inhibitory synaptic decay, which is empirically observed with GABA-ergic anesthetics (such as propofol, sevoflurane, isoflurane, halothane, etc.) that act as positive allosteric modulators of the GABA_A receptor^{43,44}, potentiating GABA-mediated inhibition

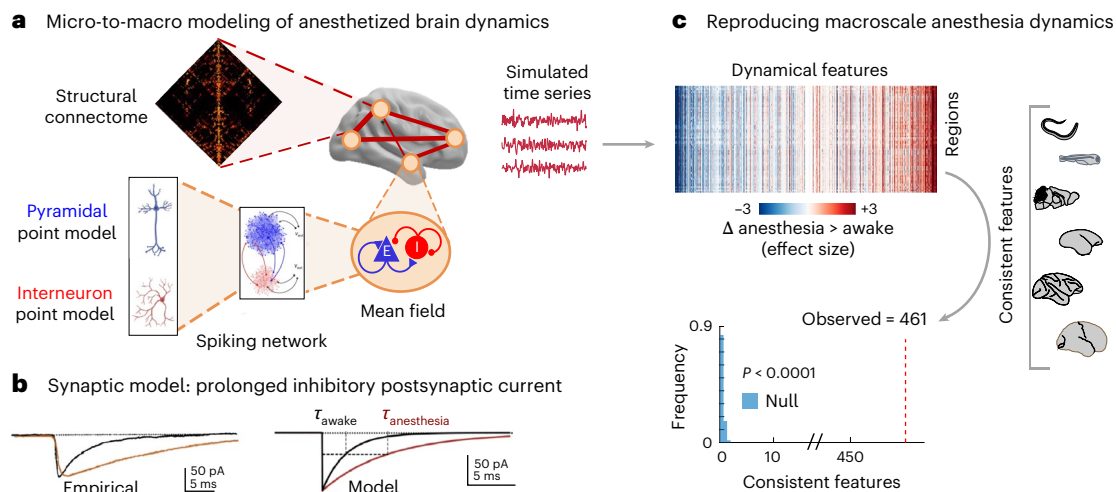


Fig. 7 | Computational modeling of anesthetic-induced changes in macroscale local dynamics from microscale synaptic mechanisms.

a, Computational model to assess how microscale molecular mechanisms impact macroscale brain dynamics. The whole-brain model consists of biophysically grounded mean-field reductions (one for each brain region) of networks of excitatory and inhibitory neurons, integrating microscale cellular and molecular properties (membrane conductances and AMPA, NMDA and GABA_A synaptic receptors) to simulate regional fMRI signals. Once connected according to empirical anatomical connectivity of the human brain from in vivo diffusion tractography, the resulting whole-brain model links biophysically meaningful synaptic-level mechanisms to macroscale dynamics. **b**, At the microscale, the model simulates the empirically observed prolongation of inhibitory postsynaptic currents induced by GABA-ergic anesthesia, as an increase in the time constant of inhibitory synaptic decay. See Extended Data Fig. 4 for

an alternative model for simulating the shortening of excitatory postsynaptic currents induced by NMDA receptor antagonists such as ketamine. **c**, At the macroscale, we apply comprehensive dynamical phenotyping to the simulated BOLD signals from the model in the awake and anesthetized regimes ($n = 19$ simulations for each condition), following the same workflow as for our empirical data. Among the 485 features that had shown consistent changes across all empirical contrasts from Fig. 3, 461 features (>95%) also show changes in the same direction in the computational model. This number is significantly greater than expected by chance, as assessed by a null model where each feature's direction of change (increase or decrease) is assigned at random, repeated 10,000 times (one-sided $P < 0.0001$). Credit: schematics in **a** and **b** adapted from ref. 50, Springer Nature Limited. Brain icons in **c** adapted from SciDraw under a Creative Commons license CC BY 4.0.

by prolonging the duration of inhibitory postsynaptic potentials⁵⁰. Mean-field reductions of the microscale model are used to simulate regional BOLD activity. Once connected according to the empirical structural connectivity of the human brain, the resulting whole-brain model links biophysically meaningful synaptic-level mechanisms to macroscale dynamics⁵⁰.

Thus, molecular mechanisms are propagated consistently from the single-cell synaptic scale to mesoscale mean-field regional dynamics and finally to macroscale structure-constrained whole-brain activity. Crucially, here we do not perform any additional fitting or tuning of the model discussed in ref. 50, instead using the published parameters for awake and anesthetized dynamics. In other words, we use the model to ask whether anesthetic-induced prolongation of inhibitory postsynaptic potentials, a phenomenon experimentally observed at the microscale, could be mechanistically sufficient to reproduce the dynamical phenotype of anesthesia that we observed at the macroscale. To test this hypothesis, we apply comprehensive dynamical phenotyping to evaluate the model's capacity to reproduce the empirical changes in local dynamics induced by anesthesia. Remarkably, we find that 95% of features that are consistent across all empirical contrasts (461/485; significantly more than expected by chance, $P < 0.0001$) are also successfully reproduced by this biophysical model that simulates anesthesia as prolonged inhibitory postsynaptic current (Fig. 7). We also show that, in the biophysical model, the timescale is significantly reduced across regions, analogous to what we observed empirically (Supplementary Fig. 17a). In addition, we find a negative correlation between the regional reduction in timescale and a region's original timescale, consistent with the empirical observation that across species, the timescale loss induced by anesthesia is greater for regions with longer initial timescale (Supplementary Fig. 17b). Please note that the model is not trained or tuned based on the htcsa features, but rather using a biologically realistic change in microscale postsynaptic

potential. Nevertheless, it still manages to reproduce the vast majority of the macroscale changes that we observed empirically.

Although potentiation of inhibitory postsynaptic potentials is a prominent mechanism for many widely used anesthetics, including many of those used in the present study (propofol, sevoflurane, halothane, isoflurane), other cellular-level and molecular-level mechanisms may also be at play. Indeed, ref. 50 also provides a model that implements the synaptic-level effects of a different class of anesthetics, antagonists of the glutamatergic NMDA receptor (for example, a high dose of ketamine). At the microscale, such drugs induce a shortening of the excitatory postsynaptic current, which was implemented in the same multiscale computational modeling framework developed in ref. 50, as a decrease in the excitatory synaptic decaytime. To ensure robustness and convergence of our modeling results, we therefore also assess this second, distinct model of a biologically observed synaptic-level mechanism of anesthesia in terms of its ability to reproduce (without any additional fine-tuning or fitting) the changes in local neural dynamics induced by anesthesia at the macroscale. We find that this alternative model also successfully reproduces >90% of anesthetic-induced changes in macroscale local dynamics (Extended Data Fig. 4). Hence, we demonstrate that the biophysical model's ability to reproduce the empirical effects of anesthesia on local dynamics is not critically dependent on the specific combination of model parameters. Instead, having found that anesthetics with different molecular targets converge to produce convergent macroscale effects on brain dynamics (and ultimately behavior), we can now provide a possible computational implementation whereby different biologically plausible synaptic mechanisms can induce those same convergent effects at the macroscale.

Sensitivity, robustness and validation

In the Supplementary Results, we conduct several additional sensitivity and robustness analyses and validation. We show that the number of

features showing consistent change across every anesthetic and species could not occur purely due to chance alone, as a result of the large number of features that we test. We also provide extensive evidence that results are not due to specifics of data selection or data processing, such as denoising method, temporal resolution, temporal filtering or motion confounds.

Discussion

Here we provided a systematic and comprehensive exploration of how diverse anesthetics reshape local dynamics of fMRI and calcium signals, across 6 species—from nematode to fish to human—and across over 6,000 time-series features. We adopted a data-driven approach to triangulate on a conserved dynamical signature of anesthesia across imaging modalities, scales, species and anesthetics. Through this unbiased, data-driven approach, we identified an evolutionarily conserved dynamical profile of anesthesia, indicating that what is common across species and anesthetics is not only the behavioral response to anesthesia (isolation from the environment), but also anesthesia's effect on specific features of neural activity. The anesthetized state is characterized by features that indicate reduced temporal autocorrelation, shorter intrinsic timescale and faster decay of neural activity. A consistent effect in the opposite direction is induced by DBS of the centromedian thalamus in the macaque, whereupon the animal re-awakens, providing a further link between neural and behavioral effects. The finding that anesthetics' suppression of sensation and action is consistently accompanied by specific changes in neural activity hints at the existence of evolutionarily conserved circuit dynamics that may be necessary for information processing.

The comprehensive strategy adopted here aims to overcome a fundamental limitation of the existing literature (despite some notable exceptions^{21–24}), whereby each study only picks a handful of ad hoc measures for analysis, potentially introducing bias and leaving large gaps in our understanding of how anesthetics reshape neural dynamics. Consistent with the present work, shorter fMRI intrinsic timescale has been previously reported in humans under deep general anesthesia (but not under mere sedation) and in patients with disorders of consciousness⁵¹; reduced fMRI autocorrelation was also reported in anesthetized macaques⁹. Likewise, under anesthesia, human fMRI shows a reduction in the power of slow frequencies⁵²; a shift to faster neuronal activity was also reported in anesthetized *C. elegans* with 2 Hz calcium imaging⁵³, and medetomidine-isoflurane anesthesia in mice is known to shift the spectral components of fMRI signal fluctuations toward higher frequencies⁵⁴. In Supplementary Note 1, we contextualize the present results with the electrophysiology literature about anesthetic-induced slowing down of neural dynamics. Taken together, the present findings of infra-slow fMRI becoming faster under anesthesia, and the literature indicating that fast electrophysiology becomes slower, suggest convergence toward a narrower, less diverse range of timescales during anesthesia. More broadly, the present results of anesthetic-induced desynchronization are also in excellent agreement with recordings from local field potentials and intracranial electrocorticograms in humans, which led the authors to conclude that, under propofol anesthesia, neuronal activity becomes desynchronized and functionally fragmented across both time and space⁵⁵. Here we confirm that desynchronization of slow neural dynamics generalizes even more broadly across species and across scales, from neuronal calcium imaging to mammalian hemodynamics.

A challenge of data-driven approaches lies in the need for post hoc interpretation of results. Here we adopted a three-step strategy to interpret the results. First, to guide and aid interpretation, we grouped dynamical features into ten broad categories, based on associated keywords from hctsa^{27,28} and further inspection. We emphasize that this is not a formal or definitive taxonomy of dynamics, and that each category may include features that change in opposite directions in response to the same manipulation. For example, forecasting error is reduced whenever forecasting accuracy increases. Likewise, measures

of autocorrelation decay 'time' (for example, the number of time points until first zero crossing of the autocorrelation function) tend to decrease as intrinsic timescale shortens, whereas features quantifying exponential decay 'rates' of the autocorrelation increase, reflecting an approximately reciprocal relationship and therefore opposite directionality. In other words, what these categories provide is a broad overview of the kinds of properties of the signal that are sensitive to our manipulation. Therefore, for the feature categories most prominent among the data-driven anesthesia signature (autocorrelation, forecasting, symbolic motifs), the second step in our interpretation strategy is to identify representative individual features that are clear to understand and are informative about the direction of change induced by our manipulation (for example, lag-3 autocorrelation is reduced under anesthesia; forecasting error is increased). Based on these results, we interpret the dynamical signature of anesthesia as suggesting that, in the anesthetized brain, intrinsic neural timescales become systematically shorter. Although the time-series features that characterize the dynamical profile of anesthesia originate from different fields of science and perform different computations on the input time series of neural activity, they are broadly related to reduced stability and greater unpredictability of the signal's future from its past, coinciding with decreased measures of linear and nonlinear autocorrelation. Finally, we situate these findings in the broader context of the existing literature on anesthesia, neural timescales and their intersection. In the awake mammalian brain, short timescales (whereby autocorrelation decays quickly) are thought to encode rapidly-changing sensory information. Conversely, long timescales reflect longer 'temporal receptive windows', supporting integrative processes and the encoding of contextual information^{1,3,38–41,56–58}. Indeed, recent applications of hctsa have highlighted the prominence of autocorrelation-related measures for both brain organization and human aging^{32,33}. In turn, shorter timescale means that the brain is less capable of encoding contextual information in its ongoing dynamics, and less capable of integrating information over time^{3,56,57}. This faster decay of local activity, preventing integration, may explain why, under anesthesia, incoming stimuli fail to escalate the processing hierarchy and achieve global relevance^{713,59}, up to the point that the organism will fail to respond even to noxious stimuli.

Anesthetic-induced breakdown of the relationship between local and global activity is also consistent with work that shows that, during anesthesia and sleep, spontaneous and stimulus-evoked activity fail to propagate globally—a potential account for the concomitant loss of behavioral responsiveness¹³. Indeed, here we found that when centromedian thalamic DBS exerts changes on the brain's dynamical phenotype in the opposite direction, the animal also re-awakens from anesthesia—with neither effect occurring upon stimulation of the control site in VT (Supplementary Note 2). Putting the region-level and network-level perspectives together, we speculate that the present findings suggest that, under anesthesia, local neural activity becomes functionally isolated in space and time: less able to influence processing at other regions (reduced functional synchrony) and also less able to persist in time and influence future activity (reduced autocorrelation)—generating a dynamical regime that may be altogether 'inhospitable to the information exchange (...) critical to the coordination of events that allows both the sensation and response that is characteristic of a bidirectional relationship with the environment'⁵. Altogether, we interpret the present results as lending data-driven support to theoretical accounts wherein functional uncoupling/failure of integration was pinpointed as potential 'final common mechanism' or common endpoint of how diverse anesthetics exert their shared behavioral effects—a hypothesis that has stood the test of time for over two decades^{5–7,30,31}. Our results are consistent with such theoretical accounts, although more targeted experimental validation will be required to obtain more precise insight. In Supplementary Note 3, we consider why anesthesia may show consistent neural markers across such vast evolutionary differences.

If the effects of anesthesia on local dynamics are stereotyped across species, do they also have a common molecular origin? Broadly, two main themes emerge from the multivariate analysis of gene–dynamics relationships. First, a statistical association with biological substrates for brain rhythms and timescales (for example, the pacemaker hyperpolarization-activated cyclic nucleotide (HCN)-gated channels, which are present from invertebrates to mammals). *HCN1*-mediated inhibition was recently identified as a shared mechanism of propofol and ketamine anesthesia in humans¹⁸. Second, we found prominent spatial correspondence between anesthetic effects and molecular machinery of excitation and inhibition (Supplementary Note 4).

Our biophysical computational model further offers potential mechanistic support for key roles of both excitation and inhibition, and local timescales. The model links synaptic-level biophysical changes in local activity, based on microscale experimental findings, to their macroscale dynamical consequences⁵⁰ (see Supplementary Note 5 for additional discussion). Anesthesia is implemented in two distinct ways, corresponding to the main molecular mechanisms of GABA-ergic anesthetics (such as propofol, sevoflurane) and ketamine anesthesia^{43,50}. In one case, the time constant of inhibitory synaptic decay is increased, effectively potentiating the inhibitory postsynaptic current. In the other case, the excitatory synaptic decay time is decreased. Hence, both mechanisms involve an interaction between timescale and excitation or inhibition. Intuitively, both have the effect of reducing the postsynaptic neuron's ability to integrate incoming signals into a response—either by shrinking the temporal window over which an excitatory signal can facilitate subsequent postsynaptic spiking (which in turn makes it less likely that enough such signals will be received together) or by increasing the time over which an inhibitory signal can keep the postsynaptic neuron silenced. Altogether, our multiscale biophysical model demonstrates that a shorter timescale of postsynaptic excitation (respectively, prolonged inhibitory timescale) at the microscale mechanistically translates into shortening of the timescale of neural activity at the macroscale—not only at the level of individual neurons, but also entire brain regions, recapitulating our empirical results.

The consistency of dynamical effects across species suggests that dynamical phenotypes may provide a common frame of reference for cross-species comparison. Identifying mappings between the brains of humans and other species is a perennial question of translational neuroscience. The traditional approach has focused on anatomy, whereby homologous brain areas are identified according to shared morphological or cytoarchitectonic properties, or similar connectational patterns, or genetic fingerprints^{46,60–62}. A complementary approach involves finding homologs by identifying which brain regions show consistent responses to the same stimuli. Here we combined these two approaches—we used the high-dimensional common space of local dynamics (that is, same time-series features in every species) to enable interspecies comparison in response to the same intervention (anesthesia), which does not require direct one-to-one mapping between regions of different species. We then combined the availability of the same features with the availability of transcriptomic maps for the same genes across the same species to identify consistent mappings between features and genes. Because dynamics are ubiquitous across nervous systems, our findings show that dynamical phenotyping may provide a common reference frame to embed a wide and diverse range of neuroscientific datasets, from human fMRI to nematode calcium imaging.

The present work should be considered in light of inevitable methodological limitations (see Supplementary Note 6 and Supplementary Results for extensive discussion and control analyses). Our focus here was on anesthesia's effect on the brain's capacity to process environmental information, which is indexed by the loss of behavioral responsiveness—a marker that is widely shared across species and anesthetics^{4,5,7,8}. Although the generalization of our results across different species is a key strength of the present work, combining

datasets from different species and modalities is challenging due to methodological heterogeneity in acquisition modality and preprocessing. Although here we were interested in what is similar across species and anesthetics, differences between species and anesthetics were also evident. Some of these differences are likely biological, due to the different molecular mechanisms of specific anesthetics, different doses used in different species, or interspecies and interindividual differences in neural architecture and other biological phenotypes. Understanding their origins and behavioral relevance may represent an interesting avenue for future pursuit. Crucially, the driving question of the present work was about the shared effects of anesthesia on local dynamics. Therefore, here we focused only on those effects that are the same across anesthetics, species and imaging modalities. Logically, such consistent effects cannot be explained by the differences across drugs, species or data modalities. In this context, differences in how the various datasets were acquired and processed may even be seen as an asset—combining multiple species and anesthetics strengthens our ability to triangulate on a 'final common endpoint' of anesthesia at the neural level to match the common behavioral endpoint, while convergence of results across extraneous methodological variations can be interpreted as additional support for the robustness of our findings.

In conclusion, through comprehensive phenotyping of brain dynamics and systematic comparison across species, we have identified a dynamical regime that characterizes anesthetic-induced breakdown of information processing. Across diverse species and scales, anesthesia is characterized by consistent deviations from the dynamical regime of the awake brain. Under anesthesia, local neural activity becomes spatiotemporally isolated—both at the level of single neurons and at the level of brain regions. DBS of the CT has the opposite effect, demonstrating bidirectional control over brain dynamics. Biophysical modeling further indicates possible mechanistic links between the macroscale dynamical phenotype of anesthesia and microscale effects of key molecular targets on the timescales of synaptic excitation and inhibition.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41593-026-02460-4>.

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Methods

Human fMRI anesthesia dataset

The human sevoflurane data included in this study have been published before^{34,63,64}. For clarity and consistency of reporting, we use the same wording as in those previous publications, and for details we refer the reader to ref. 34.

Participants and ethics. The ethics committee of the medical school of the Technische Universität München approved the current study, which was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from volunteers at least 48 h before the study session. Twenty healthy adult men (20–36 years of age; mean = 26 years) were recruited through campus notices and personal contact, and compensated for their participation in the study. Before inclusion in the study, detailed information was provided about the protocol and risks, and medical history was reviewed to assess any previous neurologic or psychiatric disorder. A focused physical examination was performed, and a resting electrocardiogram was recorded. Further exclusion criteria were the following: physical status other than American Society of Anesthesiologists physical status I, chronic intake of medication or drugs, hardness of hearing or deafness, the absence of fluency in German, known or suspected disposition to malignant hyperthermia, acute hepatic porphyria, history of halothane hepatitis, obesity with a body mass index more than 30 kg m⁻², gastrointestinal disorders with a disposition for gastroesophageal regurgitation, known or suspected difficult airway and the presence of metal implants. Data were acquired between June and December 2013.

Anesthesia protocol. Sevoflurane concentrations were chosen so that participants tolerated artificial ventilation (reached at 2.0 vol%) and that burst suppression (BS) was reached in all participants (around 4.4 vol%). To make group comparisons feasible, an intermediate concentration of 3.0 vol% was also used. In the MRI scanner, participants were in a resting state with eyes closed for 700 s. Because electroencephalographic (EEG) data were simultaneously acquired during MRI scanning³⁴ (although they are not analyzed in the present study), visual online inspection of the EEG was used to verify that participants did not fall asleep during the pre-anesthesia baseline scan. Sevoflurane mixed with oxygen was administered through a tight-fitting facemask using an fMRI-compatible anesthesia machine (Fabius Tiro, Dräger). Standard American Society of Anesthesiologists monitoring was performed—concentrations of sevoflurane, oxygen and carbon dioxide were monitored using a cardiorespiratory monitor (DatexaS, General Electric). After administering an end-tidal sevoflurane concentration (etSev) of 0.4 vol% for 5 min, sevoflurane concentration was increased in a stepwise fashion by 0.2 vol% every 3 min until the participant became unconscious, as judged by the loss of responsiveness to the repeatedly spoken command ‘squeeze my hand’ two consecutive times. Sevoflurane concentration was then increased to reach an end-tidal concentration of approximately 3 vol%. When clinically indicated, ventilation was managed by the physician and a laryngeal mask suitable for fMRI (i-gel, Intersurgical) was inserted. The fraction of inspired oxygen was then set at 0.8, and mechanical ventilation was adjusted to maintain end-tidal carbon dioxide at steady concentrations of 33 ± 1.71 mmHg during BS, 34 ± 1.12 mmHg during 3 vol% and 33 ± 1.49 mmHg during 2 vol% (throughout this article, mean $\pm$ s.d.). Norepinephrine was given by continuous infusion (0.1 ± 0.01 μ g kg⁻¹ min⁻¹) through an intravenous catheter in a vein on the dorsum of the hand to maintain the mean arterial blood pressure close to baseline values (baseline = 96 ± 9.36 mmHg; BS = 88 ± 7.55 mmHg; 3 vol% = 88 ± 8.4 mmHg; 2 vol% = 89 ± 9.37 mmHg; follow up = 98 ± 9.41 mmHg). After insertion of the laryngeal mask airway, sevoflurane concentration was gradually increased until the EEG showed BS with suppression periods of at least 1,000 ms and about 50% suppression of electrical activity (reached at 4.34 ± 0.22 vol%), which is characteristic of deep anesthesia. At that point, another

700 s of electroencephalogram and fMRI data were recorded. Further 700 s of data were acquired at steady etSev of 3 and 2 vol%, respectively (corresponding to Ramsay scale level 6, the deepest), each after an equilibration time of 15 min. In a final step, etSev was reduced to twice the concentration at loss of responsiveness. However, most of the participants moved or did not tolerate the laryngeal mask any more under this condition; therefore, this stage was not included in the analysis. Sevoflurane administration was then terminated, and the scanner table was slid out of the MRI scanner to monitor postanesthetic recovery. The participant was manually ventilated until spontaneous ventilation returned. The laryngeal mask was removed as soon as the patient opened his mouth on command. The physician regularly asked the participant to squeeze their hand—recovery of responsiveness was noted to occur as soon as the command was followed. Fifteen minutes after the time of recovery of responsiveness, the Brice interview was administered to assess for awareness during sevoflurane exposure; the interview was repeated on the phone the next day. After a total of 45 min of recovery time, another resting-state combined fMRI-EEG scan was acquired (with eyes closed, as for the baseline scan). When participants were alert, oriented, cooperative and physiologically stable, they were taken home by a family member or a friend appointed in advance.

MRI data acquisition. Although the original study acquired both fMRI and EEG data, in the present work we only considered the fMRI data. Data acquisition was carried out on a 3-T MRI scanner (Achieva Quasar Dual 3.0T 16CH) with an eight-channel, phased-array head coil. The data were collected using a gradient-echo-planar imaging (EPI) sequence (echo time = 30 ms, TR = 1.838 s, flip angle = 75°, field of view (FOV) = 220×220 mm², matrix = 72×72 , 32 slices, slice thickness = 3 mm and 1 mm interslice gap; 700-s acquisition time, resulting in 350 functional volumes). The anatomical scan was acquired before the functional scan using a T1-weighted magnetization-prepared rapid gradient-echo sequence with $240 \times 240 \times 170$ voxels ($1 \times 1 \times 1$ mm voxel size) covering the whole brain. A total of 16 volunteers completed the full protocol and were included in our analyses; one participant was excluded due to high motion, leaving $n = 15$ for analysis³⁴.

fMRI preprocessing and denoising. We applied a standard preprocessing pipeline in accordance with our previous publications with anesthesia data^{63,65}. Preprocessing was performed using the CONN toolbox (v17f; <http://www.nitrc.org/projects/conn>)⁶⁶, implemented in MATLAB 2016a. The pipeline involved the following steps: removal of the first 10 s, to achieve steady-state magnetization; motion correction; slice-timing correction; identification of outlier volumes for subsequent scrubbing by means of the quality assurance/artifact rejection software ‘art’ (http://www.nitrc.org/projects/artifact_detect); and normalization to Montreal Neurological Institute (MNI-152) standard space (2 mm isotropic resampling resolution), using the segmented gray matter image from each participant’s T1-weighted anatomical image, together with an a priori gray matter template.

Denoising was also performed using the CONN toolbox, using the same approach as in our previous publications with pharmacological MRI datasets^{63,65}. Pharmacological agents can induce alterations in physiological parameters (heart rate, breathing rate, motion) or neurovascular coupling. The anatomical CompCor (aCompCor) method removes physiological fluctuations by extracting principal components from regions unlikely to be modulated by neural activity; these components are then included as nuisance regressors⁶⁷. After this approach, five principal components were extracted from white matter and cerebrospinal fluid signals (using individual tissue masks obtained from the T1-weighted structural MRI images)⁶⁶, and regressed out from the functional data together with six individual-specific realignment parameters (three translations and three rotations), as well as their first-order temporal derivatives, followed by scrubbing of outliers identified by ART, using ordinary

least squares regression⁶⁶. Finally, the denoised BOLD signal time series were linearly detrended and band-pass filtered to eliminate both low-frequency drift effects and high-frequency noise, thus retaining frequencies between 0.008 and 0.09 Hz.

The step of global signal regression (GSR) has received substantial attention in the literature as a denoising method^{68–70}. However, recent work has demonstrated that the global signal contains behaviorally relevant information⁷¹ and, crucially, information about states of consciousness across pharmacological and pathological perturbations²¹. Therefore, in line with ours and others' previous studies, here we avoided using GSR to denoise our human fMRI data in favor of the aCompCor denoising procedure, which is among those recommended.

Finally, denoised BOLD signals were parcellated into 100 cortical regions-of-interest (ROIs) from the Schaefer atlas⁷².

fMRI preprocessing and denoising. HCP-minimally preprocessed data⁷³ were used for all acquisitions. The minimal preprocessing pipeline includes bias field correction, functional realignment, motion correction and spatial normalization to MNI-152 standard space with 2 mm isotropic resampling resolution⁷³.

We used the same denoising procedure as for the human anesthesia dataset, based on the aCompCor method implemented in CONN⁶⁶.

Macaque fMRI anesthesia datasets

The macaque fMRI datasets used here have been previously reported; for clarity and consistency of reporting, where possible, we use the same wording as in these previous reports, and we refer the reader to them for details^{13,35,74}.

Animals and ethics. For the macaque multi-anesthesia dataset, $n = 5$ rhesus macaques were included for analyses (*M. mulatta*, one male, monkey J, and four females, monkeys A, K, Ki and R, 5–8 kg, 8–12 years of age), in a total of six different arousal conditions—awake state, deep ketamine, light propofol, deep propofol, light sevoflurane and deep sevoflurane anesthesia. Here we used the awake, deep propofol, deep sevoflurane and ketamine data. Three monkeys were used for each condition—awake state (monkeys A, K and J), ketamine (monkeys K, R and Ki), propofol (monkeys K, R and J), sevoflurane (monkeys Ki, R and J). Each monkey had fMRI resting-state acquisitions on different days and several monkeys were scanned in more than one experimental condition. Sex was not considered in this study. Because of the small sample sizes, the sex balance per group could not be secured. All procedures are in agreement with the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes (Directive 2010/63/EU) and the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. Animal studies were approved by the Institutional Ethics Committee of Commissariat à l'Énergie atomique et aux Énergies alternatives (protocols CETEA 10-003 and 12-086). Additional details of the acquisitions can be found in refs. 9,35.

For the macaque DBS dataset, $n = 5$ male rhesus macaques (*M. mulatta*, 9–17 years of age and 7.5–9.1 kg) were included, three for the awake (non-DBS) experiments (monkeys B, J and Y) and two for the DBS experiments (monkeys N and T). Only males were included in the DBS dataset to avoid the menstrual cycle and hormone variations. All procedures are in agreement with 2010/63/UE, 86-406, 12-086 and 16-040. For additional details, we refer the reader to ref. 13.

Anesthesia protocol. For the multi-anesthesia dataset, monkeys received anesthesia either with ketamine, propofol or sevoflurane^{9,35}, with two different levels of anesthesia for propofol and sevoflurane anesthesia (light and deep). The anesthesia levels were defined according to the monkey sedation scale (Supplementary Table S), based on spontaneous movements and the response to external stimuli (presentation, shaking or prodding, toe pinch), and corneal reflex³⁵

and EEG. EEG data were simultaneously acquired during MRI scanning (although they are not analyzed in the present study). For each scanning session, the clinical score was determined at the beginning and end of the scanning session, together with continuous visual monitoring of electroencephalography. Monkeys were intubated and ventilated^{9,35}. Heart rate, noninvasive blood pressure, oxygen saturation, respiratory rate, end-tidal carbon dioxide and cutaneous temperature were monitored (MAGLIFE, Schiller) and recorded online (Schiller).

During deep ketamine, deep propofol and deep sevoflurane anesthesia, monkeys stopped responding to all stimuli, reaching a state of general anesthesia. For ketamine anesthesia, ketamine was injected intramuscularly (20 mg kg⁻¹; Virbac) for induction of anesthesia, followed by a continuous intravenous infusion of ketamine (15–16 mg kg⁻¹ h⁻¹) to maintain anesthesia. Atropine (0.02 mg kg⁻¹ intramuscularly; Aguettant) was injected 10 min before induction to reduce salivary and bronchial secretions. For propofol anesthesia, monkeys were trained to be injected with an intravenous propofol bolus (5–7.5 mg kg⁻¹; Fresenius Kabi), followed by a target-controlled infusion (TCI; Alaris PK Syringe Pump, CareFusion) of propofol (light propofol sedation = 3.7–4.0 µg ml⁻¹; deep propofol anesthesia = 5.6–7.2 µg ml⁻¹) based on the Paedfusor pharmacokinetic model. During sevoflurane anesthesia, monkeys received first an intramuscular injection of ketamine (20 mg kg⁻¹; Virbac) for induction, followed by sevoflurane anesthesia (light sevoflurane, sevoflurane inspiratory/expiratory, 2.2/2.1 vol%; deep sevoflurane, sevoflurane inspiratory/expiratory, 4.4/4.0 vol%; Abbott). Only 80 min after the induction, the scanning sessions started for the sevoflurane acquisitions to get a washout of the initial ketamine injection. To avoid artifacts related to potential movements throughout MRI acquisition, a muscle-blocking agent was co-administered (cisatracurium, 0.15 mg kg⁻¹ bolus intravenously, followed by continuous intravenous infusion at a rate of 0.18 mg kg⁻¹ h⁻¹; GSK) during the ketamine and light propofol sessions. Here we include the ketamine, deep propofol and deep sevoflurane data.

For the DBS dataset¹³, anesthesia was induced with an intramuscular injection of ketamine (10 mg kg⁻¹; Virbac) and dexmedetomidine (20 µg kg⁻¹; Ovion Pharma) and then the same method as reported above for deep propofol sedation was used (monkey T—TCI = 4.6–4.8 µg ml⁻¹; monkey N—TCI = 4.0–4.2 µg ml⁻¹). Awake scanning data were obtained from the remaining three animals, which did not provide anesthesia data.

DBS protocol. Two monkeys (N and T) were implanted with a clinical DBS electrode (Medtronic, lead model 3389). The DBS lead had four active contacts for electrical stimulation (1.5-mm contact length, 0.5-mm spacing and 1.27-mm diameter). Stereotactic surgery targeting the right centromedian thalamus was performed using a neuro-navigation system (BrainSight, Rogue), guided by rhesus macaque atlases^{75,76} and preoperative and intraoperative anatomical MRI. MRI was acquired using a magnetization-prepared rapid gradient-echo (MPRAGE), T1-weighted sequence (TR, 2,200 ms; TI, 900 ms; 0.80-mm isotropic voxel size; sagittal orientation). The electrode was stabilized with the StimLoc lead anchoring device (Medtronic). The extracranial part of the DBS lead was housed using a homemade three-dimensional (3D) printed MRI-compatible chamber. We waited at least 20 days after implantation before starting the DBS-fMRI experiments. Two methods were used to ensure the anatomical localization of the DBS lead and the DBS contacts. First, a reconstruction method was used based on in vivo brain imaging. Second, a histology study was used in one of the implanted monkeys (for more details, see ref. 13).

For stimulation, the DBS electrode was connected to an external stimulator (World Precision Instrument, DS8000), and all the parameters were tuned to fixed values of frequency ($f = 130.208$ Hz, $T = 7.68$ ms), waveform (monopolar signal), and pulse width (monkey N, $w = 320$ µs; monkey T, $w = 140$ µs). The absolute voltage amplitude was set to 3V ('low' DBS) or 5V ('high' DBS). The fMRI experiments were

acquired either in the awake state or under propofol anesthesia without ('off' condition) or with low or high DBS, during the entire run on either the CT or VT thalamic nuclei. The DBS started a few seconds before the beginning of the fMRI sequence and stopped just after the end of the MRI sequence¹³. Here we included the awake and no-DBS conditions, as well as 5V CT and 5V VT stimulation conditions.

As reported in ref. 13, 'DBS significantly affected the general physiological parameters of the anesthetized monkeys such as the mean heart rate ($P = 3.38 \times 10^{-26}$) and mean blood pressure ($P = 5.78 \times 10^{-17}$). For example, for monkey T, high CT DBS significantly increased mean heart rate ($P = 1.23 \times 10^{-23}$, compared to anesthesia; $P = 6.76 \times 10^{-19}$, compared to low CT-DBS condition) and mean blood pressure ($P = 8.66 \times 10^{-14}$, compared to anesthesia condition; $P = 6.67 \times 10^{-11}$, compared to low CT-DBS condition)'.

Behavioral assessment of arousal. We used a preclinical behavioral scale to assess the arousal levels of the monkeys⁷⁷. This scale, based on the Human Observers Assessment of Alertness and Sedation Scale⁷⁸ and previously used in nonhuman primate research⁷⁹, was used consistently across all experimental conditions in both datasets. The arousal testing occurred outside the MRI environment and was conducted at the beginning and end of each scanning session, for each condition, once the animals were no longer under paralysis. The assessment encompassed six criteria as described in Supplementary Table 5. The behavioral score ranged from 0 to 11, where 11 represented the maximum score achievable and 0 the lowest.

In all cases, and for both datasets, we observed no differences in arousal scores between different animals in the same condition. For both datasets, the behavioral score during wakefulness was the maximum of 11/11 for all the animals (monkeys A, K and J from the multi-anesthesia dataset, and monkeys B, J and Y from the DBS dataset)—exploration of the surrounding world = 2; spontaneous movements = 2; shaking/prodding = 2; toe pinch = 2; eyes opening = 2; corneal reflex = 1.

For results pertaining to the different anesthesia conditions of the multi-anesthesia dataset, see Supplementary Table 25 of ref. 74. As a summary, deep anesthesia with ketamine, propofol or sevoflurane induced an arousal score of 0, consistently in all animals. In contrast, light anesthesia induced an arousal score of 3 for sevoflurane and 4 for propofol.

In the anesthesia without DBS ('off') condition, monkeys N and T displayed the minimum behavioral score of 0 out of 11, the same as the deep anesthesia from the multi-anesthesia dataset—exploration of the surrounding world = 0; spontaneous movements = 0; shaking/prodding = 0; toe pinch = 0; eyes opening = 0; corneal reflex = 0. When the CT electrical stimulation amplitude was increased to 5V (high-amplitude CT DBS), animals reached a total score of 9 out of 11 (exploration of the surrounding world = 1; spontaneous movements = 1; shaking/prodding = 2; toe pinch = 2; eyes opening = 2; corneal reflex = 1). For VT DBS, both low (3V) and high (5V) amplitude stimulation led to a clinical score of 0, identical to what is observed in the absence of any stimulation.

MRI data acquisition. To minimize head motion, monkeys were head fixed using an implantation with a magnetic-resonance-compatible headpost. For the awake scanning sessions, monkeys were trained to sit in the sphinx position in a primate chair inside the dark MRI scanner and fixate without any task, and the eye position was monitored at 120 Hz (Iscan). The eye tracking was performed to make sure that the monkeys were awake during the whole scanning session and not sleeping⁸⁰. The eye movements were not regressed out from rfMRI data. For the anesthesia sessions, animals were positioned in a sphinx position, mechanically ventilated and their physiologic parameters were monitored. No eye tracking was performed in anesthetic conditions.

For the multi-anesthesia dataset, before each scanning session, a contrast agent, monocrystalline iron oxide nanoparticle (Feraheme,

AMAG Pharmaceuticals; 10 mg kg⁻¹, intravenous), was injected into the monkey's saphenous vein⁸¹. Monkeys were scanned at rest on a 3-T horizontal scanner (Siemens Tim Trio) with a single transmit-receive surface coil customized to monkeys. Each functional scan consisted of gradient-echo-planar whole-brain images (repetition time = 2,400 ms; echo time = 20 ms; 1.5-mm³ voxel size; 500 brain volumes per run).

For the DBS dataset, the absence of motion was ensured by paralyzing the animals with curare. Monkeys were scanned at rest on a 3-T horizontal scanner (Siemens, Prisma Fit) with a customized eight-channel phased-array surface coil (KU Leuven). The parameters of the fMRI sequences were—EPI, TR = 1,250 ms, echo time (TE) = 14.20 ms, 1.25-mm isotropic voxel size and 500 brain volumes per run. Event-related data pertaining to auditory stimulation were also acquired and are reported in ref. 13, but here we only used the rfMRI data, and will not discuss the event-related data further. Scalp EEG data were also acquired using an MR-compatible system and custom-built caps (EasyCap, 13 channels), an MR amplifier (BrainAmp, Brain Products) and the Vision Recorder software (Brain Products). These results are reported in ref. 13, but here we did not consider the EEG data and will not discuss them further.

Macaque fMRI preprocessing, denoising and time-series extraction. For the multi-anesthesia dataset, a total of 157 functional magnetic imaging runs were acquired³⁵—awake, 31 runs (monkey A, 4 runs; monkey J, 18 runs; monkey K, 9 runs); ketamine, 25 runs (monkey K, 8 runs; monkey Ki, 7 runs; monkey R, 10 runs); light propofol, 25 runs (monkey J, 2 runs; monkey K, 11 runs; monkey R, 12 runs); deep propofol, 31 runs (monkey J, 9 runs; monkey K, 10 runs; monkey R, 12 runs); light sevoflurane, 25 runs (monkey J, 5 runs; monkey Ki, 10 runs; monkey R, 10 runs); and deep sevoflurane anesthesia, 20 runs (monkey J, 2 runs; monkey Ki, 8 runs; monkey R, 10 runs). Additional details are available in refs. 9,35,82.

Functional images were reoriented, realigned and rigidly coregistered to the anatomical template of the monkey MNI space with the use of Python programming language and FMRIB Software Library (FSL) software (<http://www.fmrib.ox.ac.uk/fsl/>; accessed 4 February 2018)³⁵. From the images, the global signal was regressed out to remove confounding effects due to physiologic changes (for example, respiratory or cardiac changes). As an alternative, robustness analyses were performed after using the aCompCor method⁶⁷ for denoising instead of GSR.

For the DBS dataset, a total of 199 rfMRI runs were acquired—awake 47 runs (monkey B = 18 runs; monkey J = 13 runs; monkey Y = 16 runs), anesthesia (DBS-off) 38 runs (monkey N = 16 runs; monkey T = 22 runs), low-amplitude centromedian thalamic DBS 36 runs (monkey N = 18 runs; monkey T = 18 runs), low-amplitude ventro-lateral thalamic DBS 20 runs (monkey T), high-amplitude centromedian thalamic DBS 38 runs (monkey N = 17 runs; monkey T = 21 runs) and high-amplitude ventro-lateral thalamic DBS 20 runs (monkey T = 20 runs)¹³.

Images were preprocessed using PyPreclin (Python preclinical pipeline)⁸³. Functional images were corrected for slice timing and B0 inhomogeneities, reoriented, realigned, resampled (1.0 mm isotropic), masked, coregistered to the MNI macaque brain template⁸⁴ and smoothed (3.0-mm Gaussian kernel). Anatomical images were corrected for B1 inhomogeneities, normalized to the anatomical MNI macaque brain template and masked.

For both datasets, data were parcellated according to the Regional Map parcellation⁶⁰. This parcellation comprises 82 cortical ROIs (41 per hemisphere). Voxel time series were filtered with low-pass (0.05-Hz cutoff) and high-pass (0.0025-Hz cutoff) filters and a zero-phase fast-Fourier notch filter (0.03 Hz) to remove an artifactual pure frequency present in all the data^{913,35}.

Furthermore, an extra quality control (QC) procedure was performed to ensure the quality of the data after time-series extraction⁸². This QC procedure is based on trial-by-trial visual inspection by an expert neuroimager (C.M.S.), and it is the same as was previously

implemented in refs. 74,82. Its adoption ensures that we use consistent criteria across our two macaque datasets by adopting the more stringent of the two. We plotted the time series of each region, as well as the static FC matrix, the dynamic connectivity (dFC) and a Fourier analysis to detect unconventional spikes of activity. For each dataset, visual inspection was first used to become familiar with the characteristics of the entire dataset—how the amplitude spectrum, time series, FC and dFC look. Subsequently, each trial was inspected again with particular focus on two main types of potential artifacts. The first one may correspond to issues with the acquisition and is given by stereotyped sinusoidal oscillatory patterns without variation. The second one may correspond to a head or other movement not corrected properly by our preprocessing procedure. This last artifact can sometimes be recognized by bursts or peaks of activity. Sinusoidal activity generates artificially high functional correlation and peaks of frequency in the amplitude spectrum plot. Uncorrected movements generate peaks of activity with high functional correlation and sections of high functional correlations in the dynamical FC matrix. If we observed any of these anomalies, we rejected the trial, opting to adopt a conservative policy. See Supplementary Figs. 19–21 from ref. 74 for examples of artifact-free and rejected trials.

As a result, for the multi-anesthesia dataset, a total of 119 runs are analyzed in subsequent sections (the same as used in ref. 82)—awake state 24 runs, ketamine anesthesia 22 runs, light propofol anesthesia 21 runs, deep propofol anesthesia 23 runs, light sevoflurane anesthesia 18 runs and deep sevoflurane anesthesia 11 runs. For the DBS dataset, a total of 156 runs are analyzed in subsequent sections—awake state 36 runs, off condition (propofol anesthesia without stimulation) 28 runs, low-amplitude CT stimulation 31 runs, low-amplitude VT stimulation 18 runs, high-amplitude CT stimulation 25 runs and high-amplitude VT stimulation 18 runs.

Marmoset fMRI anesthesia dataset

The marmoset data included here have been published before³⁶. For clarity and consistency of reporting, we use the same wording where possible, and we refer the reader to the original work for details³⁶.

Animals and ethics. This study was approved by the Animal Experiment Committees at the RIKEN Center for Brain Science and was conducted per the guidelines for Conducting Animal Experiments of the RIKEN Center for Brain Science. Three male and one female healthy common marmosets (*C. jacchus*) between 3 and 6 years of age were included. All marmosets were examined eight times to collect fMRI data in all conditions. After awake data were first collected, and sedate/anesthetic data were collected in a random order for sedate/anesthetic condition, with an interval of 1 month between each examination in each individual. For further details, we refer the reader to ref. 85.

Anesthesia protocol. We used data from awake scans, and from scans under general anesthesia induced with isoflurane, sevoflurane or propofol. Essential details are reported below, and for additional detail we refer to ref. 36.

Isoflurane. Three percent isoflurane with 100% O₂ as carrier gas was administered through a facial mask to the marmosets retained with leather gloves. Once sufficient sedation was achieved, an 8-Fr catheter (Atom multi-use tube, Atom Medical) was inserted into the trachea as an intratracheal tube. The isoflurane concentration was reduced to 2.5%, and 50 µg kg⁻¹ of atropine and 3.0 ml of physiological saline were administered subcutaneously to prevent intratracheal secretion and dehydration, respectively. After intratracheal intubation, general anesthesia was maintained with 1.8% isoflurane. The marmosets were connected to artificial ventilation for small animals (Shinano Seisakusho, SN-480-7), and mechanical ventilation was performed under the following conditions: 50% inspiratory oxygen, 8 ml of tidal

volume and 30 breaths per min RR. PR, SpO₂, RR, EtCO₂, inspiratory and end-tidal isoflurane concentrations, and rectal temperature were measured with a vital sign monitor.

Sevoflurane. All procedures were performed in the same way as isoflurane, except for dosages. The induction of general anesthesia, intratracheal intubation and maintenance of general anesthesia were performed with 5.0% and 3.0% sevoflurane (Pfizer), respectively.

Propofol. Propofol (12 mg kg⁻¹) was administered as induction of general anesthesia over 3 min through an indwelling needle. Atropine (50 µg kg⁻¹) was administered subcutaneously to prevent intratracheal secretions. Immediately after bolus administration, the predicted plasma concentration of propofol was titrated to 7–9 µg ml⁻¹ for intratracheal intubation with continuous infusion. The administration dose and protocol were calculated beforehand using a pharmacokinetic parameter reported in ref. 85 and pharmacokinetic analysis software, NONMEM ver. VII (GloboMax ICON Development Solutions). Once a sufficient plasma concentration was obtained, the propofol dose was controlled to maintain that concentration. Intratracheal intubation, respiratory management and vital sign monitoring were performed in the same manner as for isoflurane.

MRI data acquisition. All marmosets underwent a surgical procedure to attach a headpost to the cranial bones to prevent head movement during data collection³⁶. During imaging, the marmosets were placed on a custom-made imaging table (Takashima Seisakusho) and immobilized by fixing the headpost using a headpost fixing tool attached to a custom-made imaging table in all conditions. The marmosets were fitted with earplugs. A hot water circulator was used during imaging to maintain body temperature at 36–38 °C under all conditions³⁶.

In the awake condition, data were collected in the dark and monitored with an infrared camera to prevent the marmosets from falling asleep. If the marmosets were observed closing their eyes during a scan, they were awakened with a loud noise before the next scan was started. They were rewarded with a highly palatable food at the end of each imaging. In anesthetic condition, the marmosets were monitored in the same way to observe spontaneous movement or coughing for intratracheal tube. If spontaneous movement or coughing was observed, additional sedatives/anesthetics were administered, and the infusion rate or concentration of inhalational anesthesia was increased.

An ultrahigh field MRI system with a static magnetic field strength of 9.4 T (Bruker BioSpin), a custom-made eight-channel receiver coil for the marmoset head (Takashima Seisakusho) and a 154-mm inner diameter transmitter coil (Bruker BioSpin) was used to collect structural and functional data. Structural data and T2-weighted images were imaged using rapid acquisition with relaxation enhancement sequence with the following conditions and parameters: TR = 4,331 ms, time echo (TE) = 15.0 ms, FOV = 42.0 × 28.0 × 36.0 mm, matrix size = 120 × 80 voxels, resolution = 0.35 × 0.35 mm, slice thickness = 0.7 mm, number of slices = 52, scan time = 1 min and 26 s, rapid acquisition with relaxation enhancement factor = 4. Functional images were captured using a gradient-recalled EPI sequence with the following conditions and parameters: TR = 2,000 ms, TE = 16.0 ms, FOV = 42.0 × 28.0 × 36.0 mm, matrix size = 60 × 40 voxels, resolution = 0.7 × 0.7 mm, slice thickness = 0.7 mm, number of slices = 52, repetition = 155, scan time = 310 s. Functional imaging was performed 12 times per animal, per condition³⁶.

Marmoset fMRI preprocessing and denoising. After the acquired data were converted to Neuro Informatics Technology Initiative format, the voxel size was changed from 0.7 mm isotropic to 3.5 mm isotropic using SPM (Wellcome Trust Center for Neuroimaging). Estimation and correction of geometric distortions induced by magnetic susceptibility were performed with the top-up tool of the FSL software (FMRIB) because all cross-sections were imaged with a single excitation in EPI.

Slice-timing correction was performed to correct for signal acquisition timing discrepancies in each section. Realignment was applied to compensate for head movements caused by body movements. The deviations in six directions were obtained— x (left/right), y (front/back), z (up/down), pitch (rotational direction of nodding and looking up), roll (rotational direction of moving the ear closer to the shoulder) and yaw (rotational direction of looking left/right). For each measurement time point (TR), the deviation from the reference time point, and the first functional brain image, was determined, and the image was moved and rotated by the rigid body model based on this deviation. The method of finding the parameters of the linear transformation was used to minimize the difference between the first functional brain image and the affine transformation of the series of functional brain images to be corrected, by calculating convergence using the method of least squares. After correcting the spatial scale error between the structural and functional images with coregistration, segmentation was performed to provide information on the tissue to which each voxel belongs in terms of brain tissue classification. The voxels were spatially standardized by normalization, which aligns the voxels to the standard brain image to correct for structural differences between individuals. Smoothing was applied to suppress excessive voxel value fluctuations within individuals and apply normal probability field theory. Functional data were smoothed using spatial convolution with a Gaussian kernel of two voxels (7 mm). Then, physiological noise was denoised using ordinary least squares regression with cerebrospinal fluid pulsation, heart rate and respiratory artifacts as regressors. Temporal band-pass filtering was performed by frequency filtering (0.01–0.1 Hz) using the fMRI denoising pipeline of CONN⁶⁶. Finally, preprocessed functional data were parcellated into 70 cortical regions from the marmoset atlas of ref. 86.

Mouse fMRI anesthesia dataset

The mouse fMRI data used here have been published before¹². For clarity and consistency of reporting, where possible, we use the same wording as in ref. 12.

Animals and ethics. In vivo experiments were conducted in accordance with the Italian law (DL 26/214, EU 63/2010, Ministero della Sanità) and with the National Institute of Health recommendations for the care and use of laboratory animals¹². The animal research protocols for this study were reviewed and approved by the Italian Ministry of Health and the animal care committee of Istituto Italiano di Tecnologia. All surgeries were performed under anesthesia.

Adult (<6 months old) male C57BL/6J mice were used throughout the study. Mice were group housed in a 12-h light/12-h dark cycle in individually ventilated cages with access to food and water ad libitum and with temperature maintained at $21 \pm 1^\circ\text{C}$ and humidity at $60 \pm 10\%$. All the imaged mice were bred in the same vivarium and scanned with the same MRI scanner and imaging protocol used for the awake scans (see below).

A first group of mice ($n = 10$, awake dataset) underwent headpost surgery, scanner habituation and fMRI image acquisitions as described below. See ref. 12 for the full surgical, habituation and scanner protocol. The scans so obtained constitute the awake rsfMRI mouse dataset we used throughout our study. Two additional groups of age matched male C57BL/6J mice were used as reference rsfMRI scans under anesthesia.

Anesthesia protocol. The first group of animals ($n = 19$, halothane dataset) was previously scanned under shallow halothane anesthesia (0.75%)⁸⁷. The anesthesia regimen used is well-characterized^{12,88}; it is representative of the network architecture observed with different anesthesia regimens in rodents⁵⁴ and it shows rich spatiotemporal dynamics by preserving spectral properties of fMRI signal fluctuations⁸⁷.

A second separate group ($n = 14$) of mice were imaged under medetomidine-isoflurane anesthesia (0.05 mg kg⁻¹ bolus and

0.1 mg kg⁻¹ IV infusion, as well as 0.5% isoflurane)¹². While this anesthetic combination is known to shift the spectral components of fMRI signal fluctuations toward higher frequencies (hence departing from the characteristic $1/f$ power law distribution that characterizes awake and halothane rsfMRI datasets^{54,87}), it nonetheless represents the most-widely used anesthetic mixture in the rodent imaging community⁵⁴.

MRI data acquisition. To prevent motion, each mouse was secured using an implanted headpost in the custom-made MRI-compatible animal cradle and the body of the mouse was gently restrained (for details of the headpost implantation and habituation protocol, see ref. 12). For scanning under anesthesia, mice were first deeply anesthetized with isoflurane (4% induction), intubated and artificially ventilated (90 BPM). In one group, anesthesia was then switched to halothane (0.75%). In a second group, a bolus of medetomidine (0.05 mg kg⁻¹) was given through tail vein cannulation before waiting for 5 min and starting an infusion of medetomidine (0.1 mg kg⁻¹) with isoflurane reduced to 0.5%. In both cases, the rsfMRI acquisition started 30 min after the switch to light anesthesia¹².

All scans were acquired at the Istituto Italiano di Tecnologia laboratory in Rovereto on a 7.0-T MRI scanner (Bruker BioSpin) with a BGA-9 gradient set, a 72 mm birdcage transmit coil, and a four-channel (awake, halothane) or three-channel (medetomidine-isoflurane) solenoid receive coil. Awake and medetomidine-isoflurane rsfMRI scans were acquired using a single-shot EPI sequence with the following parameters: TR/TE = 10,00/15 ms, flip angle = 60° , matrix = 100×100 , FOV = 2.3×2.3 cm, 18 coronal slices (voxel size = $230 \times 230 \times 600$ mm), slice thickness = 600 μm and 1,920 time points, for a total time of 32 min. Mice under halothane anesthesia ($n = 19$) were scanned with a TR/TE = 1,200/15 ms, flip angle = 60° , matrix = 100×100 , 24 coronal slices (voxel size = $200 \times 200 \times 500$ mm), for a total of 1,600 time points and total acquisition time of 32 min as described in ref. 12.

Mouse fMRI preprocessing and denoising. Preprocessing of fMRI images was carried out as described in previous work¹². Briefly, the first 2 min of the time series were removed to account for thermal gradient equilibration. fMRI time series were then time despiked (3dDespike, AFNI), motion corrected (MCFLIRT, FSL), skull stripped (FAST, FSL) and spatially registered (Advanced Normalization Tools registration suite) to an in-house mouse brain template with a spatial resolution of $0.23 \times 0.23 \times 0.6$ mm³. Denoising involved the regression of 25 nuisance parameters. These were as follows: average cerebrospinal fluid signal as well as 24 motion parameters determined from the three translation and rotation parameters estimated during motion correction, their temporal derivatives and corresponding squared regressors. No GSR was used. In-scanner head motion was quantified through calculations of framewise displacement (FD). Average FD levels in awake conditions were comparable to those obtained in anesthetized animals (halothane) under artificial ventilation ($P = 0.13$, Student's t test)¹². To rule out a contribution of residual head motion, we further introduced framewise fMRI scrubbing (FD > 0.075 mm). The resulting time series were band-pass filtered (0.01–0.1 Hz band) and then spatially smoothed with a Gaussian kernel of 0.5 mm full width at half maximum. Finally, the time series were trimmed to ensure that the same number of time points was included for all animals, resulting in 1,414 volumes per animal. Finally, data were parcellated into 72 cortical symmetric regions from the Allen Mouse Brain Atlas (CCFv3).

Larval zebrafish calcium imaging dataset

Animals and ethics. All experiments were conducted on Tg(elavl3: H2B-GCaMP6s) zebrafish larvae (*D. rerio*) at 6 or 7 days postfertilization. Sex cannot be determined at the larval stage. This transgenic line expresses a nuclear-localized calcium sensor pan-neuronally⁸⁹. Larvae were raised in embryo medium in an incubator at 28°C on a 14-h

day/10-h night cycle. From 5 days postfertilization onward, the medium was replaced daily and larvae were fed live *Tetrahymena thermophila* CU428.2 (Cornell University). All protocols were approved by the Animal Care Committee of Université Laval (CPAUL protocol 2022-1012).

Anesthesia protocol. Larvae were immobilized in 2% low-melting point agarose (Invitrogen, 16520100) in a 30-mm glass-bottom Petri dish (Mattek, P35G-1.0-14-C). Once solidified, agarose was carefully removed around the tail below the swim bladder using a small scalpel (Thermo Fisher Scientific, 35-205) to allow tail monitoring (Flir BFS-U3-28S5M-C camera with Navitar Zoom 7000 lens) while keeping the head completely immobilized during brain imaging experiments. The imaging chamber was submerged in standard embryo medium, then larvae were brought under the microscope and imaged under baseline awake conditions for 10 min, with constant red illumination projected under the chamber (AAXA Technologies KP-750-00 DLP Projector with a Kodak dark red filter). After baseline imaging, a tricaine methane sulfonate solution (MS-222; Sigma-Aldrich, E10521; sodium channel blocker, 750 mg l⁻¹ dissolved in embryo medium with pH adjusted using NaHCO₃; Thermo Fisher Scientific, S233-500)⁹⁰ was introduced into the imaging chamber using a gravity perfusion system (ALA Scientific Instruments). Drug perfusion was sustained for at least 5 min to clear out the chamber volume several times and reach a stable incubation concentration. Full anesthesia was confirmed in each animal through the complete loss of tail and ocular movements, assessed using both a behavioral monitoring camera or using autofluorescence from the eyes in brain-wide recordings. Imaging experiments lasted between 20 and 30 min, with variable recording lengths during the anesthesia period due to variations in perfusion velocity. The drug concentration used was within established safety margins⁹⁰, and full behavioral recovery was confirmed after the drug washout in participants that were kept in separate Petri dishes with fresh embryo medium.

Calcium imaging of neuronal activity. Imaging experiments were conducted using equipment and protocols that were detailed in a previous publication⁹¹. Briefly, brain-wide calcium activity was captured at single-cell resolution using a resonant-scanning two-photon microscope (Scientifica SliceScope with SciScan LabView software) equipped with a piezo-driven water-dipping objective (Nikon, ×16, 0.8 NA). Volumetric stacks of 21 imaging planes (zoom ×1.4, 512 × 730 pixels, 12 microns in z spacing) were acquired at a volume rate of 0.986 Hz for a total recording length of 20–30 min. Imaging planes intersected roughly 50,000 neurons spanning most brain regions from dorsal to ventral anatomical locations⁹¹. GCaMP6s fluorescence was excited at a 920 nm wavelength using a Spectra-Physics InSight X3 tunable laser and detected using a GaAsP photomultiplier tube. Laser power after the objective was fixed below 20 mW. Brain imaging ran continuously throughout the drug perfusion phase, which caused flow-induced z drift in the preparation. Full recordings were thus truncated into two different segments during which there was no solution flow and samples had fully stabilized. Experiments in which z drift persisted after perfusion were discarded entirely. After functional imaging, anatomical stacks (2 micron z spacing, 24× frame averaging) were acquired near the isosbestic (calcium-independent) excitation wavelength (860 nm) of the fluorescence sensor, yielding homogeneous nuclear intensities used for anatomical registration in subsequent steps, as per ref. 91.

Processing of neuronal activity traces. Calcium imaging planes were motion corrected using the NoRMCorr algorithm⁹² implemented within the CalmAn package⁹³. Fluorescent nuclei were identified using local intensity maxima in the temporal averages of each calcium imaging plane⁹⁴, and fluorescence traces were extracted from each nucleus within a small disk (3-pixel radius). Each trace was detrended from slow baseline drifts and converted to relative $\Delta F/F_0$ units using a smoothed minimum filter applied within a 60-s temporal window.

Large fluorescence transients observed at the onset of the drug delivery phase were excluded from anesthetized traces to capture steady-state activity. To situate each neuron in anatomical coordinates, calcium imaging volumes were registered to the mapZeb brain larval brain atlas⁹⁵ using a stepwise advanced normalization tools registration procedure described previously^{91,96}. After registration, native neuron coordinates were transformed to brain atlas coordinates, then each neuron was assigned to 1 of 200 anatomical locations (3D ROIs) per brain hemisphere. ROIs were established by subdividing 65 brain region masks uniformly using an iterative clustering approach. Briefly, for each brain region and within each hemisphere, a number of clusters were first determined by the region's volume (larger regions requiring more clusters). K-means clustering was then applied 30 times on the voxel coordinates of a region's 3D mask, yielding a set of cluster centroids that was then reclustered iteratively to yield consensus centroids across all animals. Mask voxels were finally assigned to the consensus clusters based on their nearest neighboring centroid, effectively partitioning each 3D mask into a Voronoi diagram. This approach was used to obtain a larger set of ROIs (groups of neighboring neurons) with comparable volumes, thereby providing a finer anatomical resolution and reducing neuron sampling biases. After this parcellation procedure, the fluorescence signals of individual neurons were averaged within each ROI, and 48 ROIs were excluded from further analysis as they did not contain sampled neurons in at least one animal. This resulted in 352 coarse-grained and anatomically comparable activity traces per larva. Time series were finally truncated to 250 time steps in both awake and anesthetized conditions to obtain comparable lengths across all conditions and animals.

Nematode calcium imaging dataset

The *C. elegans* data included in this study have been published before. For clarity and consistency of reporting, where possible, we use the same wording as in refs. 37,53.

C. elegans strains. All experiments were on young adult hermaphrodites of the transgenic strain QW1217 (zfls124(Prgef-1::GCaMP6s); otIs355(Prab-3::NLS::tagRFP)). GCaMP6s, a fluorescent calcium reporter, and nuclear-localized red fluorescent protein are both expressed pan-neuronally in this strain (gift of M. Alkema, University of Massachusetts). *C. elegans* were cultivated at 20 °C on nematode growth medium seeded with *Escherichia coli* OP50 (ref. 53).

Anesthesia protocol. *C. elegans* become anesthetized on exposure to isoflurane with a minimum alveolar concentration value of approximately 3% at room temperature. At 17 °C, isoflurane is 2.3 times more soluble in tissues such as muscle and fat than at 37 °C and consequently absorption of a larger quantity of isoflurane is required to produce a similar chemical potential gradient at cooler temperatures. A concentration of 3% isoflurane at 17 °C is thus pharmacodynamically similar, with respect to its physical chemistry, to a concentration of 1.3% at 37 °C. Alterations in *C. elegans* neuronal activity in response to isoflurane exposure were assessed using two experimental regimes—stepwise anesthetization and emergence⁵³. Here we include data from the stepwise anesthetization regime.

Three 5-min-long neuronal activity recordings were taken from each animal ($n = 10$) after progressive equilibration to 0%, 4% and 8% atmospheric isoflurane⁵³. These concentrations correspond to 1.3 and 2.6 minimum alveolar concentrations, respectively. For the main analysis, we include data from the 0% and 4% isoflurane conditions. Imaging was performed at time $t = 30$ min, 150 min and 270 min from the start of the experiment at isoflurane levels of 0%, 4% and 8%, respectively. Isoflurane levels were stepped by exchanging the immersion medium for fresh S-basal buffer with the addition of 13 or 26 μ l of pipetted isoflurane for 4% and 8% isoflurane, respectively. The atmosphere within the covered Petri dish was then equilibrated, during the time between

imaging sequences, to a concentration of 4% or 8%, respectively, using continuous monitoring with an infrared spectrometer (Ohmeda 5250 RGM; GE Healthcare) and instillation of isoflurane through syringe pump as necessary to maintain the targeted concentration⁵³.

Calcium imaging of neuronal activity. To prevent any motion, the animals were immobilized for imaging by encapsulation in a pad of permeable hydrogel consisting of 13.3% polyethylene glycol diacrylate (Advanced BioMatrix) with 0.1% Irgacure (Sigma-Aldrich)⁵³. Hydrogel pads containing animals to be imaged were cured with ultraviolet light onto silanated glass coverslips, which were affixed to the bottom of 50-mm Petri dishes with vacuum grease. Petri dishes were then filled with 50 ml of S-basal buffer (100 mM NaCl, 50 mM KPO4 buffer and 5 $\mu\text{g ml}^{-1}$ cholesterol) as the immersion medium. Tetramisole was added to this buffer at 5 mM to further immobilize the animals.

GCaMP6s and red fluorescent protein fluorescence in the *C. elegans* head ganglia were captured in volumetric stacks using a dual inverted selective plane illumination microscope (Applied Scientific Instrumentation) and water-immersed 0.8 NA $\times 40$ objective (Nikon). GCaMP6s and red fluorescence protein were, respectively, excited using 5-mW 488-nm and 561-nm lasers (Vortan Laser Technology). Volumes for each fluorescence channel (GCaMP6s and red fluorescence protein) were obtained at a rate of 2 Hz.

For each animal imaged, 120 neurons (ordered from anterior to posterior in each animal) were tracked in the head region using the nuclear-localized red fluorescence protein fluorophore, and their activity was extracted using the fluctuations in cytoplasmic GCaMP6s neurofluorescence. This tracking and extraction procedure was performed as a massively parallel computation executed at the Massachusetts Green High Performance Computing Center using computational techniques as previously detailed in ref. 37.

Preprocessing of neuronal activity traces. In recordings from the stepwise equilibration regime, neuronal activity intensity for all three recordings in each animal (0%, 4% and 8%) was normalized against the average intensity across all neurons and time points in the 0% isoflurane recording. The first 100 time points were excluded to remove large transients, leaving 500 for analysis. Because the animals are immobilized and encapsulated in a hydrogel for imaging, it is not possible to normalize to an alternative behavioral endpoint⁵³.

Comprehensive dynamical phenotyping

hctsa. To extract the dynamical phenotype of each brain region or neuron, we performed massive time-series feature extraction using the hctsa toolbox^{27,28}. For each region/neuron, in each individual, under each condition, the hctsa toolbox extracted >7,200 univariate dynamical features, derived from diverse fields including neuroscience, physics, ecology and economics^{27,28}. Features range from basic statistics of the distribution of time points, linear correlations among time points and stationarity, to measures of entropy, time-delay embeddings and signal complexity, among others. Each individual feature is the implementation of a computation (termed ‘master operation’) on the input time series, using specific parameters. For example, sample entropy (SampEn) computes the probability that similar sequences of observations in a time series will remain similar as their size increases. Its computation therefore requires a threshold r for deciding when two sequences will be considered similar, and an embedding dimension m that determines the size of the sequences. Multiple individual features are obtained from this master operation as different combinations of r and m .

We performed an initial prefiltering and did not compute any features that had returned NaN across all regions, or that had displayed no variance, in an independent dataset of human fMRI (Human Connectome Project⁹⁷). The values of different features can vary across several orders of magnitude. Unless otherwise specified, here we do not normalize features across regions, because this could obscure differences

across conditions. Instead, we use effect sizes computed on the original features. Effect sizes are expressed in units of s.d., and therefore they are readily comparable across features and also across regions and datasets. Despite our initial prefiltering, not all of the remaining time-series features could be extracted successfully from all our datasets. We therefore performed an additional postfiltering. Features that failed to be extracted were excluded. To ensure consistency, features were only included in the final analysis if they could be included for each dataset. Features that failed to produce a finite effect size for a region had their effect size for that region set to zero. After prefiltering and postfiltering, a total of 6,827 dynamical features were retained across datasets.

To guide and aid interpretation, we also stratified dynamical features into ten broad categories, based on associated keywords^{27,28} and further inspection (Supplementary Table 2). These include the following: (1) distribution (for example, mean, variance, outliers and tests for distribution family); (2) autocorrelation (and its nonlinear and lagged versions); (3) periodic (for example, power spectrum, seasonality, wavelet); (4) entropy and related quantities; (5) symbolic (discretization of the signal and resulting motifs and transitions between them); (6) forecasting and model fit from past to future; (7) transformations of the data (for example, scaling, surrogates); (8) variability in time (for example, change points, stationarity); (9) measures from the complex systems literature (for example, time reversal, fractality, embeddings); and (10) miscellaneous others (for example, visibility graph). We emphasize that this should not be considered a formal or definitive taxonomy—some features may plausibly belong to more than one category, and some categories are only loosely defined. Different categories could also be devised. Please note that each category may include features that change in opposite directions in response to the same manipulation. For example, forecasting error is reduced whenever forecasting accuracy increases. Likewise, measures of autocorrelation decay time (for example, the number of time points until first zero crossing of the autocorrelation function) tend to decrease as intrinsic timescale shortens, whereas features quantifying exponential decay rates of the autocorrelation increase, reflecting an approximately reciprocal relationship and therefore opposite directionality. In other words, the goal is to provide a broad overview of which types of properties of the time series are sensitive to our manipulation, to guide subsequent selection of individual features for more targeted interpretation, whereby directionality of effects can also be ascertained.

Please note that there can be many decision points in time-series analysis, including the choice of how to aggregate data. For the fMRI datasets, here we follow previous work in considering time series at the level of parcellated brain regions^{29,32,98–101}. Other approaches would also be possible, such as examining time series of individual voxels, or combining the entire gray matter/all neurons into a single brain-wide time series. Each would provide a different perspective. The approach that we adopted here is intermediate between these two extremes, allowing us to examine local changes at a resolution comparable with the gene expression datasets, as time-series properties are known to be regionally heterogeneous across the cortex^{29,32,98}, while also allowing for subsequent brain-wide aggregation of features to obtain a global perspective.

DPS. To quantify the similarity between the temporal profiles of each pair of brain regions (neurons in the nematode), each dynamical feature is z scored across regions. The vectors of z-scored regional features are then correlated for each pair of brain regions, producing a matrix of ‘DPS’ (also termed ‘temporal profile similarity’²⁹) that represents the strength of the similarity of the local dynamical fingerprints of brain areas. This procedure is performed separately within each individual and condition of each dataset.

The coupling between DPS and FC is in turn obtained by correlating the vectorized DPS and FC matrices. FC is computed as the zero-lag correlation between pairs of regional time series.

catch22 subset of representative features. Among all `hctsa` dynamical features, a reduced set of 22 features (23 after adding s.d.) has been identified in ref. 47 that captures a diverse range of interpretable time-series properties from the broader literature on dynamical systems (Supplementary Table 3). The features in this subset (known as the catch22) were identified as a way of reducing the dimensionality of the full `hctsa` feature set to simplify computation and interpretation. The catch22 set consists of time-series features that (1) show strong classification performance across 93 natural and artificial time-series classification datasets, comparable to the performance of the full `hctsa` set; and (2) are minimally redundant on those same datasets⁴⁷. We use this reduced set for our multivariate association analysis with regional gene expression. Please note that 1 of these 23 features, `CO_HistogramAMI_even_2_5`, was excluded by our prefiltering and therefore is not included among the features that we extract. A second feature, ‘`acf timescale`’ (`first1e_acf_tau`), occasionally failed to produce finite effect sizes for every region of every dataset due to no variance, and therefore had to be excluded from the PLS analysis, leaving 21 for the final analysis.

Intrinsic timescale. To quantify the intrinsic timescale at which each region operates^{38,40,58,102}, we follow the definition discussed in ref. 41, as the product of TR and the sum of autocorrelation function values up to the point where autocorrelation drops to zero, such that the future of the time series becomes independent of its past.

Cortical gene expression

Human brain gene expression from microarray. Regional human gene expression profiles were obtained using microarray data from the Allen Human Brain Atlas (AHBA)¹⁰³, with preprocessing as recently described¹⁰⁴. The AHBA is a publicly available transcriptional atlas containing gene expression data measured with DNA microarrays and sampled from hundreds of histologically validated neuroanatomical structures across normal postmortem human brains from six donors (five male and one female; age = 24–55 years). We extracted and mapped gene expression data to the 100 cortical ROIs of the Schaefer parcellation using the `abagen` toolbox (<https://abagen.readthedocs.io/>)¹⁰⁵. Data were pooled between homologous cortical regions to ensure adequate coverage of both left (data from six donors) and right hemisphere (data from two donors). Distances between samples were evaluated on the cortical surface with a 2 mm distance threshold. Only probes where expression measures were above a background threshold in more than 50% samples were selected. A representative probe for a gene was selected based on the highest intensity. Gene expression data were normalized across the cortex using scaled, outlier-robust sigmoid normalization. A total of 15,633 genes survived these preprocessing and quality assurance steps. We also replicated the main results in the Desikan–Killiany atlas, using human gene expression data from an alternative modality, RNA sequencing, which was available from two of six AHBA donors¹⁰³.

Macaque cortical gene expression from stereo-seq. We used cortex-wide macaque gene expression data recently made available in ref. 106, who combined single-nucleus RNA sequencing with high-resolution, large FOV spatial transcriptomics from ‘stereo-seq’¹⁰⁶. Specifically, the authors made available (<https://macaque.digital-brain.cn/spatial-omics>) postmortem gene expression data covering 143 regions of the left cortical hemisphere of one 6-year-old male cynomolgus macaque (*Macaca fascicularis*; see ref. 106 for details). The animal protocol was approved by the Biomedical Research Ethics Committee of CAS Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences (ION-2019011). Animal care complied with the guidelines of this committee¹⁰⁶.

Briefly, 119 coronal sections were obtained at 500- μ m spacing, covering the entire cortex of the left hemisphere, and were used

for Stereo-seq transcriptomics¹⁰⁶. Adjacent 50- μ m thick sections were also acquired for regional microdissection and single-nucleus RNA-sequencing analysis, as well as 10- μ m sections adjacent to each stereo-seq section, which were used for the anatomical parcellation of brain regions through immunostaining¹⁰⁶. Stereo-seq is a DNA nanoball barcoded solid-phase RNA capture method¹⁰⁶. It involves reverse transcription of RNAs released from frozen tissue sections fixed onto the stereo-seq chip, and subsequent PCR amplification. The resulting ‘amplified-barcoded complementary DNA is used as template for library preparation, and sequenced’ to obtain high-resolution spatially resolved transcriptomics¹⁰⁶.

Gene expression data were made available for 143 cortical regions of the left hemisphere, including prefrontal, frontal, cingulate, somatosensory, insular, auditory, temporal, parietal, occipital and piriform areas. As reported in ref. 106, for each coronal section, the cortical region and layer parcellation were manually delineated on stereo-seq data background, based on cytoarchitectural pattern (for example, cell density, cell size) revealed by total mRNA expression, nucleic acid staining and NeuN staining of adjacent sections. To make the gene expression data compatible with our macaque fMRI datasets, the aggregated gene expression across layers was manually mapped onto 80 regions of the ‘regional mapping’ macaque atlas in ref. 60, mirroring data between hemispheres⁴⁵.

Mouse brain gene expression from ISH. Mouse gene expression profiles were obtained using ISH data from the Allen Mouse Brain Atlas¹⁰⁷. We followed the same preprocessing as recently described¹⁰⁸. Briefly, the Allen Mouse Brain Atlas consists of data acquired from a pipeline that includes semi-automated riboprobe generation, tissue preparation and sectioning, ISH, imaging and data postprocessing. These data were acquired both sagittally and (for a smaller set of genes) coronally, and were further processed, aligned by the Allen Institute to their Common Coordinate Framework (v3; CCFv3) reference atlas¹⁰⁹ and summarized voxelwise through a measure termed gene expression energy (defined as the sum of expressing pixel intensity divided by the sum of all pixels in a division), resulting in 3D gene expression images at a 200 μ m isotropic resolution. This gene expression energy increases in regions of high expression and is bounded by zero in regions of no expression. For our study, we used gene expression energy data from the coronal dataset (4,345 gene expression images corresponding to 4,082 unique genes), because of its whole-brain coverage and data quality. The details mentioned in ref. 110 provide tools to work with these gene expression data; these tools are available online (github.com/DJFernandes/ABlGeneRMINC). Voxelwise gene expression data were further summarized as normalized mean expression within ROIs as defined by the CCFv3 reference atlas. For each ROI and each gene, voxelwise expression energy data were averaged over voxels containing valid expression signal. Finally, independently for each region, gene expression data were normalized by regressing out mean gene expression across the brain.

We also replicate the main results using mouse gene expression data from two recently released alternative databases from MERFISH, as reported in refs. 111,112. Briefly, the database from ref. 111 is a whole mouse brain spatial transcriptomics dataset containing 3.9 million segmented cells passing QC (MERFISH-C57BL6J-638850). It was acquired using multiplexed error-robust fluorescence ISH (MERFISH) technique with a 500-gene panel. The MERFISH data were registered to the Allen CCFv3 standard template, acquired CCF coordinates for each segmented cell and assigned to predefined brain structures. A separate single-cell RNA sequencing dataset was acquired using 10x (v3) technique and imputed (projected) into MERFISH space, deriving 8,460 marker genes for each MERFISH cell. A region-by-gene matrix was derived from the cell-by-gene tabular data by aggregating within the assigned Allen CCFv3 atlas regions and taking the average hierarchically following a predefined simplified anatomical hierarchy. The

database¹¹² is a whole mouse brain spatial transcriptomics dataset acquired using MERFISH technique with a 1,122-gene panel, containing 9.3 million segmented cells passing QC (Zhuang-ABCA-1/2/3/4). The MERFISH data were registered to the Allen CCFv3 standard template, and coordinates were acquired for 5.4 million cells, which were then assigned to predefined brain structures. We derived the region-by-gene matrix similarly to the above. Of 23 brain-related genes, 11 are also available in the Yao database and 13 are also available in the Zhang database.

Marmoset brain gene expression from ISH. Gene expression profiles for the common marmoset (*C. jacchus*) were also obtained from the Marmoset Gene Atlas, a recent database of ISH transcriptomics across the entire marmoset brain (<https://gene-atlas.bminds.brain.riken.jp/>) available within the brain/MINDs data portal (<https://data-portal.brainminds.jp/>). Detailed information is provided in refs. 113,114. All procedures were performed in accordance with a protocol approved by RIKEN Institutional Animal Care^{113,114}. Briefly, brains were sectioned on a freezing microtome at 28 μm . ISH staining for each probe consisted of 60 coronal sections evenly spaced at 196 μm intervals. Whole-section images were scanned and digitized. Converted images were aligned with Nissl-stained reference atlas. The Marmoset Gene Atlas database provides gene expression data for marmosets from newborn to 1 year old. The available age of each gene expression dataset varies by gene; transcriptomic data from 1-year-old animals were used when available. For genes lacking 1-year-old data (*HCN1*, *HTR1A*, *ADRA1A*, *ADRA2A*, *CHRNA2*, *GRIN3A*, *CALB1*, *GABRA1*, *OXT*, *CNR1*, *OPRK1*, *VIP*, *GRM1*, *GRM5*, *MOBP*), the available neonatal brain data were used instead. This database allows investigation of gene expression levels using anatomical location information referenced from hematoxylin and eosin-stained histological images. Although each ISH section is complemented by an adjacent neuroanatomically stained section, enabling users to compare gene expression against a brain atlas, mapping gene expression patterns over the entire brain is both time and labor intensive. From the database, 300×300 pixel images (approximately $750 \times 750 \mu\text{m}$) were extracted using ImageJ (<https://imagej.net/ij/>) at three to five locations per region across 70 cortical regions from the marmoset atlas⁸⁶ corresponding to our MRI data. A total of 66 regions had available gene expression data. Because each gene is expressed in different layers of the cortex, images from the layer that shows the highest gene expression were selected¹¹⁴. The extracted images were converted to grayscale, and the pixel values for all images were obtained for each gene. The bottom 1 percentile of the overall values for each gene was used as the threshold for binarization of the image. The number of black pixels was calculated for each binarized image, representing the expression level for that image. The expression levels of the images extracted for each region were averaged, and this value was used as the expression level for that region.

Macaque parvalbumin density from immunohistochemistry. The details in ref. 115 assembled data on the immunohistochemically measured densities of parvalbumin-expressing inhibitory interneurons for several macaque brain areas, from multiple immunohistochemistry studies^{116–119}. We used these data as provided in ref. 45, which mapped parvalbumin density onto the Regional Mapping macaque atlas used in the present study.

Biophysical computational model

We provide here a compact synthesis of the multiscale biophysical adaptive exponential integrate-and-fire (AdEx) whole-brain model from ref. 50—we refer the reader to the original publication for full details of the implementation. For the present work, all parameters were kept the same as in ref. 50. Please note that only the BOLD signals from the final whole-brain scale realized through the integration in

‘The Virtual Brain’ simulator^{120,121} were used in the present analysis. However, for the purpose of illustrating our modeling framework, we briefly introduce each of the multiscale components that were developed and analyzed in detail in ref. 50, progressing from single-neuron dynamics to mesoscale mean-field formulations and large-scale whole-brain models.

At the microscopic level, neuronal activity is described using the AdEx model⁵⁰. Synaptic currents arise from excitatory and inhibitory conductances defined by quantal synaptic events, while adaptation is controlled by voltage-dependent and spike-triggered mechanisms. Mesoscopically, a Master Equation formalism yields population-averaged firing rates, covariances and adaptation variables. The population transfer function maps the statistics of membrane potential fluctuations to output firing rates through a semi-analytic expression involving mean, variance and correlation timescales of voltage dynamics. A first-order reduction leads to a compact system for excitatory and inhibitory mean-field populations driven by external input composed of deterministic and Ornstein–Uhlenbeck noise terms, representing the activity of an individual brain region⁵⁰. At the whole-brain scale, multiple mean-field nodes (corresponding to the 68 regions of the Desikan–Killiany anatomical parcellation¹²², as in ref. 50) are coupled through anatomically defined connectivity from diffusion MRI tractography and associated propagation delays. Here we used the same anatomical data, atlas and parameters as mentioned in ref. 50. Finally, regional BOLD signals are generated through a Balloon–Windkessel hemodynamic model¹²³. Below, equations are followed by a short explanatory note. For the present work, all parameters were kept the same as in ref. 50.

Single-cell AdEx model.

$$c_m \frac{dv}{dt} = g_L (E_L - v) + g_L \Delta e^{\frac{v-v_{thr}}{\Delta}} - w + I_{syn} \quad (1)$$

$$\frac{dw}{dt} = \frac{1}{\tau_w} (a(v - E_L) - w) + b \sum_{t_{sp}} \delta(t - t_{sp}) \quad (2)$$

These equations describe the membrane voltage and adaptation current of an AdEx neuron, driven by leak, exponential spike-initiation currents, synaptic input and spike-triggered adaptation.

Synaptic conductance.

$$I_{syn} = G_{syn}^e (E_e - v) + G_{syn}^i (E_i - v), \quad (3)$$

This expresses synaptic current as the sum of excitatory and inhibitory conductance-driven components.

$$G_{syn}^x(t) = Q_x \sum_{t_{sp,jx}} \Theta(t - t_{sp,jx}) e^{-\frac{t-t_{sp,jx}}{\tau_x}} \quad (4)$$

Conductances follow exponential decays triggered by presynaptic spikes of type $x \in \{e, i\}$.

Mean-field equations.

$$T \frac{\partial v_\mu}{\partial t} = (F_\mu - v_\mu) + \frac{1}{2} c_{\lambda\eta} \frac{\partial^2 F_\mu}{\partial v_\lambda \partial v_\eta} \quad (5)$$

$$T \frac{\partial c_{\lambda\eta}}{\partial t} = \delta_{\lambda\eta} \frac{F_\lambda (1/T - F_\eta)}{N_\lambda} + (F_\lambda - v_\lambda) (F_\eta - v_\eta) \quad (6)$$

$$+ \frac{\partial F_\lambda}{\partial v_\mu} c_{\eta\mu} + \frac{\partial F_\eta}{\partial v_\mu} c_{\lambda\mu} - 2c_{\lambda\eta} \quad (7)$$

$$\frac{\partial W}{\partial t} = \frac{1}{\tau_w} (a(\mu_V(v_e, v_i, W) - E_L) - W) + bv_e \quad (8)$$

These equations evolve the mean firing rates, covariances and population adaptation based on the transfer function F_μ .

Transfer function.

$$F = v_{\text{out}} = \frac{1}{2\tau_V} \times \text{Erfc} \left(\frac{V_{\text{thr}}^{\text{eff}} - \mu_V}{\sqrt{2}\sigma_V} \right) \quad (9)$$

This semi-analytic expression converts voltage statistics to output firing rate.

$$\mu_{G_s}(v_e, v_i) = v_s K_s \tau_s Q_s \quad (10)$$

$$\sigma_{G_s}(v_e, v_i) = Q_s \sqrt{\frac{v_s K_s \tau_s}{2}} \quad (11)$$

These formulas give mean and variance of synaptic conductances assuming Poisson presynaptic firing.

$$\mu_G(v_e, v_i) = \mu_{G_e} + \mu_{G_i} + g_L \quad (12)$$

$$\tau_m^{\text{eff}}(v_e, v_i) = \frac{C_m}{\mu_G} \quad (13)$$

These define total conductance and effective membrane time constant.

$$\mu_V(v_e, v_i, w) = \frac{\mu_{G_e} E_e + \mu_{G_i} E_i + g_L E_L - w}{\mu_G} \quad (14)$$

This is the mean membrane potential under fluctuating conductances.

$$\sigma_V(v_e, v_i) = \sqrt{\sum_s K_s v_s \frac{(U_s \times \tau_s)^2}{2(\tau_m^{\text{eff}} + \tau_s)}} \quad (15)$$

$$\tau_V(v_e, v_i) = \frac{\sum_s (K_s v_s (U_s \times \tau_s)^2)}{\sum_s (K_s v_s \frac{(U_s \times \tau_s)^2}{\tau_m^{\text{eff}} + \tau_s})} \quad (16)$$

where $s = \{e, i\}$ and $U_s = Q_s \mu_G(E_s - \mu_V)$. These give the variance and correlation time of membrane voltage fluctuations.

The $V_{\text{thr}}^{\text{eff}}$ in equation (9) is the phenomenological spike threshold voltage (see ref. 124 for details).

Reduced first-order mean-field model.

$$T \frac{dv_e}{dt} = \mathcal{F}_e(v_e + v_{\text{aff}}, v_i, W) - v_e \quad (17)$$

$$T \frac{dv_i}{dt} = \mathcal{F}_i(v_e + v_{\text{aff}}, v_i, W) - v_i \quad (18)$$

$$\frac{dW}{dt} = -\frac{W}{\tau_w} + bv_e + \frac{a}{\tau_w} (\mu_V(v_e, v_i, W)) - E_L \quad (19)$$

$$v_{\text{aff}}(t) = v_{\text{drive}} + \sigma \xi(t) \quad (20)$$

$$d\xi(t) = -\xi(t) \frac{dt}{\tau_{OU}} + dW_t \quad (21)$$

These define the population dynamics under noisy external input.

Whole-brain coupling.

$$T \frac{dv_e(k)}{dt} = \mathcal{F}_e(v_e^{\text{input}}(k), v_i(k), W(k)) - v_e(k) \quad (22)$$

$$T \frac{dv_i(k)}{dt} = \mathcal{F}_i(v_e^{\text{input}}(k), v_i(k), W(k)) - v_i(k) \quad (23)$$

$$\tau_w \frac{dW(k)}{dt} = -W(k) + b\tau_w v_e(k) + a(\mu_V(v_e(k), v_i(k), W(k))) - E_L \quad (24)$$

$$v_e^{\text{input}}(k) = v_e(k) + v_{\text{aff}}(k) + G \sum_j C_{jk} v_e(j, t - \|j - k\| / v_c) \quad (25)$$

These equations specify the long-range excitatory coupling through structural connectivity, scaled by global coupling G (here kept fixed as in ref. 50) and delayed by propagation over tract lengths.

Simulated BOLD signals. The simulated BOLD signal was generated through the dedicated BOLD monitor provided by The Virtual Brain software. The simulated mean-field time series of the excitatory population (downsampled at 250 Hz) of each node was convolved with the hemodynamic response function (described by the first-order Volterra kernel of the Balloon–Windkessel model¹²³). This signal was finally sampled to the fMRI TR of 2 s, as in ref. 50.

Simulating molecular mechanisms of diverse anesthetics. To model state-dependent whole-brain dynamics, we manipulated the biophysical parameters of the AdEx-based mean-field model to reproduce the awake condition and the effects of propofol and ketamine at the synaptic and population levels. The awake state served as the reference regime and was obtained using the baseline synaptic decay times $\tau_e = \tau_i = 5$ ms and a weak spike-triggered adaptation $b_e = 5$ pA for the excitatory population, yielding a stable asynchronous-irregular regime. Propofol, a GABAA-potentiating agent^{43,44,125}, was implemented by prolonging inhibitory synaptic kinetics through an increased decay time $\tau_i = 7$ ms, together with a moderate increase in adaptation $b_e = 30$ pA. Ketamine, an NMDA receptor antagonist^{126,127}, was modeled by shortening the excitatory synaptic decay to $\tau_e = 3.75$ ms while keeping $\tau_i = 5$ ms and likewise setting $b_e = 30$ pA⁵⁰. These molecularly grounded perturbations alter the effective membrane statistics (μ_V, σ_V, τ_V) entering the transfer functions F_μ and thereby reshape the fixed-point structure of the mean-field system. The awake, propofol and ketamine conditions were thus fully specified by their respective parameter triplets (τ_e, τ_i, b_e) as fixed in ref. 50, propagated consistently from the single-cell synaptic mechanism to mesoscale mean-field dynamics and finally to macroscale structure-constrained whole-brain activity.

Statistical analyses

Anesthetic effect size. For each contrast (awake versus anesthesia) in each dataset, we consider each region/neuron and feature in turn. We use the ‘measures of effect size’ toolbox for MATLAB (<https://github.com/hhentschke/measures-of-effect-size-toolbox>)¹²⁸ to estimate an effect size for the difference between that feature’s values during wakefulness and during anesthesia using Hedges’ measure of the standardized mean difference, g , which is interpreted in the same way as Cohen’s d , but more appropriate for small sample sizes¹²⁹. Please note that features were not normalized across regions before analysis, as doing so could obscure differences in magnitude. Although hctsa features span several orders of magnitude, such that raw differences cannot be meaningfully compared across features, effect sizes are expressed in units of s.d., and therefore they are readily comparable across features and also across regions and datasets. For each contrast in each dataset, this procedure produces a matrix of awake-versus-anesthesia effect sizes, with dimensions n regions/neurons $\times$ f features (with $f = 6827$ for

all species after postfiltering). Hedges' g was also used to quantify the difference in motion and tSNR proxy.

Null models for the significance of the number of consistent features. To establish whether the empirically observed number of consistent dynamical features is significantly greater than the number of features that would be expected to show consistency (all increases or all decreases) across all contrasts, just by chance alone, we construct a null distribution with the same number of features and contrasts (here, 15) where the sign of each feature and contrast is assigned at random (+1 or -1). We then compute the number of features having the same sign across all 15 contrasts. Repeating this process 10,000 times produces a null distribution against which we test the empirical number of consistent features to obtain a P value for our null hypothesis.

We also implement an alternative null model, whereby, rather than computing the contrast and then randomly flipping its sign, the awake versus anesthesia labels are randomly permuted at the level of each participant, while preserving the number of individuals in each category. For datasets with within-participant design, individuals' identity is also preserved. We then compute the number of features that show a change in the same direction (that is, same sign) across all 15 contrasts, exactly as for the main analysis. Repeating this process 10,000 times produces a null distribution against which we test the empirical number of consistent features to obtain a P value for our null hypothesis.

Multivariate association with PLS. PLS analysis was used to relate regional gene expression to anesthetic-induced changes in local dynamics in a multivariate fashion. PLS analysis is an unsupervised multivariate statistical technique that decomposes relationships between two datasets $X_{n \times g}$ and $Y_{n \times f}$ into orthogonal sets of LVs with maximum covariance, which are linear combinations of the original data^{130,131}. In the present case, $X_{n \times g}$ is regional gene expression across n regions (100 for the human; 82 for the macaque; 70 for the marmoset; and 72 for the mouse) and g genes (the same set of 23 genes for each species). $Y_{n \times f}$ is the matrix of regional anesthetic-induced changes in dynamical features across f features.

To ensure consistent gene-dynamics relationships across species, we perform this analysis on matrices $X_{n \times g}$ and $Y_{n \times f}$ obtained by vertically concatenating the species-specific matrices for human, macaque, marmoset and mouse. Within each species, we separately z score the $X_{n \times g}$ and $Y_{n \times f}$ matrices column-wise. We then concatenate the species-specific X matrices of z scores vertically, and we likewise concatenate the species-specific Y matrices of z scores vertically. This is possible because the columns are the same for each species across all four species—the same 23 genes and the same dynamical features. This results in a single $X_{n \times g}$ matrix and a single $Y_{n \times f}$ matrix, each with $n = 100 + 82 + 70 + 72 = 324$ rows. Rows with missing data in either matrix were ignored by the PLS. PLS finds components from the predictor variables (regional gene expression) that have maximum covariance with the response variables (regional changes in dynamical features). The PLS components (that is, linear combinations of the weighted variables) are ranked by the covariance between predictor and response variables so that the first few PLS components provide a low-dimensional representation of the covariance across the higher-dimensional data matrices. Concretely, this is achieved by performing singular value decomposition on the matrix $Y'X$, such that:

$$Y'X = U_{g \times t} S_{t \times t} V'_{t \times f}, \quad (26)$$

where $U_{g \times t}$ and $V_{t \times f}$ are orthonormal matrices consisting of left and right singular vectors, and $S_{t \times t}$ is a diagonal matrix of singular values. The i th columns of U and V constitute an LV, and the i th singular value in S represents the covariance between singular vectors. The i th singular value is proportional to the amount of covariance between gene

expression and anesthetic-induced dynamical changes captured by the i th LV, where the effect size can be estimated as the ratio of the squared singular value to the sum of all squared singular values.

For the main analysis, we use the subset of 'catch22' representative features (excluding *acf*, *timescale* that did not return finite values for all regions; and *ami2* that did not pass our prefiltering step, leaving the same 21 dynamical features available for use in all species). As a further validation, we also repeat the analysis using all 485 consistent features. Significance of the LVs is assessed against a null distribution of null maps with preserved spatial autocorrelation, as described below.

Null models with preserved spatial autocorrelation. The statistical significance of the covariance explained by each PLS model is tested by permuting the response variables 500 times while considering the spatial dependency of the data by using spatial autocorrelation-preserving permutation tests, to control for the spatial autocorrelation inherent in neuroimaging data, which can induce an inflated rate of false positives^{132,133}.

For each species, we generate null maps using Moran spectral randomization based on the inverse Euclidean distances between parcel centroids for that species, as implemented in the 'BrainSpace' toolbox (<https://brainspace.readthedocs.io/en/latest/>)¹³⁴. Moran spectral randomization quantifies the spatial autocorrelation in the data in terms of Moran's I coefficient by computing spatial eigenvectors known as Moran eigenvector maps. The Moran eigenvectors are then used to generate null maps by imposing the spatial structure of the empirical data on randomized surrogate data^{133,134}. As for the empirical data, each null map is z scored within species and the corresponding null maps are then concatenated vertically across species to obtain a null Y matrix. PLS analysis is then applied to the original X matrix and this null is applied to the Y matrix. This procedure is repeated 500 times to obtain a null distribution of the covariance explained by each LV. This test embodies the null hypothesis that regional gene expression and regional dynamical changes induced by anesthesia are spatially correlated with each other only because of inherent spatial autocorrelation. The one-sided P value is computed as the proportion of null covariances explained that are greater in magnitude than the empirical covariance explained. Thus, these P values represent the probability that the observed spatial correspondence between genes and dynamical features could occur by randomly correlating maps with comparable spatial autocorrelation.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

For the human sevoflurane dataset, data are available from D.G. through collaboration. For the macaque multi-anesthesia dataset, raw data are available for access from B.J. through academic collaboration. For the macaque DBS dataset, raw data are available for access from B.J. through academic collaboration. For the mouse dataset, data are available from A.G. The marmoset fMRI data are available from K.M. through academic collaboration. The zebrafish calcium imaging data are available from P.D.K. through academic collaboration. The nematode calcium imaging data are available from C.W.C. through academic collaboration. Human gene expression data from the AHBA¹⁰³ are available at <https://human.brain-map.org/>. Macaque cortical gene expression data from ref. 106 are available at <https://macaque.digital-brain.cn/spatial-omics>. The dataset is provided by Brain Science Data Center, Chinese Academy of Sciences (<https://braindatacenter.cn/>). Mouse gene expression data from ISH are available from the Allen Mouse Brain Atlas¹⁰⁷ at <https://mouse.brain-map.org/>. The Marmoset Gene Atlas is available at <https://gene-atlas.bminds.brain.riken.jp/>. The MERFISH mouse transcriptomic data are available through the

Neuroscience Multi-omic Data Archive (<https://nemoarchive.org/>). Human Connectome Project data in DSI studio-compatible format are available at <http://brain.labsolver.org/diffusion-mri-templates/hcp-842-hcp-1021>. Source data are provided with this paper.

Code availability

The hctsa toolbox (v1.07) is freely available at <https://github.com/benfulcher/hctsa>. The abagen toolbox (v0.1.3) for processing of the AHBA human transcriptomic dataset is available at <https://abagen.readthedocs.io/>. The BrainSpace toolbox (v0.1.5) for Moran spectral randomization is available at <https://brainspace.readthedocs.io/en/latest/>. The measures of effect size toolbox (v1.6.1) is available at <https://github.com/hhentschke/measures-of-effect-size-toolbox>. The Virtual Brain code for the biophysical model is available at <https://www.thevirtualbrain.org/tvb/zwei/home> (v2.9).

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Author contributions

A.I.L. and B.M. conceived the analysis. A.I.L. performed the analysis and visualization. L.U., J.T. and B.J. designed the macaque experiments and collected and curated the macaque fMRI data. A.L., P.D. and P.D.K. designed the zebrafish experiments. A.L. collected and curated the zebrafish calcium imaging data. K.M. performed regional quantification of marmoset gene expression. K.M., J.H. and H.O. designed the marmoset experiments and collected and curated the marmoset fMRI data. D.G., A.R., R.I. and D.J. designed the human experiments and

collected and curated the human fMRI data. S.G. and A.G. designed the mouse experiments and collected and curated the mouse fMRI data, and provided the mouse connectome. C.W.C. designed the nematode experiments and collected and curated the nematode calcium imaging data. C.M.S., R.C. and P.C. contributed to macaque data processing. G.S. and Z.-Q.L. contributed to data analysis. Y.Y. and Z.-Q.L. contributed to mouse gene expression data. B.D.F., G.S., A.D., D.K.M., A.G., B.J. and E.A.S. contributed to interpretation. B.J. and B.M. supervised the project. A.I.L. and B.M. wrote the paper with feedback from all co-authors. All authors approved the paper.

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Competing interests

All authors declare no competing interests.

Additional information

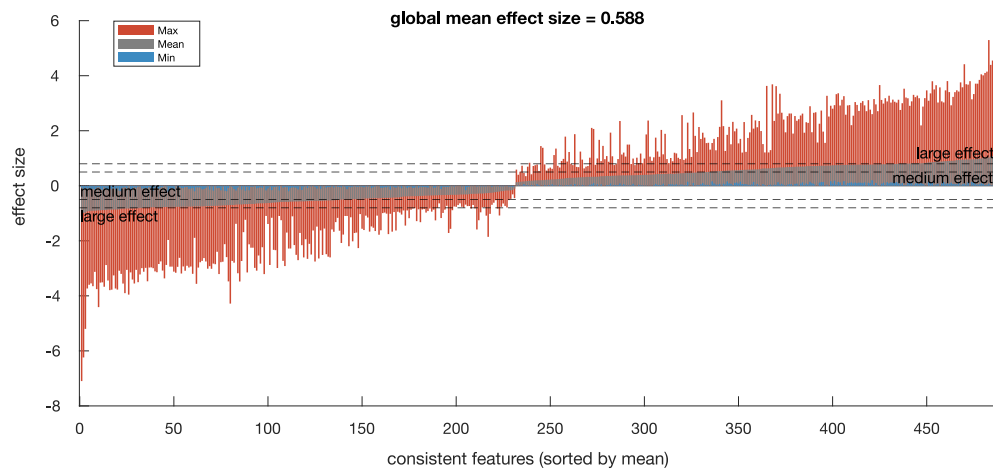
Extended data is available for this paper at <https://doi.org/10.1038/s41593-026-02460-4>.

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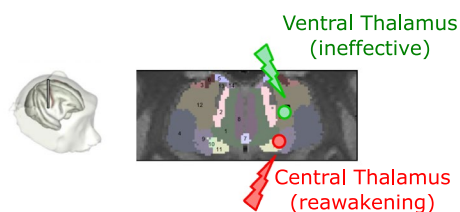
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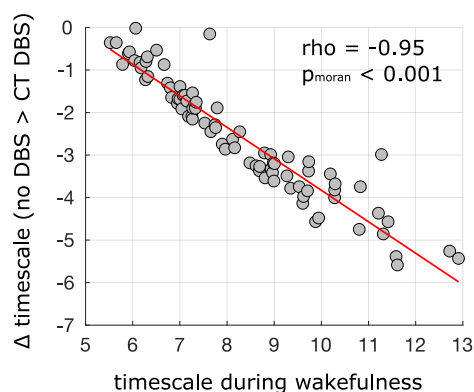


Extended Data Fig. 1 | Distribution of effect sizes for consistent features. For each consistent feature, the minimum (blue), mean (gray) and maximum (red) effect sizes obtained across $n = 15$ contrasts are shown, sorted by the mean. Horizontal dashed lines indicate a canonical medium effect size (Hedges' $g = 0.5$) and large effect size (Hedges' $g = 0.8$).

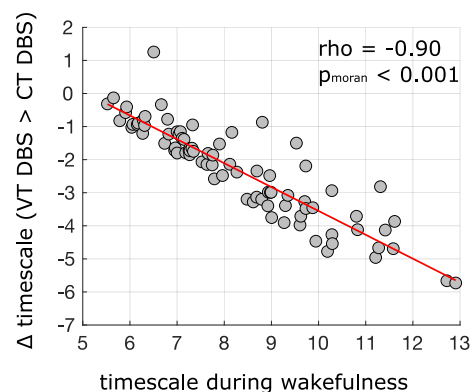
a | thalamic DBS to reawaken anaesthetised macaques



b | anaesthesia without DBS > DBS central thalamus

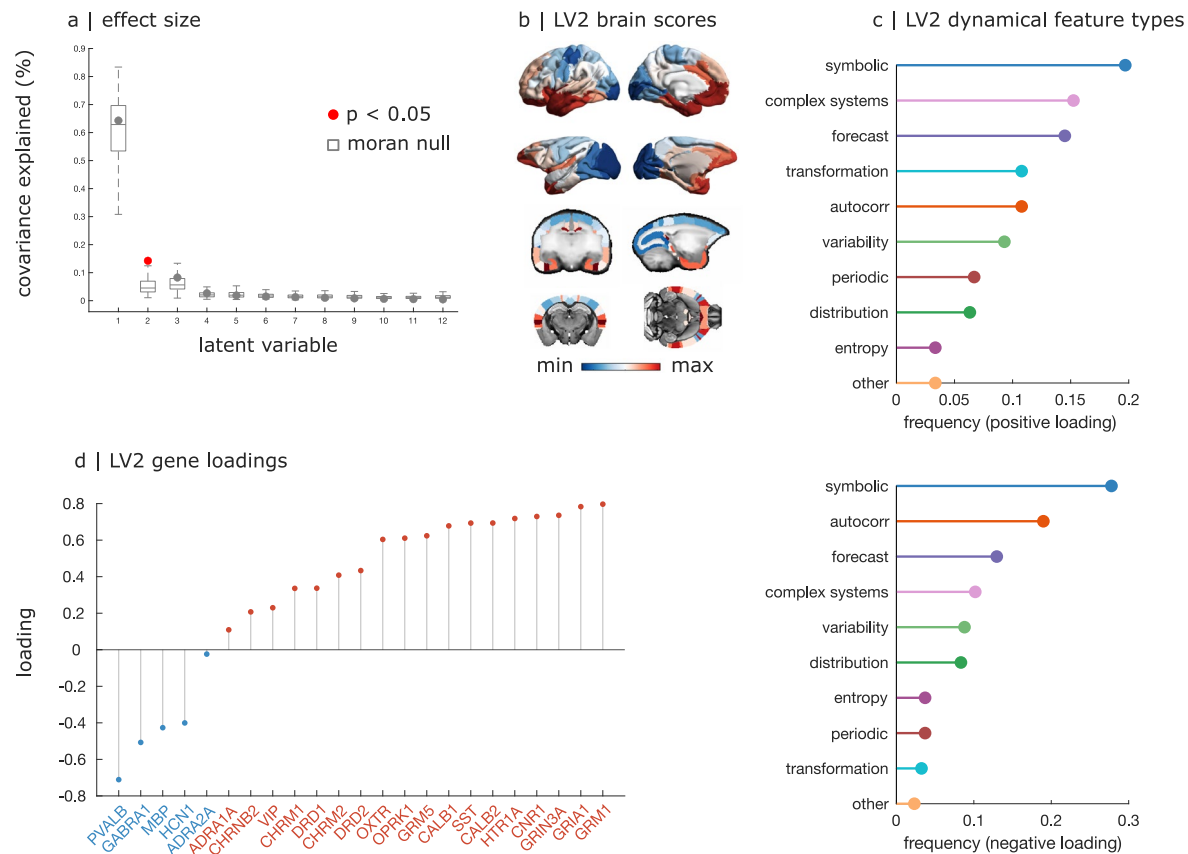


c | DBS ventral thalamus > DBS central thalamus



Extended Data Fig. 2 | DBS-induced restoration of intrinsic neural timescales in the anesthetized macaque. **a**, Illustration of deep-brain stimulation targets in the macaque thalamus: centromedian thalamus and ventro-lateral thalamus. Macaque DBS in **a** adapted from ref. 13. **b**, Regional intrinsic neural timescales are increased during re-awakening from anesthesia induced by CT DBS, compared with propofol anesthesia without DBS, and the change is proportional to the value at wakefulness (Spearman $\rho = -0.95$, $p < 0.001$, two-sided; $n = 82$ brain regions). Significance is assessed against a null distribution of 10,000 surrogate brain maps with preserved spatial autocorrelation. **c**, Regional intrinsic neural

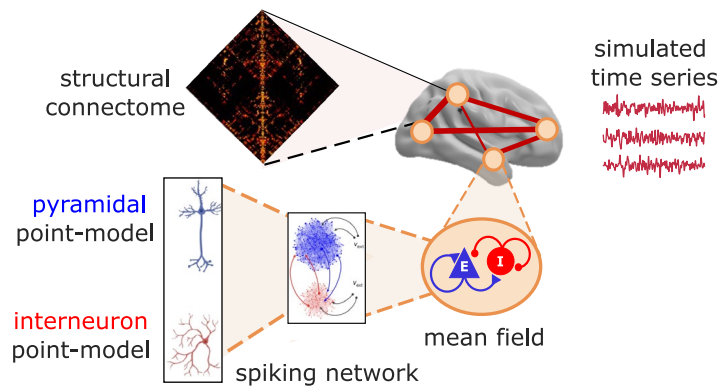
timescales are increased during re-awakening from anesthesia induced by CT DBS, compared with VT DBS at the same intensity (which does not re-awaken the animal), and the change is proportional to the value at wakefulness (Spearman $\rho = -0.90$, $p < 0.001$, two-sided; $n = 82$ brain regions). Significance is assessed against a null distribution of 10,000 surrogate brain maps with preserved spatial autocorrelation. Both effects resemble the difference between anesthesia and baseline wakefulness, although here wakefulness is achieved through stimulation while propofol is still present.



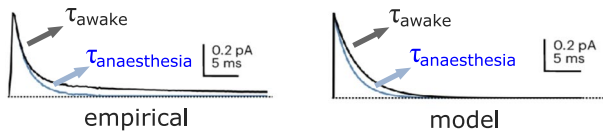
Extended Data Fig. 3 | Gene–dynamics association across the full set of dynamical features that are consistently perturbed by anesthesia. **a**, We find a statistically significant latent dimension of multivariate association between gene expression and anesthetic-induced feature change (LV2). The first latent dimension is not significant beyond the effect of spatial autocorrelation. We assess significance against a null distribution generated using Moran spectral randomization (Methods), whereby brain maps of each species are randomized, but their spatial autocorrelation is preserved, embodying the null hypothesis that local dynamics and gene expression are spatially correlated with each other purely because of inherent spatial autocorrelation. For each LV, a one-sided p -value is computed as the proportion of null covariances explained (across 500 surrogate PLS analyses) that are greater in magnitude than the empirical

covariance explained. No adjustment is made for multiple comparisons. Box plots: centerline, median; box limits, upper and lower quartiles; whiskers, $1.5 \times$ interquartile range; $n = 500$ surrogates from Moran spectral randomization. See Source Data for individual p -values. **b**, Representation of the significant LV2 on the cortex of each species, delineating an evolutionarily conserved posterior–dorsal to anterior–ventral gradient. **c**, Proportion of features belonging to each of 10 broad categories, among those with positive LV2 loading (top), and among those with negative LV2 loading (bottom). **d**, Loading of each gene onto the significant LV2 dimension of multivariate association with anesthetic-induced changes in local dynamical features. Red indicates positive loading, blue indicates negative loading.

a | biophysical modelling of anaesthetised brain dynamics

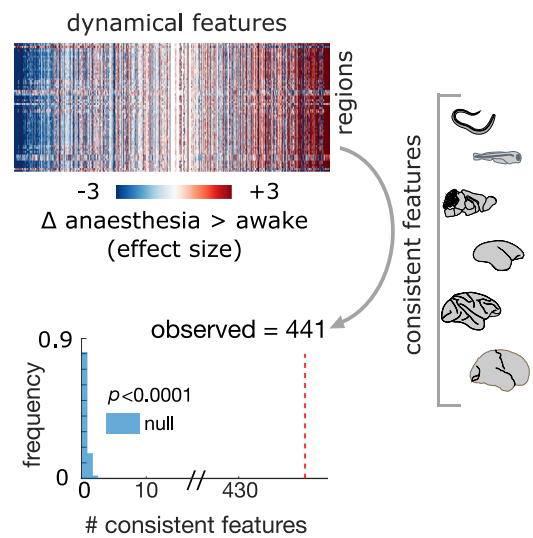


b | NMDA block shortens excitatory postsynaptic current



Extended Data Fig. 4 | Computational modeling of ketamine-induced changes in macroscale local dynamics from microscale synaptic mechanisms. a, Computational model to assess how microscale molecular mechanisms impact macroscale brain dynamics. The whole-brain model consists of biophysically grounded mean-field reductions (one for each brain region) of networks of excitatory and inhibitory neurons, integrating microscale cellular and molecular properties (membrane conductances and AMPA, NMDA, and GABA_A synaptic receptors) to simulate regional fMRI signals. Once connected according to empirical anatomical connectivity of the human brain from in vivo diffusion tractography, the resulting whole-brain model links biophysically meaningful synaptic-level mechanisms to macroscale dynamics. **b,** At the microscale, the model simulates the empirically observed shortening of excitatory postsynaptic currents induced by NMDA receptor antagonists such as ketamine, as a decrease

c | reproducing anaesthesia dynamics



in the time constant of excitatory synaptic decay. Models in **a** and **b** adapted from ref. 50. **c,** At the macroscale, we apply comprehensive dynamical phenotyping to the simulated BOLD signals from the model in the awake and anesthetized regimes ($N = 19$ simulations for each condition), following the same workflow as for our empirical data. Among the 485 features that had exhibited consistent changes across all empirical contrasts from Fig. 3, 441 features (>90%) also exhibit changes in the same direction in the computational model. This number is significantly greater than expected by chance, as assessed by a null model where each feature's direction of change (increase or decrease) is assigned at random, repeated 10,000 times (one-sided $p < 0.0001$). Brain icons in **c** adapted from SciDraw under a Creative Commons license [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/).

Extended Data Table 1 | Overview of the seven datasets included in the present study, and their key parameters

Species	Awake conditions	Anaesthesia conditions	Imaging modality	Temporal resolution	Timepoints used	Spatial coverage	Reference
Human (<i>Homo sapiens</i>) N=15	-awake (15 scans) -recovered (15 scans)	sevoflurane (15 scans)	fMRI 3T BOLD	1838 ms	346	100	Ranft et al., (2016) <i>Anesthesiology</i>
Macaque (<i>Macaca mulatta</i>) N=5	awake (24 scans)	-sevoflurane (11 scans) -propofol (23 scans) -ketamine (22 scans)	fMRI 3T MION	2400 ms	500	82	Uhrig et al., (2018) <i>Anesthesiology</i>
Macaque (<i>Macaca mulatta</i>) N=5	-awake (36 scans) -reawakened by central thalamus DBS (25 scans)	-propofol (28 scans) -propofol with ventral thalamus DBS (18 scans)	fMRI 3T BOLD	1250 ms	500	82	Tasserie et al., (2022) <i>Science Advances</i>
Marmoset (<i>Callithrix jacchus</i>) N=4	awake (48 scans)	-propofol (48 scans) -sevoflurane (48 scans) -isoflurane (48 scans)	fMRI 9.4T BOLD	2000 ms	150	70	Muta et al., (2023) <i>Cerebral Cortex</i>
Mouse (<i>Mus musculus</i>) N=43	awake (10 scans)	-med-iso (14 scans) -halothane (19 scans)	fMRI 7T BOLD	1000 ms (1200 ms halo)	1414	72	Gutierrez-Barragan et al., (2023) <i>Current Biology</i>
Nematode (<i>C. elegans</i>) N=10	0% iso (10 scans)	4% isoflurane (10 scans)	GCaMP6s calcium imaging	500 ms	500	120	Awal et al., (2020) <i>Anesthesiology</i>
Larval zebrafish (<i>Danio rerio</i>) N=7	awake (7 scans)	tricaine (7 scans)	GCaMP calcium imaging	1014 ms	250	352	This article

For human, macaque, marmoset, and mouse, 'spatial coverage' indicates the number of brain regions. For the nematode and zebrafish, it indicates the number of neurons or brain regions (groups of neurons), respectively. MION, monocrySTALLine iron oxide nanoparticle contrast agent. BOLD, blood-oxygen level dependent signal. The same number of time points is used in all conditions belonging to the same dataset.

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Software and code

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Data collection The Python processing for PreClinical data pipeline, Pypreclin version 1.0.1, is freely available at <https://github.com/neurospin/pypreclin>. FMRIB Software Library (FSL) is freely available online (<http://www.fmrib.ox.ac.uk/fsl/>; version accessed February 4, 2018).

Data analysis The Highly Comparative Time-Series Analysis (hctsa) toolbox (v1.07) is freely available at <https://github.com/benfulcher/hctsa>. The abagen toolbox (0.1.3) for processing of the AHBA human transcriptomic dataset is available at <https://abagen.readthedocs.io/>. The BrainSpace toolbox (v0.1.5) for Moran spectral randomisation is available at <https://brainspace.readthedocs.io/en/latest/>. The Virtual Brain code for the biophysical model is available at <https://www.thevirtualbrain.org/tvb/zwei/home> (version 2.9). The Measures of Effect Size Toolbox (v1.6.1) for MATLAB is freely available at <https://github.com/hhentschke/measures-of-effect-size-toolbox>.

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](#)

For the human sevoflurane dataset, data are available from author D.G. through . collaboration. For the macaque multi-anaesthesia dataset, raw data are available for access from author B.J. through academic collaboration. For the macaque DBS dataset, raw data are available for access from author B.J. through academic collaboration. For the mouse dataset, data are available from A.G. The marmoset fMRI data are available from author K.M. through academic collaboration. The zebrafish calcium imaging data are available from author P.D.K through academic collaboration. The nematode calcium imaging data are available from author C.W.C. through academic collaboration. Human gene expression data from the Allen Human Brain Atlas [102] are available at <https://human.brain-map.org/>. Macaque cortical gene expression data from [105] are available at <https://macaque.digital-brain.cn/spatial-omics>. The dataset is provided by Brain Science Data Center, Chinese Academy of Sciences (<https://braindatacenter.cn/>). Mouse gene expression data from in situ hybridization are available from the Allen Mouse Brain Atlas [106] at <https://mouse.brain-map.org/>. The Marmoset Gene Atlas is available at <https://gene-atlas.bminds.brain.riken.jp/>. The MERFISH mouse transcriptomic data are available through the Neuroscience Multi-omic Data Archive (NeMO, <https://nemoarchive.org/>). Human Connectome Project data in DSI Studio-compatible format are available at <http://brain.labsolver.org/diffusion-mri-templates/hcp-842-hcp-1021>. Source data are provided.

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

Each human dataset had been previously collected. The human sevoflurane dataset only included male participants. The design is within-subjects, and our focus was not on comparing groups or inter-individual differences but rather on comparing states of anaesthesia. The HCP dataset includes both men and women.

Reporting on race, ethnicity, or other socially relevant groupings

No grouping by race, ethnicity, or socioeconomic status was performed.

Population characteristics

human sevoflurane dataset: n=20 male participants were recruited (20 to 36 years of age; mean, 26 years). The design is within-subjects, and our focus was not on comparing groups or inter-individual differences but rather on comparing states of anaesthesia. The HCP dataset includes both men and women.

Recruitment

Data acquisition took place between June and December 2013. Participants approaches the research team to seek participation. Healthy adult men were recruited through campus notices and personal contact, and compensated for their participation in the study. Written informed consent was obtained from volunteers at least 48 h before the study session. Inclusion of only male humans may be a source of bias. Further exclusion criteria were the following: physical status other than American Society of Anesthesiologists physical status I, chronic intake of medication or drugs, hardness of hearing or deafness, absence of fluency in German, known or suspected disposition to malignant hyperthermia, acute hepatic porphyria, history of halothane hepatitis, obesity with a body mass index more than 30 kg/m², gastrointestinal disorders with a disposition for gastroesophageal regurgitation, known or suspected difficult airway, and presence of metal implants.

HCP dataset: Detailed information about the recruitment, acquisition and imaging is provided in the dedicated HCP publications.

Ethics oversight

All HCP scanning protocols were approved by the local Institutional Review Board at Washington University in St. Louis. Sevoflurane dataset: The ethics committee of the medical school of the Technische Universität München (München, Germany) approved the current study.

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

This study used previously collected data, except for the zebrafish dataset. No power analysis was performed prior to data collection; the sample sizes are within the range reported in the literature.

human sevoflurane dataset: n=20 male participants were recruited (20 to 36 years of age; mean, 26 years).

Macaque datasets: Five rhesus macaques were included for analyses (Macaca mulatta, one male, monkey J, and four females, monkey A, K, Ki, and R, 5-8 kg, 8-12 yr of age). For the DBS dataset, details were provided in (Tasserie et al., 2022). Five male rhesus macaques (Macaca mulatta, 9 to 17 years and 7.5 to 9.1 kg) were included, three for the awake (non-DBS) experiments (monkeys B, J, and Y) and two for the DBS experiments (monkeys N and T). No statistical methods were used to determine sample size, but these sample sizes are in line with similar studies in the field, due to the ethical and practical challenges of neuroscience research with nonhuman primates.

Marmoset dataset: Three male and one female healthy common marmosets (C. jacchus) between 3 and 6 years of age were included. All marmosets were examined 8 times to collect functional MRI data in all conditions.

Mouse: N=10 for awake condition; N=19 for halothane; N=14 for med-sio anaesthesia.

Zebrafish larvae: N=7 animals were included.

Nematode: N=10 for each condition.

Data exclusions

Sevoflurane dataset: A total of 16 volunteers completed the full protocol and were included in our analyses; one participant was excluded due to high motion, leaving N=15 for analysis.

Macaque: See "Noise and artifact removal" section below, for quality control criteria used to exclude individual trials from analysis. Exclusion was done prior to analysis.

Marmoset: no exclusions

Mouse: no exclusions

Zebrafish: no exclusions

Nematode: no exclusions

Replication

We replicated our results in 4 different mammalian species, one invertebrate species, one fish species, and with different anaesthetics. We also replicated mouse gene expression results with two different and independent transcriptomics databases. We replicated the results using different doses of anaesthetic in the human data.

Randomization

Human sevoflurane data, marmoset data, zebrafish data, nematode data: every individual was included in every condition in a within-subjects design, so no allocation was required.

Macaque datasets: Three monkeys were used for each condition: awake state (monkeys A, K, and J), ketamine (monkeys K, R and Ki), propofol (monkeys K, R, and J), sevoflurane (monkeys Ki, R, and J). The design involves taking multiple samples from the same animals in different conditions, and we controlled for this with linear mixed effects modelling.

For the multi-anaesthesia dataset, the acquisitions were performed over 5 years. Whenever possible, animals were scanned in different anesthesia (propofol, sevoflurane, ketamine) conditions.

Monkey R: moderate propofol, deep propofol, moderate sevoflurane, deep sevoflurane, ketamine

Monkey K: moderate propofol, deep propofol, ketamine

Monkey K could not be scanned under moderate sevoflurane and deep sevoflurane anesthesia, because this monkey had health issues not related with this study.

Monkey Ki: moderate sevoflurane, deep sevoflurane, ketamine

Monkey J: moderate propofol, deep propofol, moderate sevoflurane, deep sevoflurane

For the awake condition, monkeys need to have a headpost and be trained for awake fMRI studies. 2 monkeys of the multi-anaesthesia dataset could be scanned in the awake condition. Monkey K: and monkey J. The third monkey of this group was monkey A.

Regarding the DBS dataset, animals and experimental conditions (different location and stimulation for resting state) were randomly chosen using a Matlab function.

Mouse dataset: each individual only took part in one condition. Animals were of the same sex (all male), age, and bred in identical conditions in the same vivarium.

Blinding

No blinding is possible, since anaesthetised state is tested by means of behavioural responsiveness.

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 |

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

Macaque Multi-anaesthesia dataset: Macaca mulatta (one male and four females, 8-12 yr of age).
Macaque DBS dataset: Macaca mulatta (five males, 9 to 17 years).

Marmoset dataset: Three male and one female healthy common marmosets (*C. jacchus*) between 3 and 6 years of age were included. All marmosets were examined 8 times to collect functional MRI data in all conditions.

Mouse dataset: Adult (< 6 months old) male C57BL/6J mice (*Mus musculus*) were used. All the imaged mice were bred in the same vivarium.

N=10 for awake condition; N=19 for halothane; N=14 for med-iso anaesthesia.

Larval zebrafish: N=7 animals. All experiments were conducted on Tg(elavl3:H2BGCaMP6s) zebrafish larvae (*Danio rerio*) at 6 or 7 days post-fertilization (dpf). Sex cannot be determined at the larval stage.

Nematode: N=10 animals. All experiments were on young adult hermaphrodites of the transgenic strain QW1217 (zfls124[Prgef-1::GCaMP6s]; otIs355[Prab-3::NLS::tagRFP]).

Wild animals

No wild animals used.

Reporting on sex

For the macaque anaesthesia dataset, five rhesus macaques were included for analyses (Macaca mulatta, one male, monkey J, and four females, monkey A, K, Ki, and R, 5-8 kg, 8-12 yr of age).

For the macaque DBS dataset, five male rhesus macaques (Macaca mulatta, 9 to 17 years and 7.5 to 9.1 kg) were included, three for the awake (non-DBS) experiments (monkeys B, J, and Y) and two for the DBS experiments (monkeys N and T).

For the marmoset dataset, three male and one female animals were included.

Mouse dataset: Adult (< 6 months old) male C57BL/6J mice were used throughout the study.

Zebrafish: Sex cannot be determined at the larval stage.

Sex was not considered in this study. Because of the small sample sizes, the sex balance per group could not be secured. Only males were included in the DBS dataset in order to avoid the menstrual cycle and hormone variations.

Field-collected samples

None

Ethics oversight

Human sevoflurane: The ethics committee of the medical school of the Technische Universität München (München, Germany) approved the current study.

Macaque: All procedures are in agreement with the European Convention for the Protection of Vertebrate Animals used for

Experimental and Other Scientific Purposes (Directive 2010/63/EU) and the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. Animal studies were approved by the institutional Ethical Committee (Commissariat à l'Energie atomique et aux Énergies alternatives; Fontenay aux Roses, France; protocols CETEA \#10-003 and 12-086). All procedures are in agreement with 2010/63/UE, 86-406, 12-086 and 16-040.

Marmoset: This study was approved by the Animal Experiment Committees at the RIKEN Center for Brain Science (CBS) and was conducted per the guidelines for Conducting Animal Experiments of RIKEN CBS.

Mouse: In vivo experiments were conducted in accordance with the Italian law (DL 26/214, EU 63/2010, Ministero della Sanita, Roma) and with the National Institute of Health recommendations for the care and use of laboratory animals 29. The animal research protocols for this study were reviewed and approved by the Italian Ministry of Health and the animal care committee of Istituto Italiano di Tecnologia (IIT).

Larval zebrafish: All protocols were approved by the animal care committee of Université Laval (CPAUL protocol #2022-1012).

Nematode: research on c.elegans does not require ethical approval.

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

Plants

Seed stocks

N/A

Novel plant genotypes

N/A

Authentication

N/A

Magnetic resonance imaging

Experimental design

Design type

resting-state for all datasets

Design specifications

Human sevoflurane: : five scanning sessions: awake, 2 vol%, 3 vol% burst-suppression, and recovery. 350 volumes acquired for each scan.

Macaque multi-anaesthesia: For the anaesthesia dataset, a total of 157 functional magnetic imaging runs were acquired (Uhrig et al., 2018): Awake, 31 runs (monkey A, 4 runs; monkey J, 18 runs; monkey K, 9 runs), Ketamine, 25 runs (monkey K, 8 runs; monkey Ki, 7 runs; monkey R, 10 runs), Light Propofol, 25 runs (monkey J, 2 runs; monkey K, 10 runs; monkey R, 12 runs), Deep Propofol, 31 runs (monkey J, 9 runs; monkey K, 10 runs; monkey R, 12 runs), Light Sevoflurane, 25 runs (monkey J, 5 runs; monkey Ki, 10 runs; monkey R, 10 runs), Deep Sevoflurane anaesthesia, 20 runs (monkey J, 2 runs; monkey Ki, 8 runs; monkey R, 11 runs). For details, check the supplementary tables for (Barttfeld et al., 2015; Uhrig et al., 2018; Signorelli et al., 2021) (<http://links.ww.com/ALN/B756>).

Macaque DBS: For the DBS dataset, a total of 199 Resting State functional MRI runs were acquired: Awake 47 runs (monkey B: 18 runs; monkey J: 13 runs; monkey Y: 16 runs), anaesthesia (DBS-off) 38 runs (monkey N: 16 runs; monkey T: 22 runs), low amplitude centro-median thalamic DBS 36 runs (monkey N: 18 runs; monkey T: 18 runs), low amplitude ventro-lateral thalamic DBS 20 runs (monkey T), high amplitude centro-median thalamic DBS 38 runs (monkey N: 17 runs; monkey T: 21 runs), and high amplitude ventro-lateral thalamic DBS 20 runs (monkey T: 20 runs).

Marmoset: Functional imaging was performed 12 times per animal, per condition. After awake data were firstly collected, and sedate/anesthetic data were done in a random order for sedate/anesthetic condition with an interval of 1 month between each examination in each individual. scan time = 310s.

Mouse: Mice under halothane anesthesia (n = 19) were scanned for a total of 1600 time points, total acquisition time of 32 minutes. Awake and medetomidine-isoflurane rsfMRI scans were acquired for a total time of 32 minutes.

Behavioral performance measures

Loss of behavioural responsiveness was used to determine depth of anaesthesia. Sevoflurane dataset: loss of consciousness was judged by the loss of responsiveness (LOR) to the repeatedly spoken command "squeeze my hand" two consecutive times.

For the macaque datasets, We used a preclinical behavioural scale adapted from Uhrig et al⁶⁶ to assess the arousal levels of the monkeys. This scale, based on the Human Observers Assessment of Alertness and Sedation Scale¹¹³ and previously utilised in non-human primate (NHP) research¹¹⁴, was used consistently across all experimental conditions, in both datasets.

The assessment encompassed six criteria as follows:

- exploration of the surrounding world, from 0 to 2:
 0 = total absence,
 1 = small search of external clue,
 2 = total investigation of the environment (such as head orientation to a sound);
 - spontaneous movements, from 0 to 2:
 0 = total absence,
 1 = small torso and/or limb movement,
 2 = large torso and/or limb movement
 - shaking / prodding, from 0 to 2:
 0 = total absence,
 1 = small body movement,
 2 = large body movement;
 - toe pinch, from 0 to 2:
 0 = total absence,
 1 = small reflex (weak body movement or eye blinking or cardiac rate change),
 2 = clear reaction (strong body movement and eye blinking or eye opening and cardiac rate change);
 - eyes opening, from 0 to 2:
 0 = total absence,
 1 = small blinks or eye movements,
 2 = full eye opening;
 - corneal reflex, from 0 to 1:
 0 = absent,
 1 = present.

Acquisition

Imaging type(s)

Functional and anatomical for all datasets

Field strength

3T for human; 9.4 T for marmoset; 7.0 for mouse; 3T for macaque.

Sequence & imaging parameters

Human sevoflurane: Data acquisition was carried out on a 3-Tesla magnetic resonance imaging scanner (Achieva Quasar Dual 3.0T 16CH, The Netherlands) with an eight-channel, phased-array head coil. The data were collected using a gradient echo planar imaging sequence (echo time = 30 ms, repetition time (TR) = 1.838 s, flip angle = 75°, field of view = 220 × 220 mm², matrix = 72 × 72, 32 slices, slice thickness = 3 mm, and 1 mm interslice gap; 700-s acquisition time, resulting in 350 functional volumes). The anatomical scan was acquired before the functional scan using a T1-weighted MPRAGE sequence with 240 × 240 × 170 voxels (1×1×1 mm voxel size) covering the whole brain.

Macaque: For the awake condition, monkeys were implanted with a magnetic resonance compatible head post and trained to sit in the sphinx position in a primate chair (Uhrig, Dehaene and Jarraya, 2014)). For the awake scanning sessions, monkeys sat inside the dark magnetic resonance imaging scanner without any task and the eye position was monitored at 120 Hz (Iscan Inc., USA). The eye-tracking was performed to make sure that the monkeys were awake during the whole scanning session and not sleeping. The eye movements were not regressed out from rfMRI data. For the anesthesia sessions, animals were positioned in a sphinx position, mechanically ventilated, and their physiologic parameters were monitored. No eye-tracking was performed in anesthetic conditions. For the anesthesia dataset, before each scanning session, a contrast agent, monocrystalline iron oxide nanoparticle (Feraheme, AMAG Pharmaceuticals, USA; 10 mg/kg, intravenous), was injected into the monkey's saphenous vein (Vanduffel et al., 2001). Monkeys were scanned at rest on a 3-Tesla horizontal scanner (Siemens Tim Trio, Germany) with a single transmit-receive surface coil customized to monkeys. Each functional scan consisted of gradient-echo planar whole-brain images (repetition time = 2,400 ms; echo time = 20 ms; 1.5-mm³ voxel size; 500 brain volumes per run).

For the DBS dataset, monkeys were scanned at rest on a 3-Tesla horizontal scanner (Siemens, Prisma Fit, Erlanger Germany) with a customized eight-channel phased- array surface coil (KU Leuven, Belgium). The parameters of the functional MRI sequences were: echo planar imaging (EPI), TR = 1250 ms, echo time (TE) = 14.20 ms, 1.25-mm isotropic voxel size and 500 brain volumes per run.

Marmoset: An ultra-high field MRI system with a static magnetic field strength of 9.4 T (Bruker BioSpin, Ettlingen, Germany), a custom-made 8-channel receiver coil for the marmoset head (Takashima Seisakusho Co., Ltd, Tokyo, Japan), and a 154 mm inner diameter transmitter coil (Bruker BioSpin, Ettlingen, Germany) were used to collect structural and functional data. Structural data and T2-weighted images were imaged using rapid acquisition with relaxation enhancement (RARE) sequence with the following conditions and parameters: time repetition (TR)=4331 ms, time echo (TE) = 15.0 ms, FOV = 42.0 × 28.0 × 36.0 mm, matrix size = 120 × 80 voxels, resolution = 0.35 × 0.35 mm, slice thickness = 0.7 mm, number of slices = 52, scan time = 1 min and 26 s, RARE factor = 4. Functional images were captured using a gradient recalled echo-planar imaging (EPI) sequence with the following conditions and parameters: TR = 2,000 ms, TE = 16.0 mm, FOV = 42.0 × 28.0 × 36.0,mm matrix size = 60 × 40 voxels, resolution = 0.7 × 0.7 mm, slice thickness = 0.7 mm, number of slices = 52, repetition = 155, scan time = 310s.

Mouse: All scans were acquired at the IIT laboratory in Rovereto (Italy) on a 7.0 Tesla MRI scanner (Bruker Biospin, Ettlingen) with a BGA-9 gradient set, a 72 mm birdcage transmit coil, and a four-channel (awake, halothane) or three-channel (medetomidine-isoflurane) solenoid receive coil. Awake and medetomidine-isoflurane rsfMRI scans were acquired using a single-shot echo planar imaging (EPI) sequence with the following parameters: TR/TE=1000/15 ms, flip angle=60 degrees, matrix=100 × 100, FOV=2.3 × 2.3 cm, 18 coronal slices (voxel-size 230 × 230 × 600 mm), slice thickness=600 mm and 1920 time points, for a total time of 32 minutes. Mice under halothane anesthesia (n = 19) were scanned with a TR/TE=1200/15ms, flip angle=60 degrees,

matrix=100 x 100, 24 coronal slices (voxel-size 200 x 200 x 500 mm), for a total of 1600 time points, total acquisition time of 32 minutes.

Area of acquisition

Whole brain for all datasets.

Diffusion MRI



Used



Not used

Parameters

Human: The dMRI data were from the HCP dataset. The spatial resolution was 1.25 mm isotropic. TR=5500ms, TE=89.50ms. The b-values were 1000, 2000, and 3000 s/mm². The total number of diffusion sampling directions was 90, 90, and 90 for each of the shells in addition to 6 b0 images.

Preprocessing

Preprocessing software

Human: Preprocessing of the functional MRI data for both datasets followed the same standard workflow as in our previous studies, and was implemented in the CONN toolbox (<http://www.nitrc.org/projects/conn>), version 17f [81].

Macaque: Images were preprocessed using Pypreclin (Python preclinical pipeline) (Tasserie et al., Neuroimage 2020).

Marmoset: SPM (Wellcome Trust Center for Neuroimaging, London, UK).

Mouse: AFNI, FSL, ANTs

Normalization

Human: Direct normalisation to MNI space (nonlinear) using the segmented grey matter image from each volunteer's high-resolution T1-weighted image, together with an a priori grey matter template.

Macaque: Functional images were reoriented, realigned, and rigidly coregistered to the anatomical template of the monkey Montreal Neurologic Institute (Montreal, Canada) space with the use of Python programming language and Oxford Centre Functional Magnetic Resonance Imaging of the Brain Software Library software (United Kingdom, <http://www.fmrib.ox.ac.uk/fsl/>; accessed February 4, 2018) (Uhrig, Dehaene and Jarraya, 2014)).

Mouse: spatially registered (ANTs registration suite) to an in-house mouse brain template with a spatial resolution of 0.23 x 0.23 x 0.6mm³.

Marmoset: The voxels were spatially standardized by normalization, which aligns the voxels to the standard brain image to correct for structural differences between individuals.. functional data were parcellated into 70 regions in the cerebral cortex, corresponding to regions of the marmoset MBM atlas

Normalization template

Human: Schaefer-100 parcellation in MNI-152 volumetric template, 2x2x2mm isotropic resolution.

Macaque: Data were parcellated according to the Regional Map parcellation (Kötter and Wanke, 2005). This parcellation comprises 82 cortical ROIs (41 per hemisphere; Supplementary Table 4).

Marmoset: functional data were parcellated into 70 regions in the cerebral cortex, corresponding to regions of the marmoset MBM atlas

Mouse: data were parcellated into 72 cortical ymmetric regions from the Allen Mouse Brain Atlas (CCFv3).

Noise and artifact removal

Human: Denoising followed the anatomical CompCor (aCompCor) method of removing cardiac and motion artifacts, by regressing out of each individual's functional data the first 5 principal components corresponding to white matter signal, and the first 5 components corresponding to cerebrospinal fluid signal, as well as six subject-specific realignment parameters (three translations and three rotations) and their first- order temporal derivatives, and nuisance regressors identified by the software ART 82. The subject-specific denoised BOLD signal time-series were linearly detrended and band-pass filtered between 0.008 and 0.09 Hz to eliminate both low-frequency drift effects and high-frequency noise.

Macaque:

Voxel time series were filtered with low-pass (0.05-Hz cutoff) and high-pass (0.0025-Hz cutoff) filters and a zero-phase fast-Fourier notch filter (0.03 Hz) to remove an artifactual pure frequency present in all the data (Barttfeld et al., 2015; Uhrig et al., 2018). Furthermore, an extra quality control (QC) cleaning procedure was performed to ensure the quality of the data after time-series extraction⁷². This quality control procedure is based on trial-by-trial visual inspection by an expert neuroimager (C.M.S.), and it is the same as was previously implemented in Signorelli et al⁷². Its adoption ensures that we employ consistent criteria across our two datasets, by adopting the more stringent of the two. We plotted the time series of each region, as well as the static functional connectivity matrix (FC), the dynamic connectivity (dFC) and a Fourier analysis to detect unconventional spikes of activity. For each dataset, visual inspection was first used to become familiar with the characteristics of the entire dataset: how the amplitude spectrum, timeseries, FC and dynamic FC look. Subsequently, each trial was inspected again with particular focus on two main types of potential artefacts. The first one may correspond to issues with the acquisition and is given by stereotyped sinusoidal oscillatory patterns without variation. The second one may correspond to a head or other movement not corrected properly by our preprocessing procedure. This last artefact can be sometimes recognized by bursts or peaks of activity. Sinusoidal activity generates artificially high functional correlation and peak of frequencies in the Amplitude spectrum plot. Uncorrected movements generate peaks of activity with high functional correlation and sections of high functional correlations in the dynamical FC matrix. If we observed any of these anomalies we rejected the trial, opting to adopt a conservative policy. See Figures S17-S19 for examples of artifact-free and rejected trials.

As a result, for the Multi-Anaesthesia data set a total of 119 runs are analysed in subsequent sections (the same as used in Signorelli et al. 72): awake state 24 runs, ketamine anaesthesia 22 runs, light propofol anaesthesia 21 runs, deep propofol

anaesthesia 23 runs, light sevoflurane anaesthesia 18 runs, deep sevoflurane anaesthesia 11 runs. For the DBS data set, a total of 156 runs are analysed in subsequent sections: awake state 36 runs, Off condition (propofol anaesthesia without stimulation) 28 runs, low-amplitude CT stimulation 31 runs, low-amplitude VT stimulation 18 runs, high-amplitude CT stimulation 25 runs, high-amplitude VT stimulation 18 runs.

As an alternative, robustness analyses were performed after using the aCompCor method for denoising instead of GSR.

Marmoset: Estimation and correction of geometric distortions induced by magnetic susceptibility were performed with the top-up tool of the FMRIB Software Library (FSL) software (FMRIB, Oxford, UK) because all cross-sections were imaged with a single excitation in EPI. Slice timing correction was performed to correct for signal acquisition timing discrepancies in each section. Realignment was applied to compensate for head movements caused by body movements. The deviations in 6 directions were obtained: x (left/right), y (front/back), z (up/down), pitch (rotational direction of nodding and looking up), roll (rotational direction of moving the ear closer to the shoulder), and yaw (rotational direction of looking left/right). For each measurement time point (TR), the deviation from the reference time point, and the first functional brain image, was determined; and the image was moved and rotated by the rigid body model based on this deviation. The method of finding the parameters of the linear transformation was used to minimize the difference between the first functional brain image and the affine transformation of the series of functional brain images to be corrected, by calculating convergence using the method of least squares.

After correcting the spatial scale error between the structural and functional images with co-registration, segmentation was performed to provide information on the tissue to which each voxel belongs in terms of brain tissue classification. The voxels were spatially standardized

by normalization, which aligns the voxels to the standard brain image to correct for structural differences between individuals. Smoothing was applied to suppress excessive voxel value fluctuations within individuals and apply normal probability field theory. Functional data were

smoothed using spatial convolution with a Gaussian kernel of 2 voxels (7 mm). Then, physiological noise was denoised using ordinary least squares regression with cerebrospinal fluid pulsation, heart rate, and respiratory artifacts as regressors. Temporal band pass filtering was performed by frequency filtering (0.01–0.1 Hz) using the fMRI denoising pipeline of CONN.

Mouse: the first 2 minutes of the time series were removed to account for thermal gradient equilibration. RsfMRI timeseries were then time despiked (3dDespike, AFNI), motion corrected (MCFLIRT, FSL), skull stripped (FAST, FSL) and spatially registered (ANTs registration suite) to an in-house mouse brain template with a spatial resolution of 0.23 x 0.23 x 0.6mm³. Denoising involved the regression of 25 nuisance parameters. These were: average cerebral spinal fluid signal plus 24 motion parameters determined from the 3 translation and rotation parameters estimated during motion correction, their temporal derivatives and corresponding squared regressors. No global signal regression was employed. In-scanner head motion was quantified via calculations of frame-wise displacement (FD). Average FD levels in awake conditions were comparable to those obtained in anesthetized animals (halothane) under artificial ventilation ($p = 0.13$, Student t test) 29. To rule out a contribution of residual head-motion, we further introduced frame-wise fMRI scrubbing ($FD > 0.075$ mm). The resulting time series were band-pass filtered (0.01-0.1 Hz band) and then spatially smoothed with a Gaussian kernel of 0.5 mm full width at half maximum. Finally, the timeseries were trimmed to ensure that the same number of timepoints were included for all animals, resulting in 1414 volumes per animal.

As a robustness check, all fMRI datasets were bandpass filtered in the same frequency band that is included in all their species-specific preprocessing: 0.01-0.05 Hz.

Volume censoring

Human: the artifact rejection tool (ART), implemented in the CONN toolbox, was used to identify and regress out outlying volumes, as part of the CompCor denoising procedure described above. The default CONN settings of 5 global signal z-values and 0.9mm were used.

Mouse: To rule out a contribution of residual head-motion, we further introduced frame-wise fMRI scrubbing ($FD > 0.075$ mm).

Statistical modeling & inference

Model type and settings

We used effect sizes (Hedge's g) to quantify the change in each feature at each region between awake and anaesthesia conditions.

Effect(s) tested

We tested whether any features exhibit consistent changes in the same direction across datasets. We also tested whether regional changes are associated with regional gene expression.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☒ Both

Anatomical location(s)

Schaefer-100 cortical atlas (human); Allen cortical atlas (mouse); Regional Mapping cortical atlas (macaque); MBM cortical atlas (marmoset)

Statistic type for inference

Whole-brain analysis: data were averaged across ROIs prior to analysis. Regional analysis: we used partial least squares analysis against an autocorrelation-preserving null distribution.

(See [Eklund et al. 2016](#))

Correction

'Moran spectra randomisation was used to generate spatial autocorrelation preserving null maps for each species. For the whole-brain analysis, we excluded any features that did not display consistent changes in the same direction in each contrast. For multiple comparisons we used the False Discovery Rate (FDR) correction.

Models & analysis

n/a	Involvement in the study
☐	☒ Functional and/or effective connectivity
☒	☐ Graph analysis
☐	☒ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Whole-brain modelling was developed as detailed in the Methods. We also computed FC as the correlation between time-series, and dynamical profile similarity as the correlation between timeseries' feature profiles.

Multivariate modeling and predictive analysis

We used partial least squares (PLS) analysis against an autocorrelation-preserving null distribution to test the spatial association between regional change in dynamical features and gene expression maps.