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Graph models of brain state in deep anaesthesia reveal sink state dynamics of reduced spatiotemporal complexity

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ABSTRACT

Anaesthetisia is an important surgical and explorative tool in the study of consciousness. Much work has been done to connect the deeply anaesthetised condition with decreased complexity. However, anaesthesia-induced unconsciousness is also a dynamic condition in which functional activity and complexity may fluctuate, being perturbed by internal or external (e.g. noxious) stimuli. We use fMRI data from a cohort undergoing deep propofol anaesthesia to investigate resting state dynamics using dynamic brain state models and spatiotemporal network analysis.We focus our analysis on group-level dynamics of brain state temporal complexity, functional activity, connectivity and spatiotemporal modularization in deep anaesthesia and wakefulness. We find that in contrast to dynamics in the wakeful condition, anaesthesia dynamics are dominated by a handful of sink states that act as low-complexity attractors to which subjects repeatedly return. On a subject-level, our analysis provides tentative evidence that these low complexity attractor states appear to depend on subject-specific age and anaesthesia

susceptibility factors. Finally, our spatiotemporal analysis, including a novel spatiotemporal clustering of graphs representing hidden Markov models, suggests that dynamic functional organisation in anaesthesia can be characterised by mostly unchanging, isolated regional subnetworks that share some similarities with the brain's underlying structural connectivity, as determined from normative tractography data.

INTRODUCTION

General anaesthesia is an invaluable surgical tool that reduces the overall risk of complications and shields patients from immediate pain while being generally safe and effective Urban and Bleckwenn (2002). However, anaesthetic susceptibility and risks are patient specific and may include impaired respiration and heart function Nunn (1990), delayed recovery of consciousness and post-operative delirium in over-anaesthesia Bryson and Wyand (2006); Fritz et al. (2016). Over-anaesthetisation has been associated with cognitive decline in older patients who are also at higher risk of post-operative delirium Sevenius Nilsen, Juel, and Marshall (2019); Wu, Zhao, Weng, and Ma (2019). Conversely, under-anaesthetisation may risk psychological trauma through post-surgical recollection of pain and helplessness, especially in combination with commonly administered muscle relaxants Aceto et al. (2013); Schwender et al. (1998); Urban and Bleckwenn (2002). These factors motivate the importance of understanding how the brain dynamically maintains unconsciousness under sustained anaesthesia when subjected to passive, or, in the case of surgery, powerful forms of external stimulation Bonhomme et al. (2019).

More generally, understanding dynamic functional changes in neural configuration, or *brain state*, has been key to describing the processes involved in the transitions between and maintenance of different conscious and unconsciousness conditions He, Das, Hotan, and Purdon (2023); Mediano et al. (2023); C. Zhang et al. (2024). A popular method for determination of brain state space models has been *Hidden Markov Models* **(HMMs)**, with applications to sleep Stevner et al. (2019); Yang et al. (2024), to Disorders of Consciousness (DOCs) Bai et al. (2021), and to anaesthesia Liu et al. (2022). In HMMs, multiple signals of brain activity are generally modelled as arising from discrete hidden states; see Supplementary Section S.1 for a brief introduction. These states provide a snapshot of functional activity and connectivity that subjects transition between, probabilistically and dynamically, to support the maintenance of a condition such as aneasthesia-induced unconsciousness or resting wakefulness Vidaurre

et al. (2016). HMMs are appealing in part because of this rich spatiotemporal representations of dynamics that depend on underlying persistent and stable conditions such as in resting state Leroux (1992). Stability dependence differentiates HMMs from more sophisticated models of brain state which may be applied to non-stationary behaviours, usually at the cost of the richness of temporal dynamics in the model Ito, Yang, Laurent, Schultz, and Cole (2022); Parks et al. (2024); Rukat, Baker, Quinn, and Woolrich (2016). We focus our study on HMM analysis of resting brain state dynamics in both wakefulness and anaesthesia-induced unconsciousness in order to better understand the dynamic properties that support its stability and maintenance.

HMMs and other state-space models have been used to demonstrate a general decrease in temporal Demertzi et al. (2019); Luppi et al. (2024); Stevner et al. (2019) and signal-based complexity measures Liang et al. (2024); Ruffini (2017) during unconsciousness including under most anaesthetics, with the possible exception of ketamine Li and Mashour (2019). Of these measures, Kolmogorov complexity is thought to be a possible neural correlate of consciousness and is notable for its strong links to other proposed neural correlates such as Integrated Information and the Global Workspace Fan, Yeh, Chen, Shieh, et al. (2011); Marshall, Gomez-Ramirez, and Tononi (2016); Ruffini (2017), though its accurate quantification in practice in particular in recordings of brain activity remains computationally and mathematically intractable Sevenius Nilsen et al. (2019). Using state-space models however, the Kolmogorov complexity can be approximated by the *entropy* or *information rate* Galatolo, Hoyrup, and Rojas (2010). This approximation has been used to demonstrate a general decrease in the dynamic reachability or realisability of states during various forms of unconsciousness when compared to wakefulnessBarttfeld et al. (2015); Castro et al. (2024); Demertzi et al. (2019); Li, Vlisides, and Mashour (2022); Mediano et al. (2023). We corroborate these findings by training HMMs which are specific to each condition, wakefulness and deep anaesthesia, and propose that certain condition-specific states may act as low-complexity attractors or *sinks* that are disproportionately responsible for this reduction in complexity.

Brain states can be considered as graphs connecting brain regions, with edges depending on the functional connectivity between these regions Vidaurre et al. (2016). This representation has helped to establish the minimal resting state network features which persist to support unconsciousness dynamics Barttfeld et al. (2015); Heine et al. (2012); Luppi et al. (2019). However, consideration of states in

isolation fails to incorporate the temporal dependencies in the activity of these subnetworks. Therefore, in analogy to the static spatially-defined resting state networks Heine et al. (2012). Here we provide a spatiotemporal framework for brain state analysis to understand the spatiotemporal functional modularisation of activity in both conditions, wakefulness and anaesthesia. To this purpose we represent a fitted HMM on brain states as a graph, with brain states as nodes, and the transition probabilities between brain states taken as edge weights between nodes; the resulting graph on graphs is a **Hidden Markov Graph Model (HMGM)** as in Wilsenach, Warnaby, Deane, and Reinert (2022). This particular graph on graphs structure allows us to develop new methods to detect modular spatiotemporal subnetworks or **communities**, incorporating both functional and temporal information. In particular, we detect spatiotemporal functional stratification which occurs in anaesthesia-induced unconsciousness but not wakefulness. We also use these methods to corroborate and expand upon previous work on the close links between structure and unconscious brain state connectivity Barttfeld et al. (2015); López-González et al. (2021); Luppi et al. (2023).

Our results suggest new avenues for exploration in the study of anaesthesia, in particular how age and anaesthesia susceptibility may modulate patient trajectories both into and out of anaesthesia-induced unconsciousness. Moreover, we demonstrate that unconsciousness dynamics may involve effective restrictions on the space of possible brain states through dominant *sink* states. We find indications of the dissolution of important **functional modules** and the loss of the brain's capacity for integrating multiple streams of information under **propofol**-induced deep anaesthesia.

MATERIALS AND METHODS

Fig. 1 shows an overview of the experimental set-up (Panel A) and the processing of the blood oxygen level-dependent (**BOLD**) signals, followed by training of the HMM (Panel B); Panel C shows the construction of the HMGM from the trained HMM, and how the brain **Regions of Interest (ROIs)** and states can be decomposed in terms of both their functional module or *community* memberships. This framework builds upon previous work first introduced in Wilsenach (2022) and Wilsenach et al. (2022).

Data Acquisition and fMRI Pre-processing

BOLD fMRI data was recorded over the course of a four phase experiment in which 16 initial subjects received a phase-specific dose of the GABA-ergic general anaesthetic propofol Mhuircheartaigh, Warnaby, Rogers, Jbabdi, and Tracey (2013). In the first phase, baseline wakeful activity was recorded for 10 minutes. Subjects were asked to remain still with eyes closed. In the second phase, propofol was gradually infused to a maximum **Effective Concentration (ESC)** of $4\mu g/ml$, which is well above the minimal dose previously found to be effective in inducing loss of consciousness in subjects and is sufficient for inducing sleep-like slow waves Forrest, Tooley, Saunders, and Prys-Roberts (1994). In phase three the maximum ESC was maintained for 10 minutes, leading to a stable deep anaesthesia state. In phase four, the propofol dose was gradually decreased until subjects regained full responsiveness. The experimental overview is shown in Fig. 1A; Supplementary Section S.2 contains greater detail.

The frequency of the fMRI data was one full head volume every three seconds at a 3D voxel resolution of 2mm^3. All brain volumes were head extracted, artefact corrected and registered to a single 1mm^3, subject-specific high-resolution volume-scan in FSL Jenkinson, Beckmann, Behrens, Woolrich, and Smith (2012). The resulting volumes were mapped into the MNI152 MRI standard space. To obtain a computationally tractable anatomical partition with cortical-subcortical coverage, we used the Harvard-Oxford (HO) cortical and sub-cortical atlases with $D = 63$ ROIs developed in Desikan et al. (2006) and made into a combined atlas in Wilsenach et al. (2022).

In this analysis we focus on the 10 minutes pre-induction (phase 1) and the 10 minutes post-induction recordings (phase 3), when subjects are held at the maximum dosage. The high dosage results in a condition of deep anaesthesia-induced unconsciousness and non-responsiveness to conventional rousing stimuli. Subjects were excluded based-on whether they exhibited EEG signatures that have been linked with poor tolerance for high anaesthesia dosages and post-operative delirium (see Supplementary Section S.3) Fritz et al. (2016); Z. Zhang et al. (2019). After exclusion the total number of complete recordings for subjects in both conditions was $N = 13$.

In order to study the relationship of the brain states to the brain's structural network we accessed a large structural dataset combining data from 169 normative adult **tractographies** based on multi-shell Diffusion Tensor Imaging re-registered to MNI152 standard space. The tractographies were constructed using the Gibbs tracking algorithm Reisert et al. (2011), which were then co-registered in standard space and combined as outlined in Horn and Blankenburg (2016).

Model Training and State Selection

HMM model selection and training for both anaesthesia and wakefulness was carried out as detailed in Wilsenach et al. (2022), using the Variational Bayes HMM training procedure in Vidaurre et al. (2016). This procedure is shown in Fig. 1B for wakefulness (and is carried out analogously in anaesthesia). As the data are high-dimensional, some compression is needed for computational efficiency. First the high resolution voxel-wise data is reduced by obtaining the mean BOLD signal across each ROI over the recording. For each ROI, the recordings for all subjects are then concatenated. To further reduce computational and model complexity in the HMM fitting process, a Principal Component Analysis was carried out to find computationally efficient combinations of ROI series, with the reduced dimension selected by parallel analysis (see Supplementary Section S.4). The reduced data was then used to train an HMM. As the concatenated data obstructs the subject separation, subject-specific time series are obtained for the ROI combinations from the PCA to infer state probabilities at each time point across each subject recording.

The observations of the HMM are thus not ROIs themselves but instead combinations of ROIs. Following HMM training, the number of initial HMM states was selected by maximum entropy. The maximum entropy method has been shown to broadly agree with other methods of model size selection such as cross-validated maximum likelihood Wilsenach (2022), while often resulting in larger models that allow for more complex possible dynamics Wilsenach et al. (2022). As this selection may result in states that are not robustly expressed, HMM states were removed if they appeared in less than 20% of subjects, and transition probabilities were re-standardised so that each row sums to one (see Supplementary Fig. 3). The (fitted) probability of each HMM state occurrence at each time point is then calculated, which determines the *Fractional Occupancy (FO)* of each state. This is the expected fraction of time spent in each state over the length of a subject recording. The resulting model for each condition has a total of K_{wake} or K_{anaes} states respectively and D ROIs.

Graph Models of Dynamic Function and Structure

HMGMs are spatiotemporal graph models derived from the respective HMMs. More formally, an HMGM is a **multiplex** graph with each layer representing a brain state with the same set of ROIs as nodes, having edges determined by the functional connectivity between the ROIs, and in which the

interlayer edges are the probabilities of transition between brain states. This structure can be seen in Fig. 1C. HMGMs were derived from the HMMs for anaesthesia and wakefulness respectively.

A simpler, single-layer structural graph model was fit to the tractography data using DSI-studio's structural connectome tool Yeh, Verstynen, Wang, Fernández-Miranda, and Tseng (2013) and the HO atlas with default parameters and median streamline length normalisation, producing an undirected, weighted graph model proxy of subject structural connectivity Yeh et al. (2018).

Consensus Community Detection

One of the primary strengths of graph-based models is that they allow for the decomposition of the graph into functionally related modules or *communities*. Modularity-based community detection is a collection of methods for finding optimal groupings of nodes (brain regions) in a graph so that members of the group are preferentially connected to one another Girvan and Newman (2002); Newman (2006) in a way which numerically aims to maximise the *modularity* of the partition.

In order to determine the underlying *structural* modular organisation of the structural graph model we applied a robust version of the modularity optimisation method based on Lancichinetti and Fortunato (2012) using multiple parameters and initialisations to determine structural communities (see Supplementary Section S.5 for further details).

Beyond Static Communities...

Spatiotemporal communities can be interpreted as groups of brain regions that tend to coordinate not only in space but also over time. A generalised form of modularity-based community detection was used to partition the nodes (ROIs) of the HMGM into functionally related sets that coordinate activity across space and time into dynamic functional modules (node colour in Fig. 1C). We determine the spatiotemporal community structure of each of the HMGM models using a new modification to the modularity that combines spatial and temporal HMM properties. The modified score takes into account both functional connectivity and temporal probabilities of transition between states Mucha, Richardson, Macon, Porter, and Onnela (2010); Sen, Chu, and Parhi (2019). Using this score, communities can be interpreted as representing functional modules which can reorganise across time in order to react to external and internal stimuli. In all cases the modularity is optimised using the generalised Louvain

algorithm Mucha et al. (2010), with the same robust aggregation over multiple parameters as in Lancichinetti and Fortunato (2012); see Supplementary Section S.6 for more detail on these methods and justification of the range of parameters. Layers with similar community composition are also clustered hierarchically; in Fig. 1C members of the same cluster are given the same colour.

Sink States, Switching and Information Rates

HMMs are probabilistic state space models in which state transitions occur probabilistically depending only on the previous state in the sequence. In a sufficiently regular Markov model, the stationary probability of a state is the long-term probability of occupying this state over a sufficiently long time (see Supplementary Section S.7). Here, we use the stationary probability to define a centrality measure over states. In analogy to PageRank centrality, we term the stationary probability of each state its *sink centrality*. As our interest lies in those states which cumulatively account for the majority of the expected time spent, in each condition, to simplify the analysis, special focus was then put on "strong" sink states that disproportionately account for activity under each conditions. Here we use as cut-off for a sink state to be considered 'strong' that it has a sink centrality of at least 0.05. Other threshold choices are possible; the threshold is chosen purely to summarise the model behaviour, not for training the model and is explored further in Results.

Fig. 2 provides a sketch of how HMM and HMGM analysis can provide important axes along which to examine brain state activity by contrasting model behaviours. The switching rate, Fig. 2A, is a well established measure of the temporal complexity of brain state models Stevner et al. (2019); Vidaurre et al. (2016). It is the frequency at which state change occurs in the state trajectory that best fits the data (see Supplementary Section S.8) Brin and Page (1998). Fig. 2A shows four different four-state Markov models, where node size is proportional to the sink centrality. Edges are shaded from high (dark) to low (light) probability. A plausible state sequence is generated from each model from which the state switching events are determined and the switching rate (in Hz) is calculated. The FO is also shown, which is based on the expected time spent in each state, which is inferred directly from the model (see Supplementary Section S.1). The FO can be viewed as the distribution describing the probability of observing a subject in a given state during an entire recording.

The information (or entropy) rate measures the expected information gained by sampling from a state space model over a sufficiently long state time Cover (1999). It provides an estimate of the temporal information capacity or complexity of the underlying process (see Supplementary Section S.8), differentiating it from the switching rate, which does not account for the diversity of probabilistically realisable states. As a result, a model can have high switching rate while having relatively low complexity (Fig. 2A). Brain state diversity was also measured directly using the entropy of the FO in order to consider subject-specific (rather than model or group-level) state diversity.

Comparing States by Functional and Community Activity

HMM state functional connectivity and activity provide important modes to compare conditions of consciousness; brain activity may range from excitable (high absolute mean functional activity) to quiescent. We use paired distance correlation between states to compare them across both functional mean activity as well as functional connectivity, Fig. 2B. The states themselves encode complex connectivity relationships; these high dimensional relationships are often non-linear and in contrast to Pearson correlation, distance correlation takes into account such non-linear dependencies Geerligs, Henson, et al. (2016). Fig. 2B shows a range from dark blue (quiescent) to yellow (excitable) brain states. In addition, we apply the *signed distance correlation* from Pardo-Diaz et al. (2021) (with the sign being the sign of the standard Pearson correlation) to provide additional information on state dependencies.

High modularity and integration are both necessary properties for the brain to perform complex tasks which require efficient processing of information from multiple sources. High modularity indicates a high capacity of the state to independently process multiple input streams, while high integration allows for fast, local information sharing between brain areas Meunier, Lambiotte, and Bullmore (2010); Sarasso et al. (2021); Zamora-López, Zhou, and Kurths (2010). The bottom of Fig. 2B shows how these two factors, while not perfectly correlated, are related.

The level of information integration within each state was assessed using the average local clustering coefficient of the state functional connectivity; the local clustering coefficient is an established measure of functional integration in resting state fMRI Luppi et al. (2019); Medaglia (2017). State modules here correspond to communities which were estimated using modularity maximisation Girvan and Newman (2002) (see Supplementary Section S.5 and S.6).

Fig. 2C sketches one of the primary outputs of our spatiotemporal community analysis. The fractional membership is the long run proportion of time that each brain region is expected to spend in a given community (see Supplementary Section S.9 for further details). To characterise these dynamic communities, we organise states and regions by performing hierarchical clustering using Ward's algorithm Ward Jr (1963). This process is also used to uncover common spatiotemporal patterns of functional organisation across states and ROIs.

Comparing Functional to Structural Connectivity

Patterns of functional organisation are dependent upon an underlying structural connectome Barttfeld et al. (2015); Demertzi et al. (2019); Luppi et al. (2023); Tan et al. (2019). In order to test whether deep anaesthesia or wakeful state functional connectivity is more related to structural connectivity, we compared the degree and level of integration of each state across conditions to the structural connectome using distance correlation. We also used the Adjusted Mutual Information (AMI) to quantify the similarity in community composition between structural and dynamic state models. The AMI is a measure of agreement between two partitions of brain regions that is more robust to differences in partition size than other measures such as the Adjusted Rand Index Romano, Vinh, Bailey, and Verspoor (2016) (see Supplementary Section S.11 and S.12).

RESULTS

Selection of Models

We trained and analysed two dynamic models using data from each condition. The number of states for both wakeful and deep anaesthesia models was selected based on the maximum entropy of state occurrence (FO). This resulted in two different models that maximise the entropy, with 33 states for wakefulness, and 19 for anaesthesia, respectively (see Supplementary Fig. 2). We excluded sporadic states that featured in less than 20% of subject trajectories; this low threshold was chosen to allow for some subject-specific expression; see Supplementary Fig. 3 for the percentage of subjects visited in each state. The resulting models had $K_{wake} = 32$ and $K_{anaes} = 18$ states. For validation purposes, we also trained one combined model using both anaesthesia and wakeful data concatenated to produce a single model with the same number of initial states as wakefulness, $K_{comb} = 33$, even after applying the same state exclusion criterion.

Brain State Transition Graphs

Fig. 3 shows the transition probabilities between states as the edges in a directed graph of states (nodes) for both anaesthesia and wakefulness; wakefulness states are prefixed W-, while anaesthesia states are prefixed A-. States are organised by the integration of their functional connectivity (as measured by local clustering coefficient) and the size of states is proportional to their sink centrality. The two graph models show clear separation along the state integration axis ($p \leq 0.001$ for the null hypothesis of the local clustering coefficients of the two models coming from the same distribution, Mann-Whitney U test, two-sided). The two least integrated states are anaesthesia states, A-12 and A-17; these are also the strongest sink states (see Supplementary Fig. 4 for the distribution of sink centralities relative to the strong sink threshold of 0.05), with A-17 being the most dominant at at 0.38 (near to 40% of expected time in any state), well exceeding the threshold.

Fig. 3 shows that most sink states have many high probability in-edges. In particular, A-17 is reachable with relatively high probability from states within its own cluster, and is unlikely to be transitioned to from external states, except A-3 and A-9 which both act as bridges from the other cluster. Similarly, transitions to A-12, the second strongest sink state, generally occur from within its own cluster, but there are a few states in the A-17 dominated cluster that preferentially transition to A-12 acting as bridges between clusters. State A-5 has no strong connection to either cluster and is an outlier in terms of integration.

Wakeful dynamics are more diverse with no dominant sink state and three separate state clusters. Mean activity maps for sink states also show larger ranges (higher excitability) than in anaesthesia across all states ($p = 0.017 \leq 0.05$ for the null hypothesis of activity being equal, measured by absolute mean activity, Mann-Whitney U test, two sided). Overall, the simpler modular structure of the anaesthesia model suggests lower complexity dynamics and indeed the anaesthesia information rate of 0.940 is less than the wakeful information rate of 1.82. Supplementary Fig. 5 shows that when varying the number of states in the model a difference between the two models persists, indicating that the difference in complexity is not simply due to a difference in the number of states but is due to the emergence of dominant states in anaesthesia that affect the reachability of other brain states.

Sink State Dominance and Anaesthesia Quiescence

Fig. 4A and Fig. 4B show the stationary distribution across all subjects as pie charts with wedges representing sink states with sink centrality at least 0.05. Again, we see strong sink state dominance in anaesthesia and a more uniform stationary distribution in wakefulness. Fig. 4C and 4D show the top 50% most extreme regional activity for each sink state in wakefulness and anaesthesia, respectively. All regions shown for A-12 and A-17 have below-mean regional BOLD activity. In general, wakeful states have higher absolute mean activity across regions than in anaesthesia ($p \leq 0.001$, Mann-Whitney U test, two-sided). This also holds for the combined trial validation model (Supplementary Fig. 3) in which anaesthesia trials were dominated by a single state (state 29) with lower than baseline mean absolute functional activity.

Sink States Dominate Across Subjects in Anaesthesia but not Wakefulness

While there is some overlap in FO between subjects, Fig. 5A shows that the two sink states separate subjects into two groups depending on which sink state dominates (see Supplementary Fig. 4 for relative sink centralities across states and conditions). The majority of subjects are dominated by A-17, and the remainder have a relatively high A-12 occupancy. The FO of the two states (A-12 and A-17) have a strong negative Pearson correlation of $\rho = -0.922$ ($p \leq 0.01$, permutation test; see Supplementary Section S.10 for details). Together A-12 and A-17 account for $\geq 50\%$ of the mean FO across all subjects in deep anaesthesia, indicating that a majority of subject time is spent in one of these two states, with the overwhelming majority of time spent in A-17. This is in comparison to wakefulness in which no two states can account for more than 20% of mean FO. While it is not clear why subjects 10 and 4 are primarily dominated by other states, we note that the two subjects are the youngest in the study. In the validation models using either the combined data (including both wakeful and anaesthesia trials in a single model) or an alternative model with $K = 20$ states, anaesthesia trials were also dominated by sink states (states 29 and 20 respectively, see Supplementary Fig. 6 and 7).

Fig. 5B shows boxplots of the state switching dynamics across all subjects with higher switching in wakefulness ($p \leq 0.001$, Wilcoxon Signed-rank test, two sided) and a higher state diversity, as measured by the normalised entropy of FO ($p \leq 0.001$, Wilcoxon Signed-rank test, two sided). Together these results suggest that dynamics under deep anaesthesia are not only simpler but also less dynamic, with a lower fraction of states participating in the dynamics of most subjects, as would be expected for

dynamics with a lower information rate. However, there is also some evidence that subjects are more variable, likely due to the subject-specific anaesthesia depth which varies even when subjects are held at the same ESC, and which depends on subject-specific susceptibility factors Nunes, Alonso, Castro, Amorim, and Mendonça (2007).

Stratification of Functional Connectivity in Anaesthesia

In the wakeful condition, state diversity results in highly diverse spatiotemporal community reorganisation. Consensus clustering, combining functional and temporal relationships, reveal highly distributed dynamics, with each community including diverse and dynamically changing membership (see Fig. 6A). These communities dynamically represent shifts between resting state networks including visual, salience-default mode and sensory networks respectively. The dynamics is visible in Fig. 6B where regional switching between communities is reflected in the mosaic pattern of community associations.

The anaesthesia model (see Fig. 6C and D) reveals strikingly different results, with a greater number of less dynamic communities that are primarily restricted to closely anatomically related ROIs. There is far less change of membership between states in anaesthesia in comparison to wakefulness, resulting in stratified and near static dynamic reorganisation. Even though we see less switching in anaesthesia dynamics, sporadic co-recruitment of regions commonly associated with the so-called Resting State Networks does occur, for example in A-16 (exhibiting Default Mode-like activity in community 3).

Furthermore, the spatiotemporal consensus clustering in anaesthesia suggests that subcortical areas, most notably the thalamus and neighbouring regions (including the caudate), generally thought of as an information bottleneck for sensory inputs reaching the brain Alitto and Usrey (2003); Luppi et al. (2024), are isolated from cortical brain regions in almost all anaesthesia states. This is not seen in wakefulness, in which thalamic regions share and switch membership with multiple cortical regions depending on state, supporting the dynamic role of the thalamus in conscious homeostasis.

Sink State Similarity Across Conditions

Plots of the functional connectome of each of the sink states are shown in Fig. 7A (thresholded to the top 5% strongest connections by magnitude for illustrative purposes), with mean activity maps for each state

shown vertically. The heatmaps represent the pairwise distance correlation (displaying only strong relationships, > 0.5) between states across both conditions. Very few wakeful states share a significant relationship with any wakeful state on the basis of either functional activity (bottom left) or connectivity (top right). Fig. 7B shows that pairwise distance correlation of functional connectivity between wakeful states is significantly higher than in anaesthesia ($p \leq 0.001$, Mann-Whitney U test, two-sided). This difference in state self-similarity holds even when considering distance correlation in signed functional (Pearson) correlation between ROIs ($p \leq 0.001$ Mann-Whitney U test, two-sided). There is evidence for the suggestion that most anaesthesia states resemble neither each other nor are directly related to wakeful states, even when considering possible changes in the sign of functional relationships. A similar but weaker finding holds for functional activity ($p \leq 0.001$ Mann-Whitney U test, two-sided) with mean functional activity distance correlation lower in anaesthesia than in wakefulness, see Fig. 7C. Although anaesthesia states are generally superficially dissimilar, signed distance correlation does suggest that A-17 is at least somewhat positively related to all other anaesthesia states; this relationship between anaesthesia states makes it plausible to observe the perhaps surprising similarity in spatiotemporal community composition seen across anaesthesia states.

Structure-Function Relationships in Wakefulness and Anaesthesia

Fig. 8A shows the results of comparing structural modules, as determined by consensus multi-resolution community analysis (Supplementary Fig. 8 for these modules). Comparing the structural models to the spatiotemporal communities in the HMGM, in the anaesthesia state, spatiotemporal community composition and overall connectivity are moderately consistent with the observed structural modularisation and connectivity, having an average AMI of 0.51, when compared to wakefulness, having an AMI of 0.24 ($p \leq 0.001$, permutation test); we also validated these results using the ARI (see Supplementary Section S.11 and S.12). However, wakefulness was found to be more correlated in terms of the local clustering (integration) and degree centrality statistics ($p \leq 0.001$, Mann-Whitney U, two-sided), even when using conventional Pearson correlation in connectivity and both signed connectivity and the unsigned (absolute) connectivity measure used in our network analysis ($p \leq 0.001$, Mann-Whitney U, two-sided).

Sink State Occupancy Correlates with Age and Susceptibility

Given the overwhelmingly dominant role of the strongest sink state in determining the range of anaesthetic brain state state dynamics, it is important to determine which factors, if any, are most determinative of sink state dominance. Multivariate linear regression was performed to determine which factors most closely predict the time subjects spent (FO) in the most dominant sink state A-17. Increasing age was found to be the single variable most associated with positive increases with A-17 FO ($p = 0.005 \leq 0.01$, t-test, two-sided) when considered alone. However, time at loss of responsiveness (T_{LOBR}) in combination with age was found to be the best performing model of A-17 FO with respect to both the BIC (see Supplementary Table 2) and adjusted R^2 criteria, with significant improvements in goodness of fit over the age-only model ($p = 0.040 \leq 0.05$, Chi-squared test). The model shows that age is a significant predictor ($p = 0.004 \leq 0.01$, t-test, two-sided), while T_{LOBR} is marginally negatively associated with A-17 FO ($p = 0.079$, t-test, two-sided). Supplementary Fig. 9 shows the alternative model which includes time conditioned on age. Surprisingly, grey matter density (see Supplementary Section S.13) did not add any significant model improvement (see Supplementary Tables 3 to 6).

DISCUSSION

In this paper we contrast the dynamics of resting wakefulness and unconsciousness under deep anaesthesia using data from a multi-phase study of subjects undergoing propofol-induced anaesthesia, focusing on analysis of fMRI BOLD activity. In the analysis we apply a combined HMM-based dynamic state space model Vidaurre et al. (2016), as well as a new spatiotemporal community detection approach, in order to determine the dynamic modular reorganisation of brain activity. We provide results corroborating a general decreases in temporal complexity during unconsciousness seen in other investigations Barttfeld et al. (2015); Demertzi et al. (2019); Mediano et al. (2023), and propose that this dynamic may be due to the dominance of low complexity sink states and widespread functional disintegration. We divide these results into three primary findings which we discuss here.

First, regarding the brain state dynamics, we corroborate and expand on existing research showing that unconscious dynamics Mediano et al. (2023); Stevner et al. (2019) and anaesthesia dynamics in particular Barttfeld et al. (2015); Demertzi et al. (2019); Hudetz, Liu, and Pillay (2015); Liang et al. (2024), are temporally less complex both in terms of the effective diversity and reachability of states and in state switching. We suggest that the attraction of anaesthesia dynamics towards a small set of sink states, with

a severely reduced capacity for integration and cortical and subcortical excitability, may in part be responsible for this reduction in complexity. Such sink state dominance seems much less prevalent in wakefulness with comparatively much weaker attractor-like states, perhaps owing to a need for higher levels of responsiveness.

Second, we observe fragmentation of functional modules under anaesthesia into small, static subnetworks with little thalamocortical or even cortical-subcortical re-organisation from state to state. In particular, thalamic community associations mostly occurred between neighbouring subcortical and entorhinal regions. Notably, some interchange is observed between prefrontal, parietal and nucleus accumbens, suggesting some sporadic default mode-like activity. This thalamocortical isolation has also been shown from static measures of functional connectivity Mhuircheartaigh et al. (2013). Deteriorated but persistent default mode network activity has been observed in other studies of anaesthesia functional connectivity, with the anterior portions being most affected Luppi et al. (2019). In our model, anaesthesia is contrasted with wakefulness in which larger communities dynamically exchange members between states to facilitate more complex task performance, required for conscious awareness and for responsiveness to the external and internal environment Barttfeld et al. (2015). This result may be surprising as we find that anaesthesia state connectivity was generally less self-similar than in wakefulness. However, this is consistent with the hypothesis that there is a persistent global core to functional connectivity in wakefulness Onoda and Akama (2023), likely including the thalamus as an important hub Luppi et al. (2024); Mhuircheartaigh et al. (2013); Tasserie et al. (2022). Stratification may result in this core being partially fragmented into anatomically restricted regions during unconsciousness Hu, Wang, Zhang, Luo, and Wang (2024).

Third, we examine the dynamic structure-function relationship in relation to both connectvity and modularistion. Our results support the generally observed increase in similarity between functional and structural connectivity Demertzi et al. (2019), as well as providing new evidence of weak similarity between dynamic modularisation and structural modularisation. In particular, we note that most anaesthesia communities appear spatially constrained to specific brain areas, perhaps reflecting propagation of anaesthesia signal along local structural connections that then fail to propagate more widely as observed in Gosselin, Bagur, and Bathellier (2024); Mhuircheartaigh et al. (2013). The absence of structural connections across multiple spatial scales have been suggested to result in less robust

consciousness markers in DOCs Altmayer et al. (2024); Luppi et al. (2021). The similarity in local clustering coefficient (integration) and degree distribution may then be due to the preservation of some of these longer range connections that are absent in unconsciousness.

Finally we indicate some implications of our study regarding patient-specific targeting of anaesthesia depth. The strong attractor-like dynamics towards low complexity, low excitability anaesthesia states which we observe reflect the imperturbability of subjects from anaesthesia. In addition, we demonstrate a tentative link between sink state dominance, and anaesthetic susceptibility, specifically the age of the subject, and, to a lesser extent, time at loss of responsiveness. In combination, these results suggest that sink state dominance may correlate with other monitors of anaesthesia depth Cortínez et al. (2008); Obert et al. (2021); Warnaby, Sleigh, Hight, Jbabdi, and Tracey (2017). More tentatively, the persistence of sink state-like dynamics may be a possible future marker for recovery from DOCs.

With regards to limitations, our study was limited in its structure-function comparisons by the availability of patient-specific structural data that would enable us to make subject-specific comparisons. Finding a parcellation that was computationally tractable and relevant in a functional context was prioritised partially due to the relatively small cohort size for the ultra-slow anaesthethesia study. Due to this choice, some cortical areas lacked comparable left and right regions, preventing us from observing possible lateralisation of activity in some cases. Sample size and small age range may also explain the apparent weak association between grey matter volume and age Terribilli et al. (2011), and limit the generalisability of the result to older ages who see the most significant detrimental affects of over anaesthesia Sevenius Nilsen et al. (2019); Wu et al. (2019). In this regard, further experimental studies would be of interest.

The focus on brain state has allowed for the development of new ways of analysing the complexity of the brain in action Barnett and Seth (2023); Barttfeld et al. (2015); Mediano et al. (2022). We believe that new complexity measures should put special focus on combining both spatial and temporal complexity, while taking into account the brain's dynamic capacity for integrating the interdependent streams of information that support complex behaviour. Our HMGM approach provides a novel graphical solution to address the problem by decomposing the entire neural system into spatiotemporal subnetworks that capture the reorganisation necessary to sustain complex activity.

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SUPPORTING INFORMATION

This is an optional section. Please use this space to provide information about any supporting information referred to in your manuscript.

In your manuscript, bold the first occurrence of each **Technical Term** and then provide a list of the terms and their definitions at the end of the manuscript after the references.

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TECHNICAL TERMS

- BOLD - Blood Oxygen Level Dependent (signal), a measure of functional activity under fMRI or other imaging modalities
- community - a collection of nodes in a network which are functionally coordinated across space and/or time
- ESC - Effect Site Concentration, the concentration of a drug where it is biologically active
- FO - Fractional Occupancy, the fraction of time that a subject is expected to spend in each state, given their functional activity, over a specific recording
- functional module - a set of two or more brain regions which coordinate to perform a specific cognitive function (these modules may overlap in time and/or space)
- propofol - An intravenous anaesthetic commonly used in general anaesthesia for surgical purposes
- HMM - Hidden Markov Model, a probabilistic model of (brain) state that defines a model for observed data and the transitions between (brain) states
- HMGM - Hidden Markov Graph Model, an augmented HMM with the structure of a multiplex graph
- LOBR - Loss of Behavioural Responsiveness, the individualised point at which subjects stop responding to experimentally relevant stimuli
- modularity - a measure of the degree of coordination between members of communities when compared to the expected degree of coordination between those members

- multiplex - a network comprised of copies of the same set of nodes (layers) with edges between them
- parcellation - A 3D brain model which defines certain brain voxels as belonging to distinct brain regions
- ROI - Region of Interest, a defined region of the brain for investigation in the study
- tractography - the use of imaging data to model the connectivity of the axon bundles that physically connect brain regions

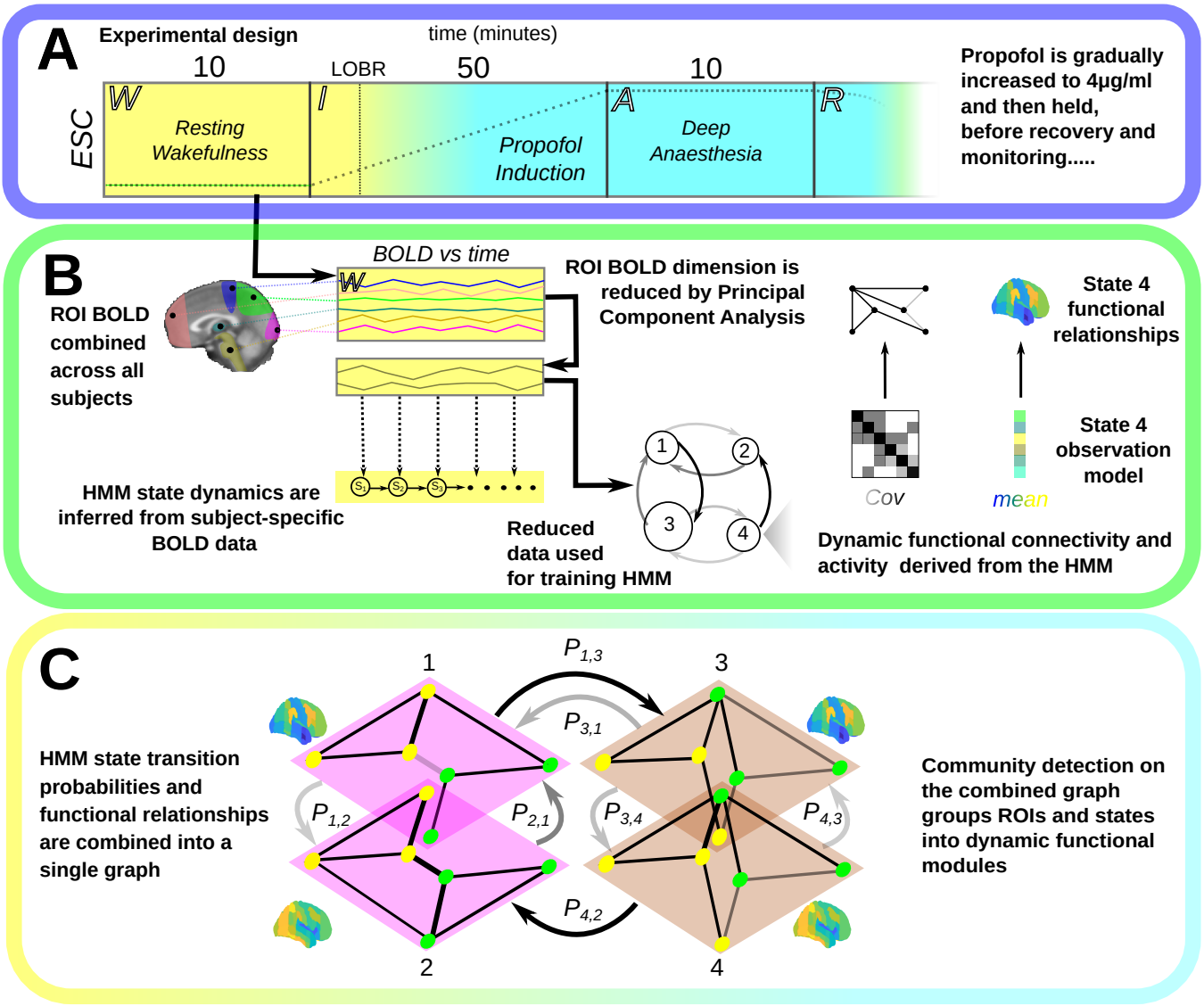

Figure 1: This figure shows our experimental and analysis framework. (A) Subject fMRI is recorded at resting wakefulness, yellow, W, followed by ultra-slow propofol induction, I, where the estimated Effect Site Concentration (ESC) is gradually increased, and **Loss of Behavioural Responsiveness (LOBR)** during induction is marked with a dotted line, before being held at 4μg/ml during the deep anaesthesia, cyan, phase A. Anaesthesia dosage is then tapered and subjects are allowed to recover, R. (B) ROI BOLD time series across all subjects were first combined and then dimensionality reduced by Principal Component Analysis (PCA). In the framework, brain dynamics arise from a sequence of hidden brain states. Occurrence of the next state is probabilistically dependent on the current state. These probabilities are shown with an arrow (darker, higher probability). Each state encodes expected functional connectivity and activity relationships that are mapped into parcellation space through the state mean (blue, low) and covariance (dark, high) parameters. The analysis is performed again for anaesthesia. (D) We combine functional and dynamic information to produce the combined HMGM graph (dark arrows, high probability transition), followed by spatiotemporal community detection.

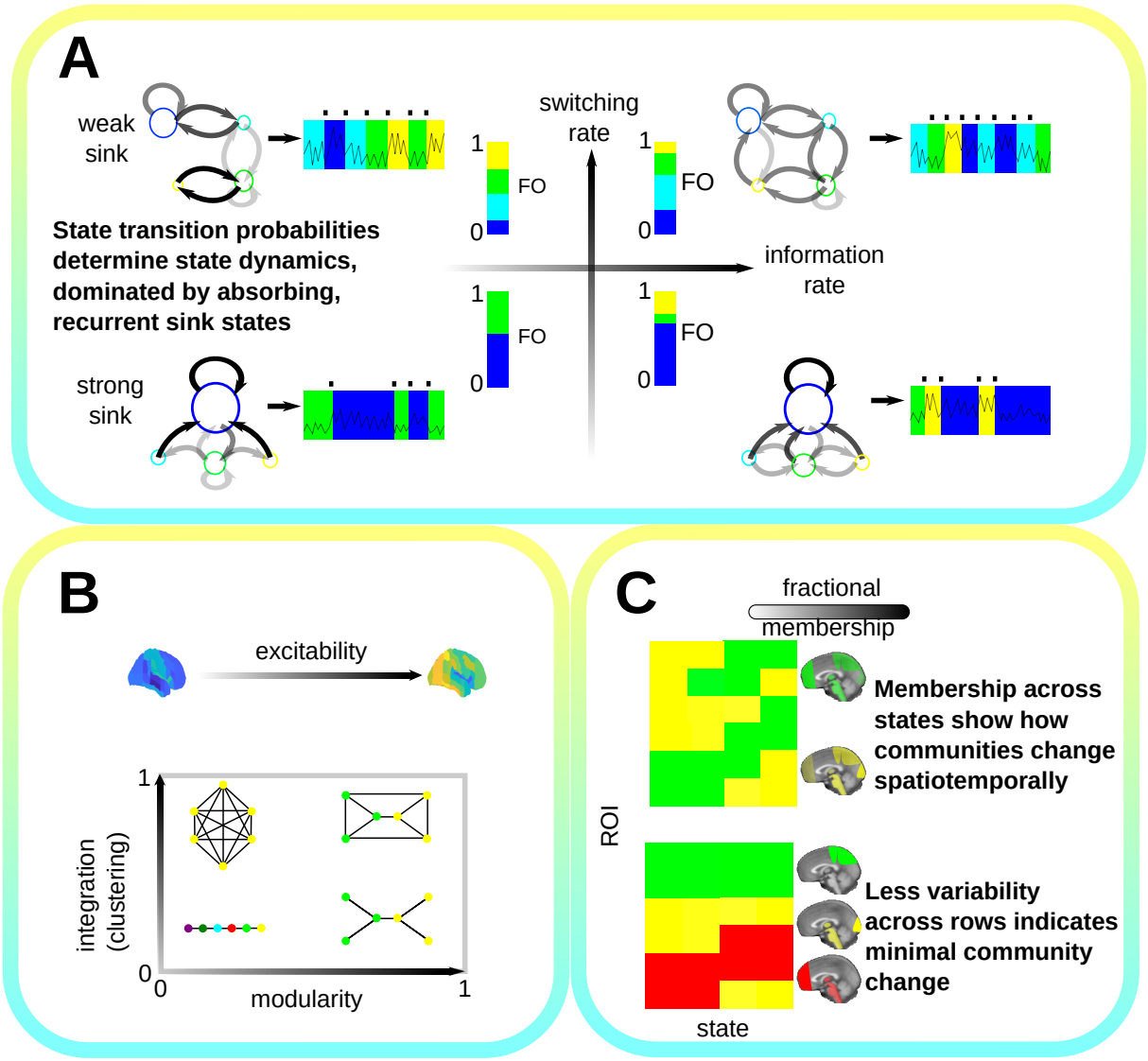

Figure 2: This figure shows our analysis framework (A) Four state models are shown to contrast their information theoretic properties along two axes switching rate increasing from top to bottom and information (entropy) rate increasing from left to right. Larger nodes correspond to sinks. Fractional Occupancy (FO) is shown as a bar plot with the length of each coloured bar corresponding to the time in that state. (B) State functional variation is important to understanding conscious processing. Mean functional activity (excitability) may vary from low to high. The community and functional connectivity structure also informs the complexity of state information processing along multiple axes, crucially modularisation (capacity for independent processing) and integration which are interdependent, for instance the maximally integrated connectome is also minimally modular (top left). (C) Spatiotemporal community analysis allows for states to be partitioned into functionally related modules that share members across temporally related states. These communities may be visualised by their fractional membership, the expected proportion of time a region spends in each community, here shown by colour opacity from light (low membership) to dark (high membership).

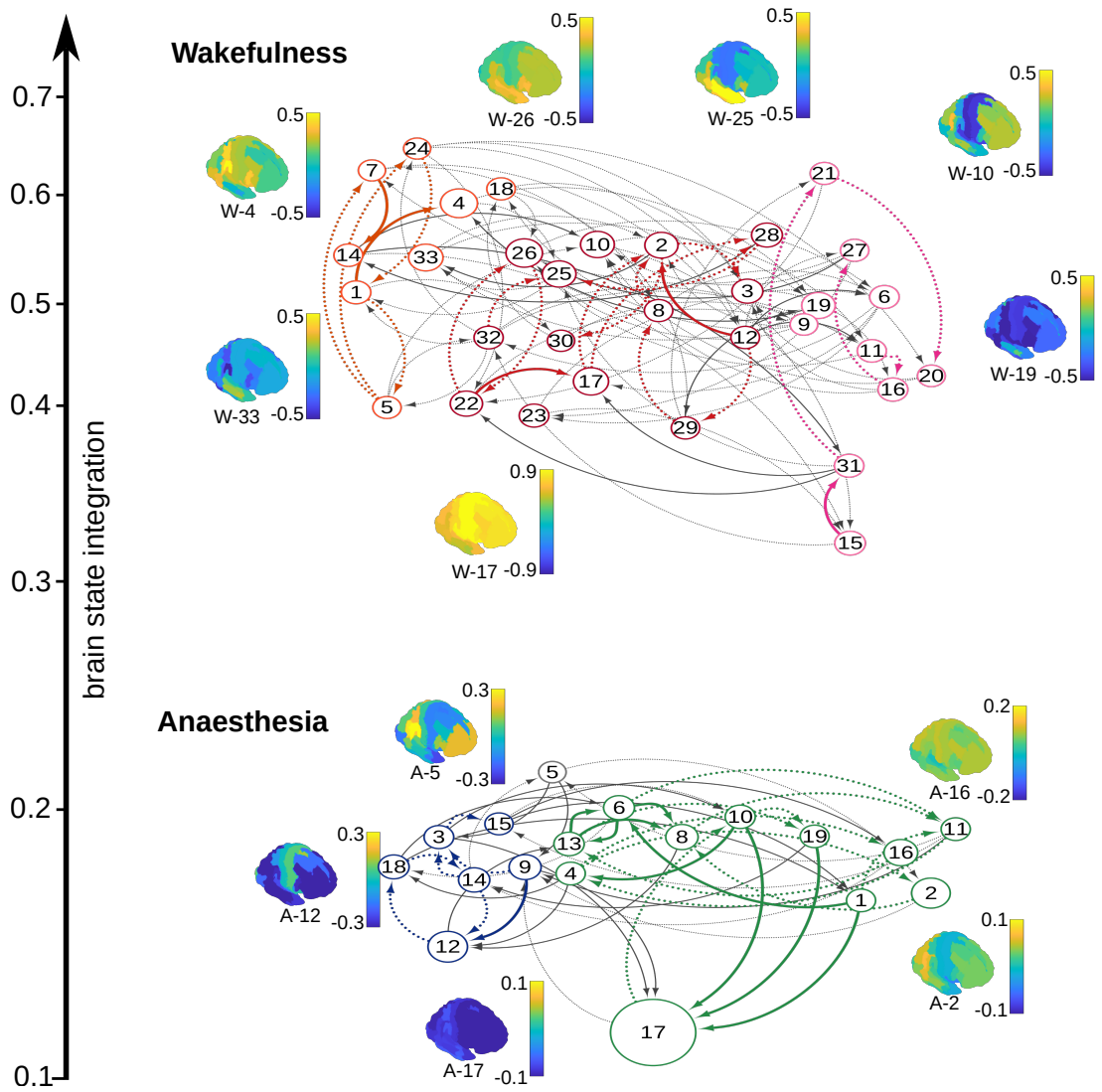

Figure 3: In the HMGM states are related by the probability of transition between them. This figure shows two graphs representing the respective state dynamics of subjects when awake or anaesthetised. Each node is a state the size of which is proportional to the state sink centrality. Edges represent that there is a non-negligible Transition Probability (TP) from one state to another. For visualisation purposes, only the two strongest edges from or to a node are shown with weaker probability edges (TP<0.05) denoted by dotted lines. The level of brain state integration (clustering coefficient) is used to order the states on the y-axis on a log10-scale. Background shading indicates the change from high integration (yellow, bottom) wakeful states to significantly less integrated (cyan, blue) anaesthesia states ($p \leq 0.001$, Mann-Whitney U test) what is the hypothesis, how measured, is it different to the one earlier in this paragraph? One sided or two sided test?. States are organised horizontally into communities with coloured edges represent connections between states that share similar functional connectivity and dynamics. Here, we show brain maps for all states that account for 0.05 or more of the stationary distribution. We show brain maps of mean functional activity for all sink states (and associated colourbar), as well as state A-5 which is a transient outlier which does not belong to any cluster.

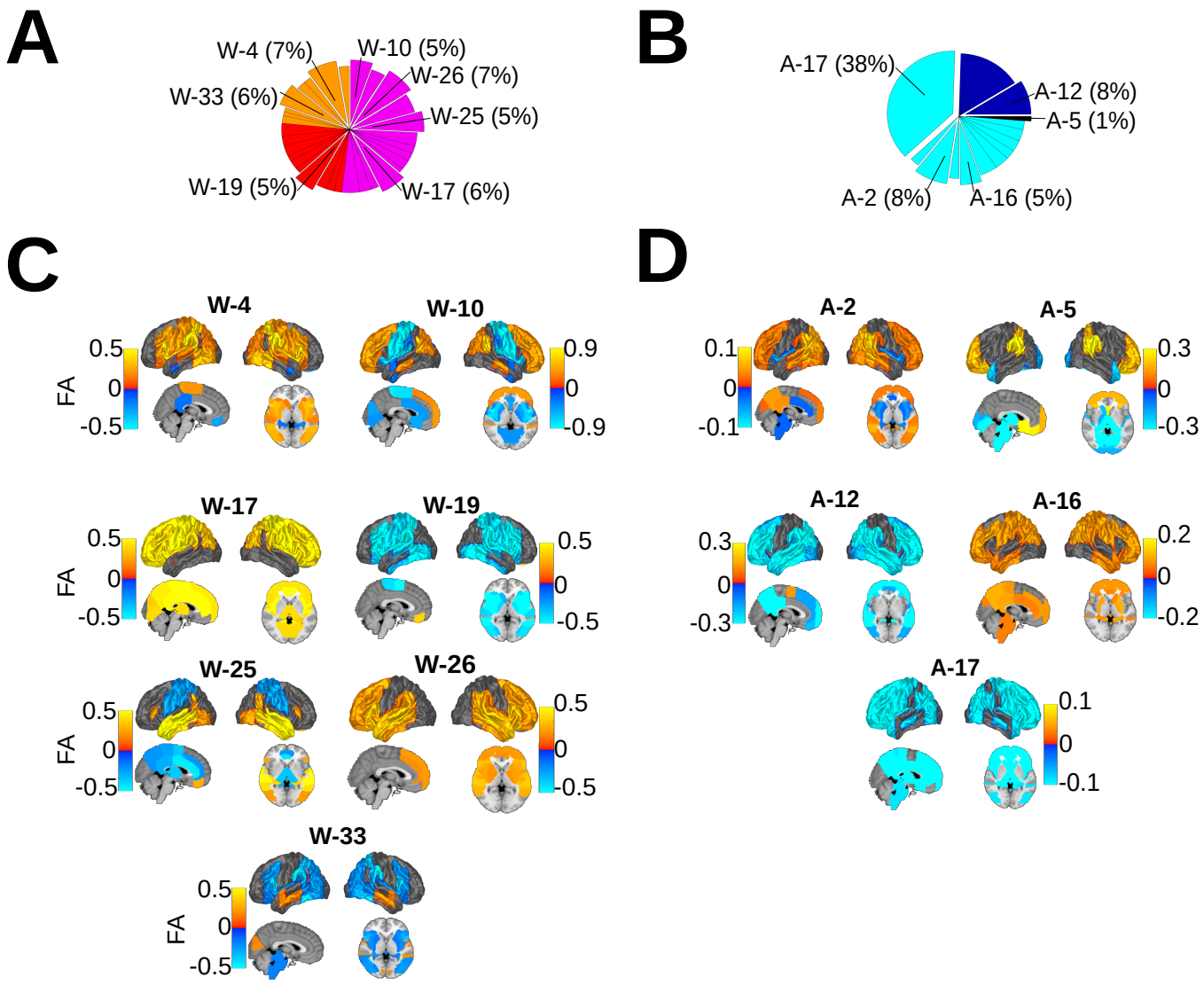

Figure 4: This figure summarizes the state activity of important states, highlighting the sink states as well as the outlying state A-5 and the prominent areas of surface Functional Activity (FA) for each. The stationary probability is shown for (A) wakefulness and (B) anaesthesia, with wedges indicating the sink states. In (C), the top 50% mean absolute functional activity in wakefulness is shown as a surface plot with a variety of high and low activity regions. (D) shows activity in the anaesthesia sink states, with much lower absolute mean functional activity across these states, indicative of lower absolute mean activity in anaesthesia as a whole ($p \leq 0.001$, Mann-Whitney U test, two-sided).

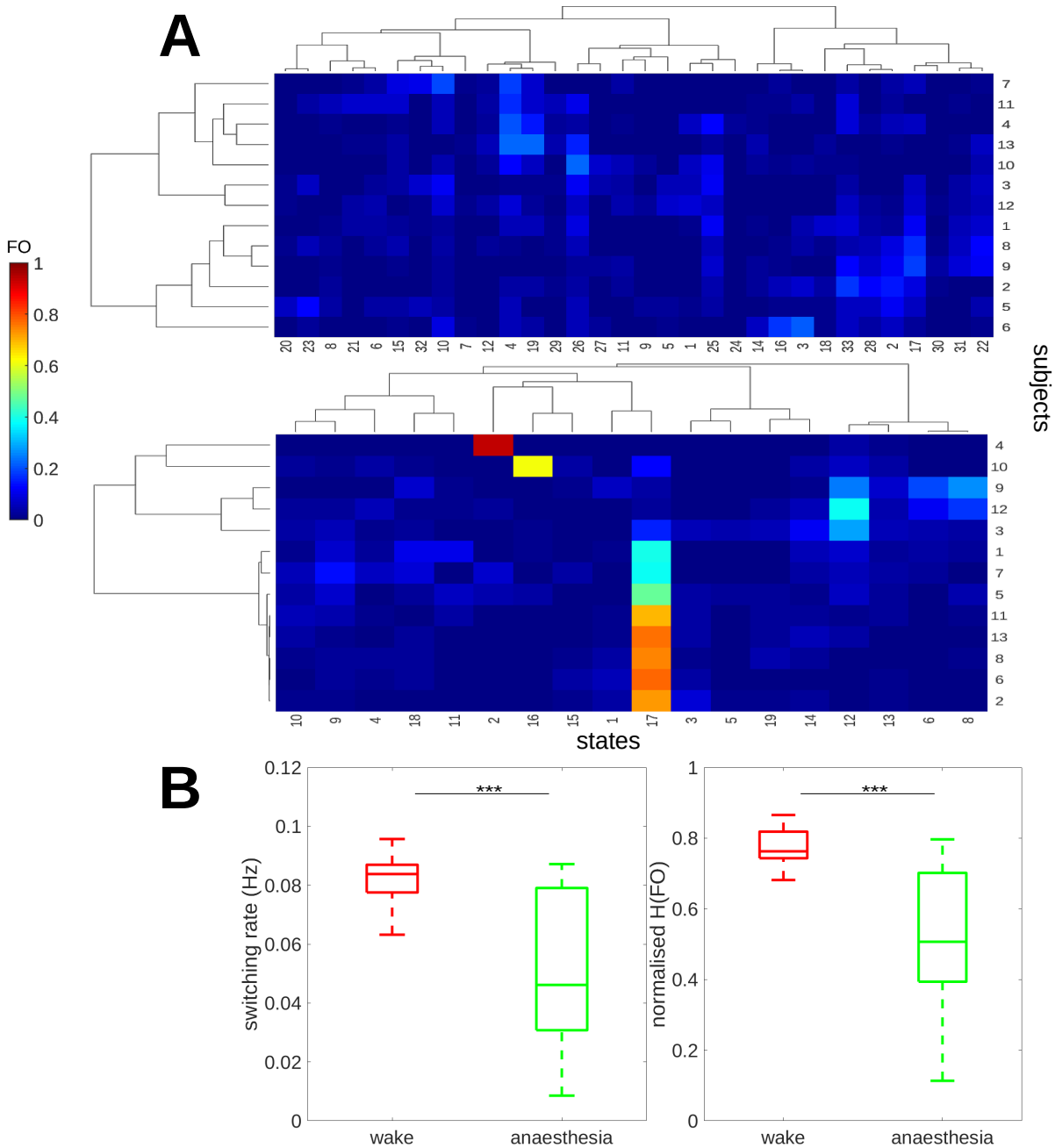

Figure 5: Subject specific state dynamics is shown for both anaesthesia and wakefulness. (A) shows the FO heat map as a clustergram where subjects (rows) and states (columns) have been hierarchically clustered by Pearson correlation using Ward's algorithm. In anaesthesia, dynamics tend to be dominated by a subset of sink states, including subjects 4 and 10 which show a strong preference for A-2 and A-16 respectively. (B) Shows a boxplot comparing wakeful and and anaesthetised switching rates and normslised occupancy entropy (H(FO)). The state switching rate (Hz) is more varied but significantly lower in anaesthesia ($p \leq 0.001$, Wilcoxon Signed-rank test, two-sided) The H(FO) shows a similar pattern to the switching rate with highly variable but overall lower state diversity present in anaesthetised versus awake subjects ($p \leq 0.001$, Wilcoxon Signed-rank test).

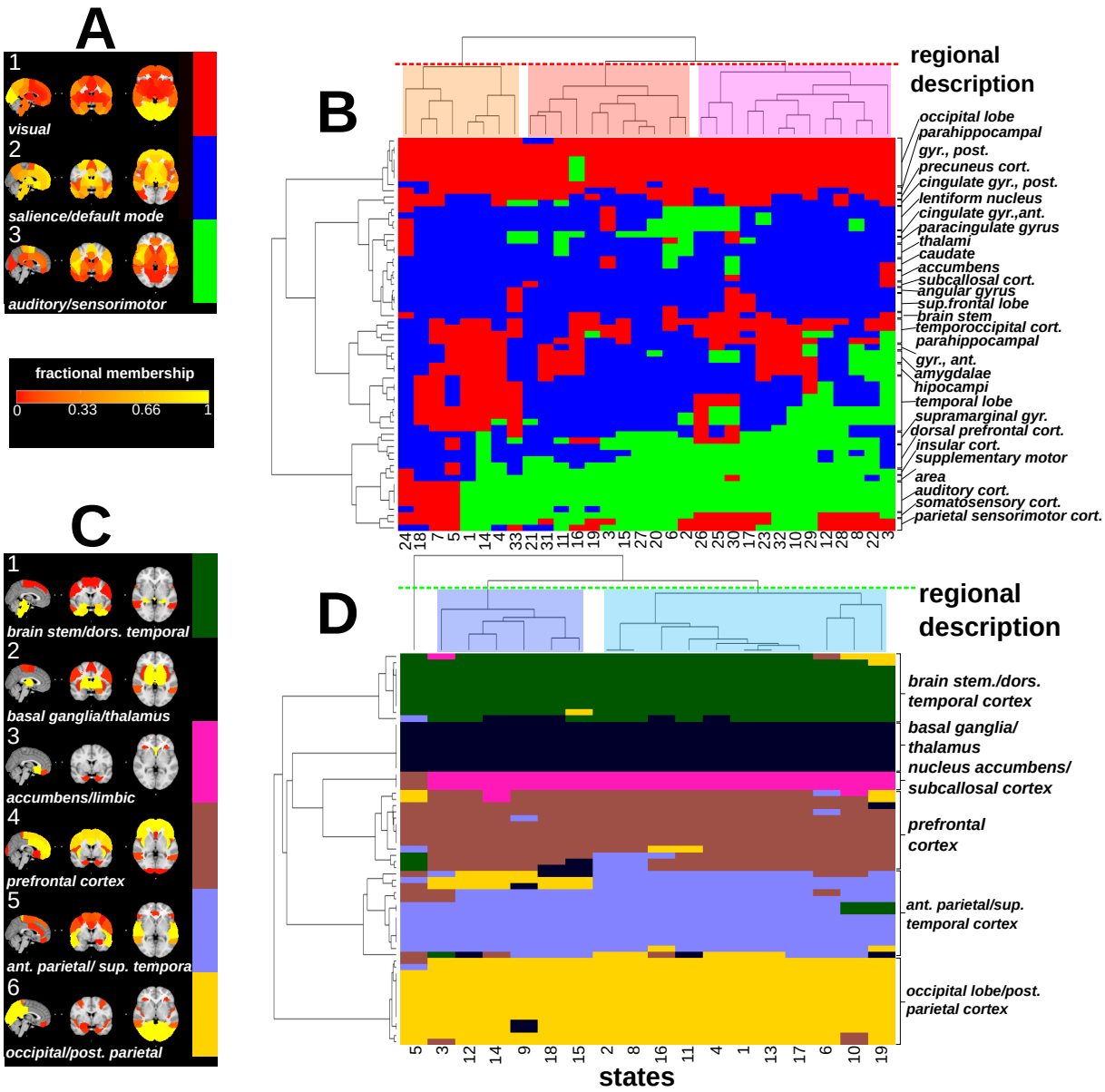

Figure 6: This figure summarises the results of spatiotemporal consensus community detection across regions (rows) and states (columns). Each ROI is coloured according to its community membership. ROIs and states have been hierarchically clustered in both deep anaesthesia and wakefulness using the Jaccard index similarity so that states with similar community composition and regions with similar membership are co-clustered (single colour patches). (A) this plot shows the regional composition of each wakeful community as a brain map where colour represent the fractional membership of the region. Communities have been broadly described according to the text labels. (B) the clustergram of wakeful communities shows a heterogeneous pattern of changing community membership. (C) shows brain maps for the deep anaesthesia condition. Brain regions are largely static (fractional membership near to one) and have a relatively restricted anatomically organisation with more total communities. (D) the anaesthesia clustergram shows regional stratification with minimal reorganisation.

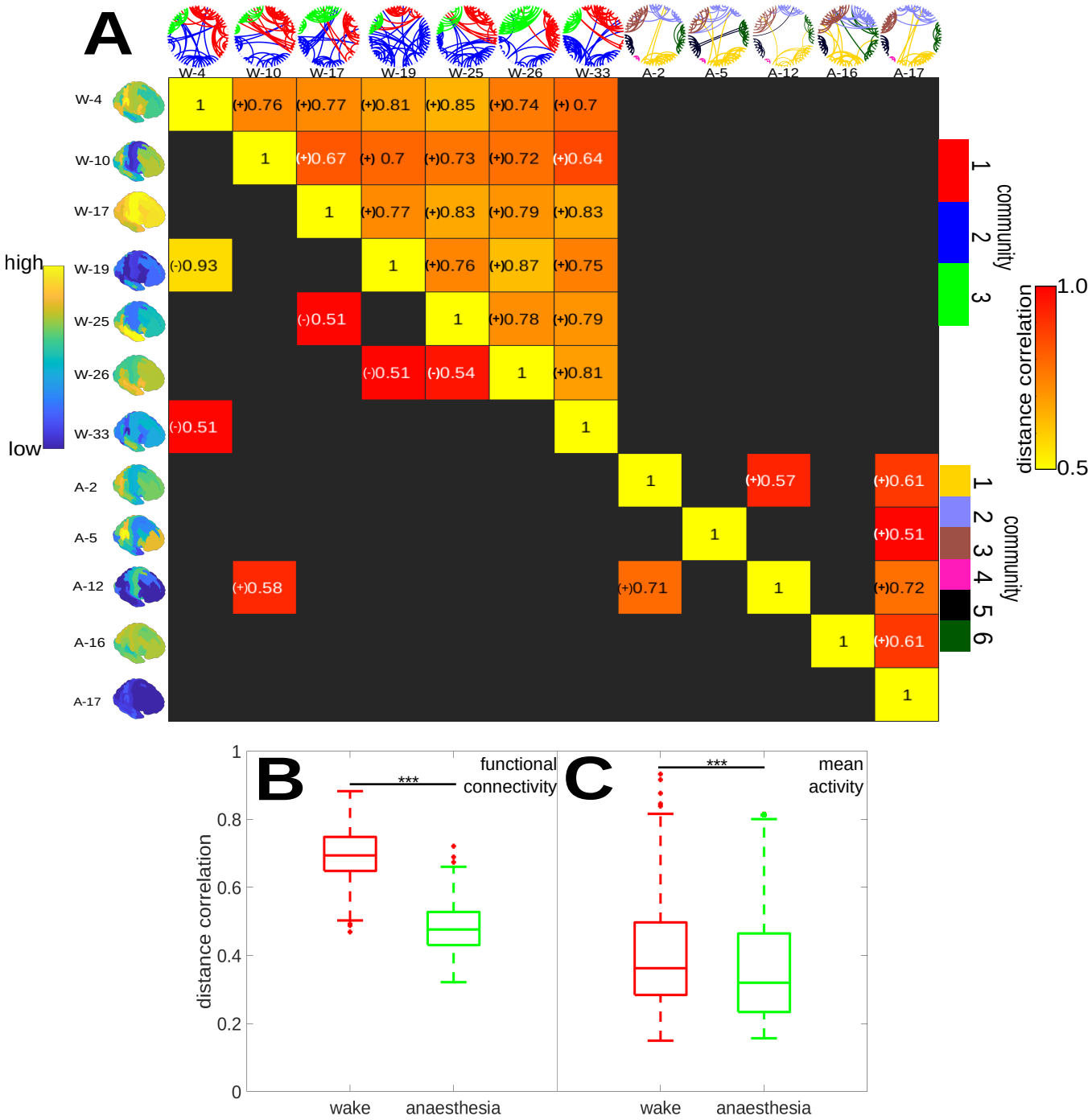

Figure 7: This figure illustrates the functional mean activity and connectivity across sink states in anaesthesia and wakefulness. (A) This figure is a heatmap of the pairwise signed distance correlation between sink states functional activity (bottom left) and sink state connectivity (top right). Brain maps (left) are the same as those in Fig. 3. Community interconnectivity (top) is shown as a circular graph, depicting the level of intercommunity connectivity in each state. (B) This boxplot shows the signed distance correlation between all states functional connectivity in wakefulness and anaesthesia (Mann-Whitney U, $p \leq 0.001$, two sided). Red dots denote outlying states. (C) Similarly, signed distance correlation is shown to be higher for mean activity amongst wakeful than anaesthesia states (Mann-Whitney U, $p \leq 0.001$, two-sided).

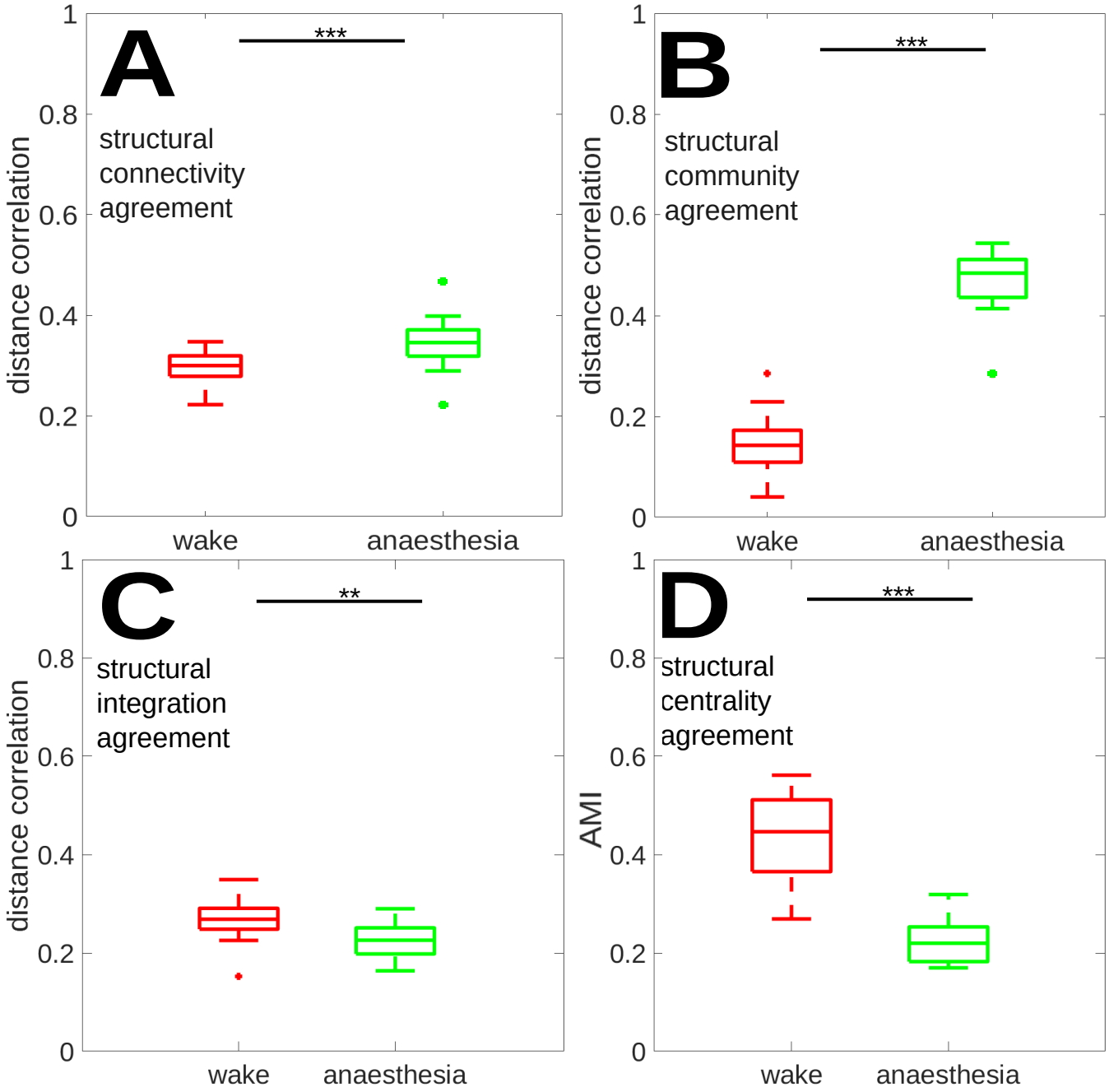

Figure 8: This figure shows the differences between brain state functional connectivity in wakefulness and anaesthesia as they relate to structural connectivity using distance correlation between each states connectivity and structural network connectivity. (A) shows the correlation in connectivity, brain state edge weights to structural network edge weights, in both conditions ($p = 0.001$, Mann-Whitney U test, two-sided). (B) shows the AMI, a measure of modular similarity, suggesting that anaesthesia functional modules are more similar to the normative structural modularisation of the brain than dynamic wakeful states ($p < 0.001$, Mann-Whitney U test, two-sided). (C) shows local clustering coefficient for each state when compared to the structural network ($p \leq 0.001$, Mann-Whitney U test, two-sided). (D) shows the degree centrality measure in each state with the structural graph model ($p \leq 0.001$, Mann-Whitney U test, two-sided). Outlying samples are shown as crosses.