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Cortical connectivity, local dynamics and stability correlates of global conscious states

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Abstract

Consciousness emerges from complex neural processes, yet its precise neurobiological correlates remain uncertain. Here a space-time-resolved inference-based framework is applied to estimate the neurophysiological variables of a whole-cortex model and analyze the neural mechanism correlates of global consciousness by way of a correlation analysis between behavioural and neural variable time-series. Using magnetoencephalography (MEG) data from 15 participants under Xenon-induced anesthesia, interconnected neural mass models (NMMs) were developed and time-evolving regional neurophysiological variables and inter-regional connectivity strengths were inferred from the data. Analyses revealed significant correlations between consciousness levels and inter-regional connectivity, particularly in posterior parietal, occipital, and prefrontal regions. Moreover, results support a parietal, rather than frontal, network backbone to facilitate global consciousness. Regional-level analyses further identified correlates of consciousness within the posterior parietal and occipital regions. Lastly, reductions in consciousness were linked to stabilized cortical dynamics, reflected by changes in the eigenmodes of the system. This framework provides a novel, inference-based approach to investigating consciousness, offering a time-resolved perspective on neural mechanism correlates during altered states.

1 Introduction

Consciousness refers to the subjective awareness and perception of one's own thoughts, feelings, and the surrounding environment [1]. Global consciousness emerges when a person transitions from a state of dreamless sleep to wakefulness and remains active throughout the day, ceasing only when the individual falls asleep, loses awareness in a coma, or experiences death. Global consciousness is also altered in disorders of consciousness or during anaesthesia. Many, if not all, philosophers, psychologists, and neuroscientists believe that consciousness is fundamentally a biological phenomenon [1–8]. Assuming that this belief is reasonable, one might ask “How exactly do brain processes cause conscious states and how exactly are those states realized in brain structures?” [1]. This question can be broken down into: “What exactly are the neurobiological correlates of conscious states (NCC), and which of those correlates are actually causally responsible for the production of consciousness?”, and “What is the right spatiotemporal scale for explaining consciousness?” [1].

The NCC refers to the specific systems or processes in the brain that are directly associated with conscious experience [9]. Considerable progress has been made in understanding the NCC [4, 5, 8]. Currently, many candidate NCCs are suggested by researchers to include brain structures and regions, neural network connectivity, and local dynamics [10–12]. Pertaining to brain structures and regions, growing evidence points to a possibility that consciousness is not supported by a single area but by a network of dispersed brain regions [13–15]. For example, global neuronal workspace theory [5, 16], which is one of the leading theories of consciousness, suggests that consciousness arises from ignition and broadcast of information between various neural networks and the global neuronal workspace, such as those in the prefrontal cortex [5]. The involvement of the prefrontal cortex is a highly debated topic in contemporary research on consciousness [17–20]. A review of lesion, stimulation, and recording studies suggests that the posterior cortex, specifically the temporal, parietal, and occipital areas, is crucial for defining consciousness contents, whereas evidence for the frontal cortex's direct role in this regard is either missing or unclear [19] (but also see [21–23]).

Pertaining to neural network connectivity, researchers have proposed various models and hypotheses to explain how neural networks in the brain give rise to consciousness [24–27]. In particular, the connectivity of all default mode network regions was negatively correlated with the degree of clinical consciousness impairment [26]. Also low levels of consciousness involved decreased integration, increased segregation, and reduced global coupling of a whole-brain computational network model [27].

Local dynamics delves into the intricacies of neuronal firing patterns, revealing how the timing, rate, and synchrony of neuronal activity are integral to conscious awareness [28–30]. It also examines the specialized roles of microcircuits within specific brain regions, focusing on their unique contributions to processing and creating conscious experiences [31]. Central to this perspective is the study of neurotransmitter and synaptic dynamics, which highlights how chemical interactions at synapses influence consciousness at a local level [15, 32, 33].

In summary, accumulating neuroscientific evidence on the NCCs indicates that consciousness emerges from the dynamic interactions among various neural correlates, rather than being solely attributable to these correlates [34–36]. Despite such an agreement in the field, there has been no framework for researchers to “simultaneously” consider all possibly relevant NCCs and their interplays in a time-resolved manner to elucidate how they regulate consciousness as a whole. This is the gap that our study tries to fill. Specifically, the problem has been approached using computational brain models. Nonlinear computational whole-cortex models were built with regional neurophysiological variables and inter-regional connectivity as the NCCs of interest. This was achieved by augmenting our previous Neurophysiological Process Imaging (NPI) framework. NPI models dynamics of cerebral cortex at a high temporal resolution and a broad spatial scale by constructing neural mass models (NMMs) [37] in a region specific way, yet also by connecting them inter-regionally according to effective connectivity derived from data. Here this new framework has been applied

to magnetoencephalography (MEG) data in 15 human subjects undergoing Xenon-induced anaesthesia to study the neural mechanistic basis of drug-induced reductions of consciousness in terms of local dynamics, network connectivity and cortical stability at the same time. Xenon is known to be a putative N-methyl-D-aspartate (NMDA) receptor antagonist that effectively reduces consciousness by reducing excitation. Xenon was chosen as the anaesthetic in this study to complement, but also look for similarities with, the vast majority of other anaesthesia studies that predominantly focused on using gamma-aminobutyric acid (GABA) receptor agonists such as propofol or sevoflurane [19].

To gain insights into the aforementioned neural mechanistic correlates of global consciousness, model variables were estimated over time from brain imaging data at the spatiotemporal resolution afforded by MEG. Correlation analyses were conducted to examine the relationships between the level of task responsiveness (a surrogate measure of the level of consciousness) and local dynamics and network connectivity, respectively. To elucidate a potentially critical interplay between brain networks, this work quantified how activity in one network influences the activity in another. Moreover, dynamic cortical stability was identified as a possible global NCC measure anchored within the framework of dynamical systems theory and using neurophysiologically plausible models constrained by data.

2 Results

Whole-cortex models of individuals were built, incorporating canonical NMMs, which are connected to each other based on the empirically estimated effective connectivity, as shown in **Fig 1a**. The neural mass model (NMM) consists of three primary neural populations: excitatory pyramidal cells (p, shown in blue in **Fig 1a**), spiny stellate excitatory cells (e, depicted in green in **Fig 1a**), and inhibitory interneurons (i, highlighted in red in **Fig 1a**). Together, these populations form a simplified representation of a localized cortical column, mirroring the structural organization of a small region in the cerebral cortex [38]. The pyramidal cell population receives external input from a source μ (illustrated in purple in **Fig 1a**), which drives activity in both excitatory and inhibitory interneurons. These interneurons, in turn, modulate the activity of the pyramidal cells through feedback mechanisms: excitatory feedback enhances activity, while inhibitory feedback suppresses it. The variable μ represents the postsynaptic membrane potential generated by neuronal activity spanning different cortical regions. The dynamic state of each neural population is characterized by its mean membrane potential, v_n , where $n \in \{p, e, i\}$ corresponds to the pyramidal, excitatory, or inhibitory populations, respectively. The interaction strength between two populations is defined by the parameter α_{mn} , which denotes the average connection strength across synapses. For instance, the connectivity from the pyramidal population ($m = p$) to the excitatory population ($n = e$) is specified as α_{pe} . This parameter aggregates several factors, including the density of synaptic connections, averaged maximum firing rate, and synaptic gain. To capture inter-regional interactions, the matrix $\mathbf{W}$ encodes the effective connectivity between different NMMs, quantifying the strength of their interdependencies. The parameters of the whole-cortex model were inferred by fitting it to magnetoencephalography (MEG) source time-series data. In this process, each MEG time series was aligned with the pyramidal membrane potential of a corresponding NMM using a time-resolved inference framework (see **Methods** for further details).

The MEG data was collected from 15 healthy participants during wakefulness and progressively increasing sedation induced by Xenon, up to a stabilized level of 1.3 minimum alveolar concentration-awake (MAC-awake). Throughout this process, participants' responsiveness was monitored using the auditory continuous performance task (ACPT) [39] (see "Methods"). 1.3 MAC-awake represents an interesting concentration as it brings most, but not all people to a state of loss of responsiveness to verbal command. Thus it represents a reasonable concentration that brings participants in the vicinity of the boundary of consciousness/unconsciousness. Moreover, deeper levels of anaesthesia were not studied for safety reasons because this data was collected in a non-hospital environment.

The ACPT presents tones of different frequencies and asks participants to respond with button presses. From the accuracy with respect to determining which tone was delivered, responsiveness (a surrogate for consciousness) levels were estimated during anaesthesia delivery. Although it is well known that unresponsiveness is not the same as unconsciousness [40], for ease of exposition it is assumed that the responsiveness level (measured here as ACPT accuracy) is a monotonically increasing nonlinear function of the global consciousness level. This assumption is reasonably true at least for sedative levels of anaesthesia. Thus until the discussion section the words ‘responsiveness level’ and ‘consciousness level’ are treated as interchangeable.

For each participant, MEG source time series were reconstructed for each brain structure of the cerebral cortex as defined in the Automated Anatomical Labeling Atlas [41], resulting in 78 region of interest (ROI) source-level MEG time series. As an example case, **Fig 1b-f** illustrate the neurophysiological variable estimation results for an individual, subject 1. **Fig 1b** shows the source-level time series of the cerebral cortex under Xenon-induced anaesthesia. **Fig 1c** and **d** show the ACPT accuracy and Xenon concentration levels, respectively, over the course of the experiment. As a result of the ACPT being easy, accuracy was always at 100% (i.e., the trial was correct, implying a high consciousness level), unless either the participant got the trial wrong because they were not paying attention or they just did not respond because of the consciousness-altering effects of the anaesthetic (both of these cases were treated as 0% accuracy or low consciousness level). Manually identified times of transition to low consciousness level (LC) and high consciousness level (HC) are labeled in the graph by the vertical lines. **Fig 1e** depicts the estimated time-evolving inter-regional connectivity from the data in **Fig 1b**. **Fig 1f** shows parameter estimates of a NMM fitted to the right precuneus (a ROI implicated previously in loss of global consciousness studies [19]). In this local NMM, the strength of excitatory connections (i.e., α_{phi} , α_{pe} , α_{ep}) decreased significantly when the subject had low consciousness level. Membrane potentials (v_i, v_e) behaved similar to these excitatory connections, except for the pyramidal neurons (v_p). On the other hand, the external input (μ), representing the sum across inputs from all other areas into the right precuneus, sharply increased at the onset of low consciousness level with high variation until high consciousness level was regained.

In the following analyses, the correlation between consciousness levels and inter-regional connectivity is examined, identifying brain structures and connections that are significantly associated with the level of consciousness. Next, the correlation between consciousness levels and functional networks is examined, focusing on the impact of intra- and inter-network connectivity on the level of consciousness. The relationship between local neurophysiological variable dynamics and consciousness levels is then analyzed. Finally, consciousness level changes and their association with dynamic cortical stability are investigated.

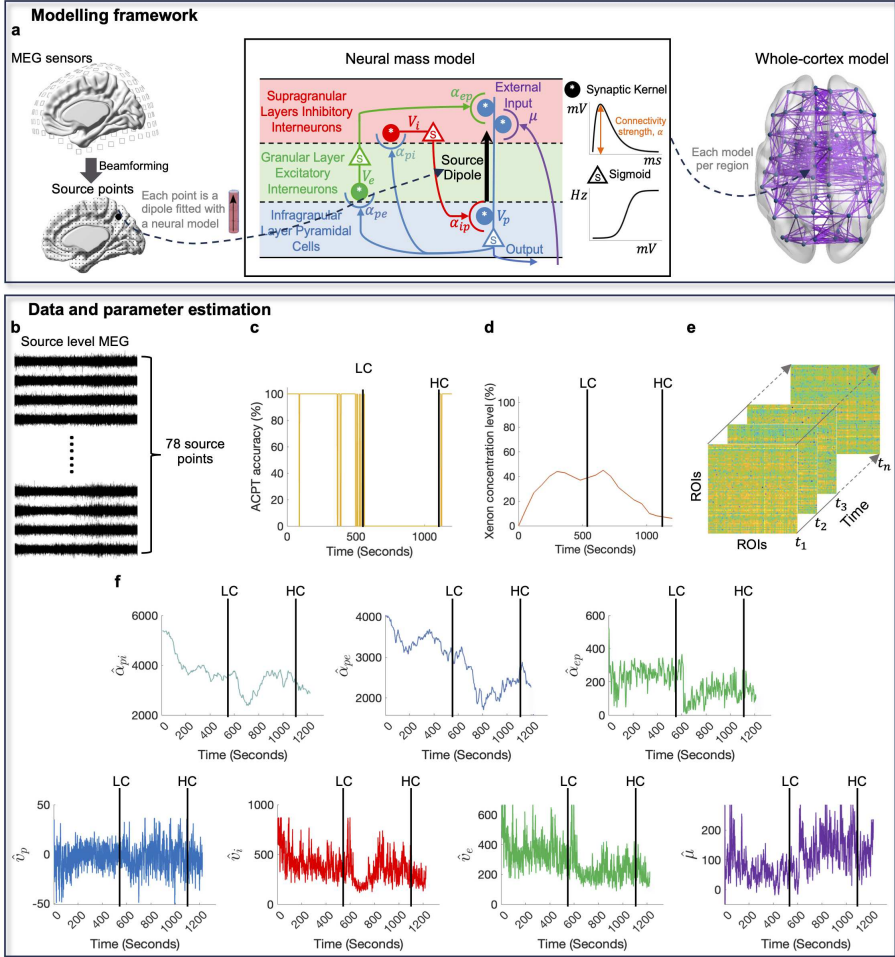


Fig. 1 Whole-cortex modelling and parameter estimation framework. **a** The schematic of the whole-cortex model fitted to source-level MEG data is shown. Each MEG source time series is modeled using a NMM, which represents a node in the whole-cortex model. The connections between the NMMs are indicated by purple lines. **b** 78 ROI MEG source time series from subject 1 during Xenon-induced anaesthesia. **c** and **d** ACPY accuracy time series and Xenon concentration levels for subject 1. LC and HC represent the estimated onset of low- and high-level consciousness, respectively. **e** Time-series estimation of the strength of effective connectivity between NMMs. **f** Time-series estimation of local model states and connectivity parameters was performed for a NMM fitted to the right precuneus of Subject 1.

2.1 Correlation of consciousness and inter-regional connectivity

Key brain networks associated with consciousness were identified by analyzing the temporal correlations between consciousness levels (i.e. ACPY accuracy) and centrality measures derived from the estimated inter-regional connectivity. These centrality measures assess the significance of a brain structure within the network, based on the strength of its connections to other regions through either incoming (in-degree) or outgoing (out-degree) connections. To ensure the robustness of our findings, a multiple comparisons permutation test was used. This is a statistical method that controls for false positives when testing multiple hypotheses

by randomly permuting the data, recalculating test statistics, and comparing the observed statistic to the resulting null distribution to determine significance (see “Methods”). With this approach at $\alpha = 0.05$, group-level significant “in-hub” and “out-hub”-brain structures were identified with in-degree and out-degree centrality measures that showed statistically significant correlations with consciousness levels.

The spatial distribution of in-hubs and out-hubs is illustrated in **Fig 2a, b**, respectively, with the corresponding statistics provided in **Table 1**. Notably, prominent negative correlations were observed between consciousness levels and centrality measures in the occipital, posterior parietal, and prefrontal regions. In particular, the right middle occipital lobe, right inferior occipital lobe, left superior parietal gyrus, and left angular gyrus showed significant decrease in both in-degree and out-degree centrality measures during consciousness reduction.

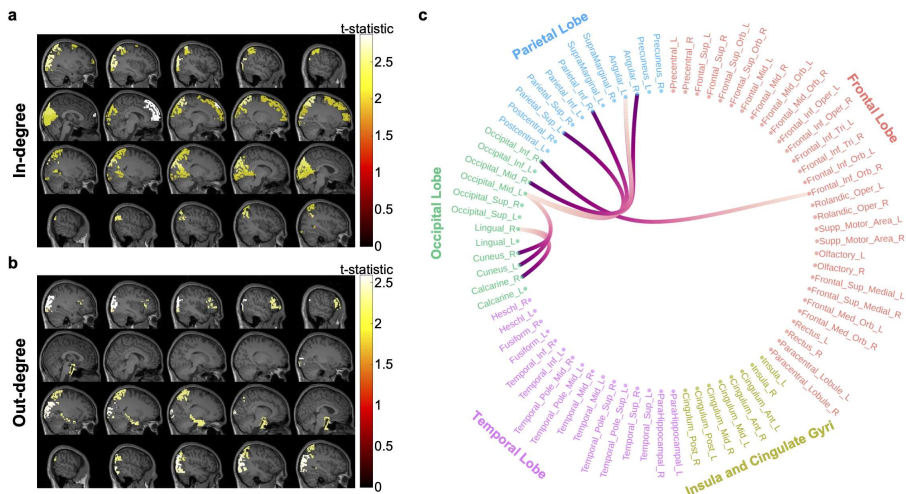


Fig. 2 Group-level significant hubs and inter-regional connections in relation to consciousness levels (i.e. ACPT accuracy). **a** Important in-hubs associated with consciousness levels are illuminated on the template MRI images. **b** Important out-hubs associated with consciousness levels are illuminated on the template MRI images. For both **a** and **b**, the colorbar denotes t-statistics obtained from multiple comparisons permutation tests (see “Methods”). **c** Significant inter-regional connections most correlated with consciousness levels. The darker end represents the originating point of the connection, while the lighter end represents the termination point. Brain structures and corresponding statistical information for **a**, **b**, and **c** are detailed in **Table 1**.

We also calculated the temporal correlation between consciousness levels and the strength of each inter-regional connection. Significant connections at the group-level were identified using a multiple comparisons permutation test (see “Methods”) with a significance level of $\alpha = 0.05$ on correlation coefficients across all subjects. As shown in **Fig 2c**, the strength of connections within and between the parietal and occipital regions is significantly correlated with consciousness levels across some inter-regional connections. Positive correlations were observed indicating that stronger connectivity in these regions corresponds to higher levels of consciousness. Notably, four out of five connections between the parietal and occipital regions originated from parietal structures, underscoring the dominant role of the parietal regions in influencing consciousness. The other connections were within the occipital regions suggesting that the connection of internal networks in the occipital regions also substantially affects the degree of consciousness. These findings suggest that variations in consciousness

		Significant brain structures			
ROI	<i>p</i>	ROI	<i>p</i>	ROI	<i>p</i>
<i>Significant in-hubs</i>					
Frontal_Sup_R	0.0402	Frontal_Sup_Medial_R	0.0021	Calcarine_L	0.0253
Cuneus_L	0.0149	Cuneus_R	0.0300	Lingual_L	0.0413
Occipital_Sup_L	0.0097	Occipital_Sup_R	0.0440	Occipital_Mid_R	0.0067
Occipital_Inf_R	0.0245	Parietal_Sup_L	0.0288	Parietal_Sup_R	0.0086
Parietal_Inf_R	0.0269	Angular_L	0.0120		
<i>Significant out-hubs</i>					
Frontal_Inf_Tri_R	0.0368	ParaHippocampal_L	0.0393	Occipital_Mid_L	0.0092
Occipital_Mid_R	0.0058	Occipital_Inf_L	0.0172	Occipital_Inf_R	0.0251
Parietal_Sup_L	0.0390	Angular_L	0.0430		
Significant connections					
Connection	<i>p</i>	Connection	<i>p</i>		
Occipital_Inf_R → Frontal_Inf_Orb_R	0.0446	Parietal_Inf_R → Occipital_Mid_L	0.0054		
Calcarine_R → Lingual_R	0.0469	Angular_L → Occipital_Mid_L	0.0232		
Cuneus_R → Lingual_R	0.0472	Angular_R → Occipital_Mid_L	0.0221		
Cuneus_L → Occipital_Mid_L	0.0431	Occipital_Mid_R → Angular_L	0.0493		
Parietal_Sup_L → Occipital_Mid_L	0.0252				

Table 1 Brain structures showing significant group-level correlation between consciousness levels (i.e. ACPT accuracy) and inter-regional connectivity. Upper panel: significant in-hubs and out-hubs in relation to consciousness levels (i.e. ACPT accuracy) are shown with p-values derived from multiple comparisons permutation tests. Lower panel: significant inter-regional connections correlated with consciousness level are shown with p-values derived from multiple comparisons permutation tests. Brain structures are shown in the format of the Automated Anatomical Labeling atlas.

levels are closely linked to connectivity strength in the occipital, posterior parietal, and pre-frontal regions, with a particular preeminence of parietal over occipital regions in modulating consciousness levels.

2.2 Correlation of consciousness and functional networks

The role of functional networks in relation to consciousness levels was explored. Seven functional networks were considered [42, 43]: Auditory Network (AN), non-ventral non-anterior Default Mode Network (DMN), anterior Default Mode Network (DMNa), ventral Default Mode Network (DMNv), Executive Control Network (ECN), Sensorimotor Network (SMN), and Visual Network (VN). The specific brain structures within each network are listed in Table S1. These networks are involved in various cognitive and perceptual processes, such as categorization, attention, memory, reasoning, sensory processing, movement, and decision-making, which operate at both conscious and subconscious levels [5, 44]. Understanding how these networks function during reduced consciousness is crucial for clarifying the relationship between brain activity and consciousness.

For each network, the time-varying intra-network connection strength was calculated by averaging the strength of connections within the network, and the inter-network connection strength was computed by averaging the strength of connections between functional networks. Correlation analyses between consciousness levels and both intra- and inter-network connection strengths were conducted, with the results summarized in Table 2. The connection strength within the VN, DMNv, and DMN networks showed strong positive correlations with consciousness levels. Consciousness was particularly associated with connections from the DMN to other functional networks and from other networks to the DMNv. Significant positive correlations were also found with the VN's connections: its bidirectional links with DMN and DMNv, outward connections to SMN and AN, and inward connection from ECN. These findings suggest that changes in consciousness levels are influenced by both the internal connections within the DMN, DMNv, and VN networks and the inter-network connections linking these networks with others.

	Network(s)	<i>p</i>	Network(s)	<i>p</i>	Network(s)	<i>p</i>	Network(s)	<i>p</i>
<i>Intra-network</i>	VN	0.0005	DMNv	0.0012	DMN	0.0146	Posterior parietal	0.0475
<i>Inter-network</i>	DMN→VN	0.0005	DMN→DMNv	0.0009	VN→DMNv	0.0009	Posterior parietal→Prefrontal	0.0495
	ECN→DMNv	0.0010	VN→AN	0.0020	DMN→AN	0.0030		
	DMNv→VN	0.0033	VN→SMN	0.0053	ECN→VN	0.0064		
	SMN→DMNv	0.0096	VN→DMN	0.0101	DMN→ECN	0.0104		

Table 2 Networks where the strength of intra-network connections shows positive correlations with consciousness levels, and connections between networks exhibiting positive correlations with consciousness levels. Arrows indicate the directions of these connections. Networks and connections without statistically significant correlations are omitted. Permutation tests were applied to find group-level *p*-values (see “Methods”) and Benjamini–Hochberg procedure was applied to control the FDR at $\alpha = 0.05$.

2.3 Correlation of consciousness and prefrontal and posterior parietal networks

To examine the relative contributions of the prefrontal and posterior parietal networks in modulating consciousness levels, the analysis was extended to include these networks (refer to **Table S2** for detailed information on the specific brain structures involved) [4, 19, 21, 45]. Correlation analyses were conducted for each network to explore the relationship between consciousness levels and both intra-network and inter-network connection strengths.

A permutation test (see “Methods”) revealed significant positive correlations between consciousness levels and two connection types: the intra-network connection strength within the posterior parietal network and the inter-network connection strength from the posterior parietal to the prefrontal network (statistical details are provided in **Table 2**). Conversely, no significant correlations were observed between consciousness levels and the intra-network connection strength of the prefrontal network or the inter-network connection strength from the prefrontal to the posterior parietal network. These results highlight the critical role of the posterior parietal network in regulating consciousness levels, with particular emphasis on its influence on the prefrontal network.

2.4 Correlation of consciousness and regional neurophysiological variables

To gain deeper insights into local neural mechanisms, estimated regional neurophysiological variables of the model were correlated with consciousness levels. The regional variables focused on here are the parameters of the NMM fitted to each brain structure reflecting local dynamics. These include the local excitatory post-synaptic potential (EPSP) amplitudes connecting the three model populations and the external cortical input from other cortical areas. To assess their impact, we calculated the temporal correlation between consciousness levels and the NMM parameter estimates. Group-level significant regions for each variable were identified using multiple comparisons permutation tests ($\alpha = 0.05$) on correlation coefficients across subjects. These regions were then visualized on template MRI images in what we refer to as “correlation imaging”.

Fig 3a shows positive correlations between the connectivity variable linking pyramidal to inhibitory populations (α_{pi}) and consciousness levels in the left orbital middle frontal gyrus and left middle temporal gyrus. Additionally, significant positive correlations were found between consciousness levels and the connectivity variables for pyramidal to excitatory populations (α_{pe}) and excitatory to pyramidal populations (α_{ep}), primarily in the posterior parietal and occipital regions (**Fig 3b** and **c**). **Fig 3d** further illustrates positive correlations between external input (μ) and consciousness level in the posterior parietal and occipital regions. Specific brain structures and their corresponding statistics are detailed in **Table 3** for each regional variable. These results suggest that the strength of excitatory synaptic connectivity (α_{ep} , α_{pe}) in the posterior parietal and occipital regions influences consciousness

levels in a manner consistent with the expected reduction in excitatory synaptic strength as Xenon concentration increases [46].

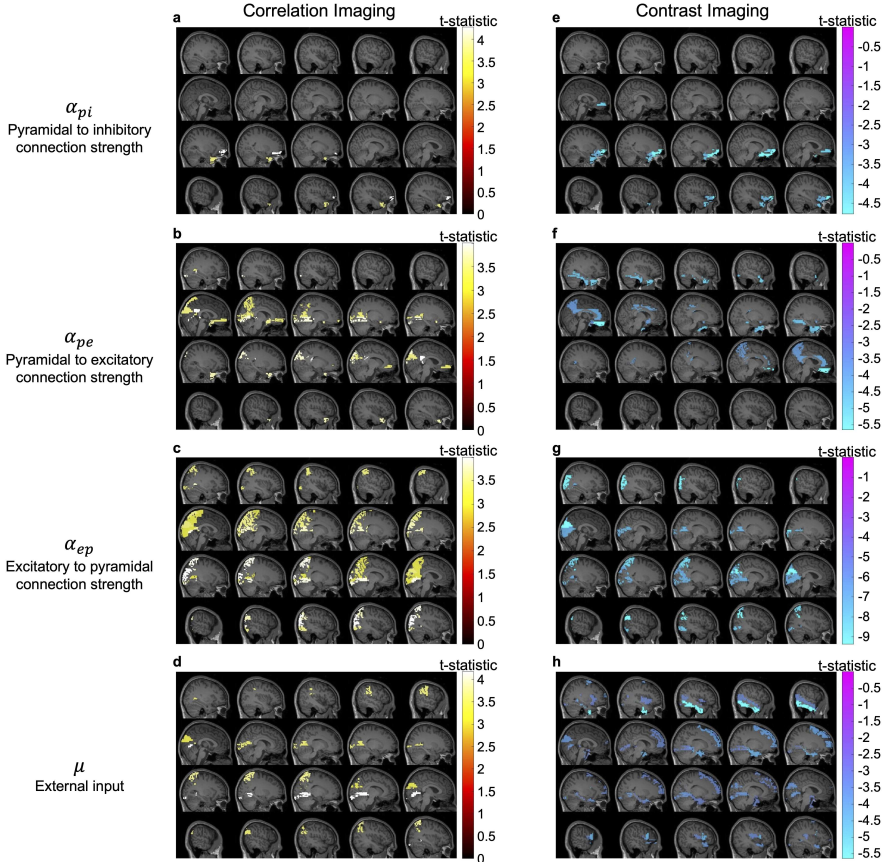


Fig. 3 Brain structures showing significant correlation between consciousness level (i.e. ACPT accuracy) and regional neurophysiological variable estimates. **a-d** Correlation imaging reveals cortical regions exhibiting notable correlations between consciousness levels and specific regional variable estimates. **e-h** Contrast imaging shows cortical regions demonstrating significant differences in specific regional variable estimates between the awake ACPT period and the equilibrated Xenon concentration period.

As an alternative to the correlation imaging and to provide a comparison against more traditional forms of contrast imaging seen in prior studies, cortical regional variables estimates before and after Xenon equilibration were contrasted. Statistically significant differences were identified using t-tests followed by multiple comparisons permutation tests at $\alpha = 0.05$ on the t-statistics across all brain regions and subjects. Subjects 5 and 9 were excluded from the analysis as their experiments were terminated before the full 5 minute long Xenon equilibrium period was completed. The significant brain regions are highlighted on the template MRI images. The result emphasizes the prefrontal, including orbitofrontal and dorsal medial frontal areas (**Fig 3e-h**, **Table 3**) as compared to the correlation imaging results.

Specifically, significant decreases were observed in EPSP strength α_{pe} across several regions, including the frontal areas, cingulate gyri, and precuneus. Decreases in α_{ep} were

	α_{pi}	t-statistic	α_{pc}	t-statistic	α_{cp}	t-statistic	μ	t-statistic
<i>Correlation Imaging</i>	Frontal_Mid_Orb_L	4.2717	Cingulum_Post_L	4.0126	Occipital_Mid_L	4.0056	Lingual_L	4.1726
	Temporal_Pole_Mid_L	3.7224	Lingual_R	3.8917	Parietal_Sup_L	3.9389	Parietal_Sup_L	3.7324
			Occipital_Sup_L	3.8459	Lingual_L	3.9112	SupraMarginal_R	3.6124
			Temporal_Pole_Mid_L	3.7168	Calcarine_R	3.8012	Calcarine_R	3.5762
			Olfactory_R	3.5871	Angular_L	3.7478	Angular_L	3.5735
			Cuneus_L	3.5177	Occipital_Sup_R	3.7282	Cuneus_L	3.3911
			Calcarine_R	3.4504	Cingulum_Post_R	3.6354		
			Frontal_Med_Orb_R	3.4348	Occipital_Inf_L	3.5362		
			Frontal_Med_Orb_L	3.4132	Precuneus_R	3.5353		
			Precuneus_R	3.4036	Cuneus_R	3.5109		
					Cuneus_L	3.4961		
					Parietal_Inf_R	3.4857		
					Parietal_Sup_R	3.4843		
					Occipital_Inf_R	3.3933		
<i>Contrast Imaging</i>	Frontal_Sup_Orb_L	-4.7673	Rectus_L	-5.6424	Angular_L	-9.3609	Temporal_Inf_R	-5.6335
	Frontal_Mid_Orb_L	-4.7284	Temporal_Pole_Mid_R	-4.8823	Cuneus_L	-9.2590	Frontal_Inf_Oper_L	-4.3361
	Frontal_Med_Orb_L	-4.1911	Fusiform_R	-4.6501	Occipital_Mid_R	-9.0837	ParaHippocampal_R	-4.2258
	Temporal_Pole_Mid_L	-4.0599	Cingulum_Ant_L	-4.1818	Occipital_Inf_R	-8.7592	Frontal_Sup_R	-3.9891
	Frontal_Inf_Orb_L	-3.7773	Cingulum_Post_L	-4.1181	Parietal_Sup_L	-8.4166	Temporal_Pole_Sup_L	-3.8030
			Cingulum_Mid_R	-4.1059	Occipital_Inf_L	-7.8248	Lingual_L	-3.8016
			Olfactory_R	-3.9628	Calcarine_R	-7.3398	Cuneus_L	-3.7809
			Precuneus_L	-3.9040	Lingual_L	-7.1325	Frontal_Sup_Medial_R	-3.5087
					Calcarine_L	-7.0919	Rolandic_Oper_L	-3.4915
					Occipital_Sup_L	-7.0552	Heschl_L	-3.4770
							Temporal_Mid_R	-3.4651
							Frontal_Sup_L	-3.4626
							ParaHippocampal_L	-3.4271
							Lingual_R	-3.4081
							Insula_R	-3.3862

Table 3 Brain structures and their corresponding group-level t-statistics are presented for each regional variable in correlation and contrast imaging.

predominantly seen in the posterior parietal and occipital regions, while reductions in α_{pi} were primarily noted in the prefrontal regions. A key difference between contrast and correlation imaging was noted for the external cortical input μ . In the contrast imaging, μ showed a significant decrease across broader regions, including the frontal cortex, middle and inferior temporal regions, and posterior cortex, whereas correlation imaging highlighted these decreases primarily in the occipital regions. These differences suggest that while some regions are central to both consciousness modulation and Xenon's effects, others play specialized roles in either maintaining consciousness or responding to the drug's pharmacological action.

Additionally, a significant reduction in the membrane potential of pyramidal populations across cerebral cortex was observed, particularly in the posterior parietal and occipital regions, as depicted in **Fig S1**.

2.5 Relationship between cortical stability, consciousness levels and Xenon concentration

As a final analysis cortical stability was correlated with consciousness levels to assess its utility as a global NCC metric and to obtain a deeper understanding within the context of dynamical systems theory. In this study, cortical stability corresponds to linear stability of the whole-cortex model. To quantify cortical stability, the eigenvalues of the Jacobian matrix derived from the whole-cortex model were analyzed. The Jacobian matrix was computed using model parameters estimated from Xenon-induced anaesthesia data. Specifically, parameters were estimated within successive one-second time windows, capturing the temporal dynamics of the cortical system under varying levels of consciousness. These time-specific parameter estimates were then used to construct a Jacobian matrix for each time window, allowing us to examine the temporal evolution of cortical stability throughout the recording. The stability of the system was assessed by analyzing the eigenvalues of the Jacobian matrix in each time window. Eigenvalues with negative real parts indicate a stable cortical state, while eigenvalues with positive real parts signify instability. The number of unstable eigenmodes, represented by eigenvalues with positive real parts, was used as a quantitative marker of cortical stability in this study. Each unstable eigenmode corresponds to a dimension in the system's state space where small perturbations grow over time, driving the

system toward instability. The count of these eigenmodes reflects the degree to which the system deviates from equilibrium.

Fig 4 illustrates the changes in cortical stability over time for individual subjects undergoing Xenon-induced anesthesia. Firstly, consistent cortical instability was observed across all subjects, indicating that the cerebral cortex remained in an unstable state throughout the duration of the Xenon-induced anesthesia. Secondly, the temporal patterns depicted in the figure reveal correlations between the number of unstable eigenmodes and consciousness levels. In general, a decrease in the number aligns with a reduction in consciousness, reflecting the stabilization of cortical dynamics. In contrast, a rising number signifies recovery phases, reflecting a shift towards destabilization of cortical activity. Notable subject-specific variations are apparent. Subject 14 displays a persistently constant number of unstable eigenmodes throughout much of the experiment. In contrast, subject 15 shows a rapid decline in instability associated with the increase of Xenon concentration levels rather than consciousness levels. The statistical analysis in **Table 4** supports and extends these observations. Significant positive correlations between cortical stability and consciousness levels were observed for 13 of 15 subjects ($p < 0.05$), indicating that greater cortical instability corresponds to reduced consciousness. However, individual variability is evident, as some subjects, such as subject 6, exhibit negligible correlations, suggesting that the relationship between cortical stability and consciousness levels is less pronounced or inconsistent in these cases. Moreover, the trajectories of unstable eigenmodes reveal transient fluctuations during both induction and recovery phases, suggesting dynamic transitions rather than abrupt state changes. These fluctuations represent intermediate cortical states as the brain transitions between less unstable and more unstable regimes.

Another important observation is that while cortical stability exhibits a significant correlation with Xenon concentration levels, its relationship with consciousness levels is notably stronger. This distinction is evident in both **Fig 4** and the correlation analyses in **Table 4**. For most subjects, the absolute correlation coefficients between cortical stability and consciousness levels are higher than those with Xenon concentration levels. This suggests that cortical stability, as reflected by the number of unstable eigenmodes, is more closely aligned with changes in consciousness levels.

Additionally, a notable dissociation between the level of consciousness and Xenon concentration levels is evident in both the figure and the statistical results. While Xenon concentration levels increase steadily during the induction phase, the corresponding decrease in consciousness levels often exhibits a time delay. This lag suggests that the pharmacological effects of Xenon on cortical activity require a critical threshold or cumulative exposure before manifesting as observable changes in consciousness levels. For example, in several subjects, such as subject 18, the level of consciousness remains relatively stable for a period despite rising Xenon concentration, before eventually declining sharply.

Substantial inter-subject variability is also apparent in the duration and degree of loss of consciousness. Some subjects, such as subjects 2 and 11, experienced prolonged periods of unconsciousness, whereas other subjects, such as subject 6, demonstrated relatively brief or incomplete loss of consciousness. This variability highlights individual differences in susceptibility to Xenon-induced anaesthesia, potentially reflecting underlying neurophysiological or pharmacokinetic differences.

	Cortical stability & consciousness level		Cortical stability & Xenon concentration level		Consciousness level & Xenon concentration level	
	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value
Subject 1	0.5930	<0.0001	0.0397	0.1922	-0.0510	0.0940
Subject 2	0.4411	<0.0001	0.0380	0.2256	-0.4221	<0.0001
Subject 3	0.3607	<0.0001	-0.0046	0.9966	-0.1828	<0.0001
Subject 4	0.4941	<0.0001	-0.1255	<0.0001	-0.3344	<0.0001
Subject 5	-0.1578	<0.0001	0.8057	<0.0001	-0.2521	<0.0001
Subject 6	0.0252	0.3726	-0.4206	<0.0001	-0.1839	<0.0001
Subject 7	0.2298	<0.0001	0.0837	0.0341	-0.6099	<0.0001
Subject 8	0.5684	<0.0001	-0.5621	<0.0001	-0.6321	<0.0001
Subject 9	0.4014	<0.0001	-0.0216	0.6221	-0.5739	<0.0001
Subject 10	0.6081	<0.0001	-0.6730	<0.0001	-0.4792	<0.0001
Subject 11	0.6058	<0.0001	-0.4715	<0.0001	-0.0944	0.0020
Subject 12	0.0818	0.0038	0.4340	<0.0001	-0.2785	<0.0001
Subject 13	0.6672	<0.0001	0.6236	<0.0001	0.6973	<0.0001
Subject 14	0.0021	0.9615	-0.1149	0.0067	-0.1644	<0.0001
Subject 15	-0.0696	0.0333	-0.7059	<0.0001	0.2055	<0.0001

Table 4 Within subject correlation between cortical stability, consciousness levels, and Xenon concentration levels. Correlation coefficients and corresponding p-values for the possible pairings of cortical stability, consciousness levels (i.e. ACPT accuracy), and Xenon concentration levels for each individual subject.

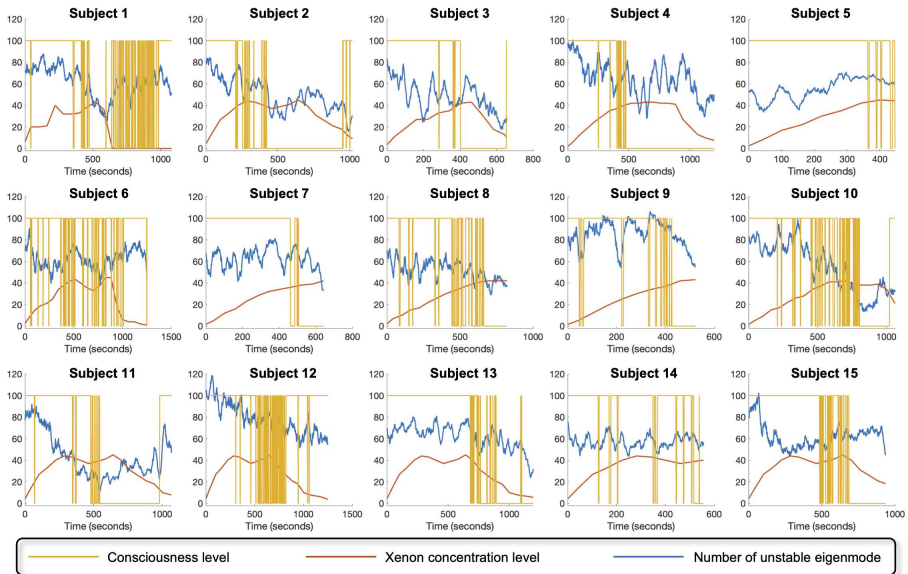


Fig. 4 Evolution of cortical stability during Xenon-induced anaesthesia for all 15 subjects. Cortical stability is represented by the number of unstable eigenvalues (blue line). The yellow lines indicate the level of consciousness/responsiveness (i.e. ACPT accuracy), with 100 denoting conscious state and 0 denoting unconscious state. Red lines represent the concentration level of Xenon anaesthesia administered over time.

3 Discussion

This study aimed to identify critical neurobiological correlates of consciousness and establish a framework to explain the neural mechanisms which are correlated with, and likely also regulate, the level of global consciousness. To achieve this a whole-cerebral-cortex model employing interconnected NMMs was proposed, with each NMM representing a specific region of interest in the cortex. The model parameters consist of regional neurophysiological variables and effective connectivity, which were estimated from source-level MEG time series of healthy human subjects exposed to varying concentration levels of Xenon to induce loss of consciousness/responsiveness and recover from it. The level of consciousness was characterised by a subject's responsiveness level measured by ACPT accuracy (Fig 1c) [39]. To

identify the critical NCCs, the relationship between consciousness/responsiveness levels and the time-evolving parameter estimates of the whole-cortex model was examined. The key findings are as follows.

First, correlation between consciousness levels and centrality measures of brain regions in the posterior parietal and occipital regions was identified (**Fig 2a** and **b**). Besides, there are hitherto few studies underscoring posterior parietal-to-occipital connectivity in the reduction of consciousness [19, 47]. However, in **Fig 2c**, we demonstrated that the strengths of several connections from brain structures in the parietal lobe to those in the occipital lobe are significantly correlated with the level of consciousness. Second, strong correlations were found between consciousness levels and the strength of connections from posterior parietal to prefrontal regions (**Table 2**). This suggests that the flow of information or activity from the posterior parietal areas (involved in processes such as spatial attention and awareness of the body's position in space) to the prefrontal cortex (responsible for complex cognitive behaviour, decision-making, and moderating social behaviour) is correlated with the level of consciousness. The posterior parietal region provides the prefrontal cortex with sensory and spatial information necessary for conscious awareness and higher-order cognitive processes. This pattern of unidirectional connectivity suggests that the posterior parietal region's role in consciousness is not as a receiver of processed information from the prefrontal cortex but rather as an active contributor to the conscious experience, possibly by integrating sensory information and relaying it forward.

Third, consciousness levels were significantly correlated with intra-posterior parietal connection strength, but not with intra-prefrontal connections (**Table 2**). This underscores the significance of internal connectivity within the posterior parietal area for sustaining global conscious states. The absence of a significant correlation within the prefrontal cortex suggests that while it is important for higher-order cognitive functions and decision-making, the strength of its internal connections is not influential on the level of consciousness. This is consistent with previous studies on brain lesion patients who sustained bilateral prefrontal cortex. While they are impaired in social and emotional domains, overall consciousness, especially in the sense of sensory and qualitative aspects, was remarkably preserved [48–52].

Fourth, it was shown in **Fig 3** that regional variables in the posterior parietal and occipital regions were significantly positively correlated with consciousness levels. Low-level consciousness was associated with reduced regional excitatory synaptic connection strength (α_{pe} , α_{ep}), diminished afferent input (μ) and lowered membrane potentials of pyramidal neuronal populations in those regions. This observation not only aligns with existing literature demonstrating that Xenon attenuates excitatory synaptic transmission [46, 53] but also highlights how this effect varies in relation to consciousness levels across the cerebral cortex.

Collectively, while the integrated information theory suggests that the posterior brain regions are critical for consciousness due to the grid-like structures in the visual cortex [54], which are highly efficient at generating large amounts of integrated information, our study independently supports this conclusion by analyzing the neurophysiological processes associated with consciousness.

Fifth, critical regional variable estimates were mapped onto functional networks in **Table S3**. Results showed that regional excitatory synaptic connection parameters in VN, DMN, and executive control network (ECN) decreased during reductions in consciousness, concurring with attenuation of the afferent input in all considered functional networks. While prior research has underscored the importance of connectivity alterations within functional networks across diverse levels of consciousness [24, 26, 55], this study advances understanding by pinpointing the precise neurophysiological variables within these networks that underpin varying levels of consciousness.

Finally in **Fig 4**, it was found that cerebral cortex never stabilized during reductions of consciousness, extending the idea of instability of resting brain networks [56] while supporting the observation obtained from monkey subjects [57]. Besides, previous studies have established that loss of consciousness is often associated with stabilized neural dynamics, as measured through decreases in brain complexity and increases in low-frequency power

[58, 59]. Our results corroborate these findings by demonstrating that reductions in the number of unstable eigenmodes are associated with lower levels of consciousness in most subjects. This reflects a stabilization of cortical activity during unconscious states, suggesting that the brain transitions toward a dynamically constrained regime under Xenon anaesthesia. However, the transient fluctuations observed during induction and recovery phases offer a more nuanced view than the abrupt state changes reported in some prior literature [60, 61], emphasizing the dynamic and gradual nature of these transitions. Another notable contribution of this study is the dissociation observed between Xenon concentration levels and consciousness levels, highlighting individual pharmacodynamic differences. While prior research has indicated that anaesthetic effects on consciousness often follow nonlinear dose-response relationships [62], our findings extend this understanding by demonstrating a temporal dissociation between Xenon concentration increases and reductions in consciousness. Moreover, the substantial inter-subject variability aligns with existing evidence of heterogeneity in anaesthetic responses [63] but further underscores the importance of individual neurophysiological and pharmacokinetic factors in determining the trajectory of consciousness loss and recovery. Future work could explore these individual differences through more detailed modeling of subject-specific parameters to elucidate their neurobiological underpinnings.

In this study, Xenon was employed to modulate the subject's global consciousness levels. Future research should consider utilizing a range of anaesthetics that target different molecular pathways, offering additional universal insights into network connectivity, local dynamics, and cortical stability across various consciousness levels. Moreover, although we treat responsiveness and global consciousness interchangeably in this paper, future work should be directed at using this framework to better understand NCCs by disentangling ideas around responsiveness, connectedness and consciousness [64]. This framework can be applied to various brain conditions (e.g., sleep [65], brain injury, deep anesthesia) and extended to animal models [66, 67], offering insights into conserved neurophysiological mechanisms and dynamic cortical behaviours to advance understanding of NCCs and brain function.

4 Methods

4.1 Dataset

The present study utilized data collected from previous research that investigated changes in EEG/MEG signals during Xenon-anaesthetic-induced reductions of consciousness. For details, see [39]. Some key points of the data are summarized below.

Male participants, aged between 20 and 40 years, who were right-handed and had a body mass index (BMI) within the range of 18 to 30, were recruited for the study. Female volunteers were excluded to avoid potential effects of pregnancy on EEG readings during anaesthesia. Individuals with a history of neurological disorders, epilepsy, mental health conditions, cardiovascular or respiratory diseases, motion sickness, asthma, claustrophobia, obstructive sleep apnea, or recent use of prescription, recreational, or psychoactive drugs were not eligible to participate.

During the recording session, participants were asked to keep their eyes closed and remain still. Neural signals were recorded using a 306-channel MEG system (Elekta Neuromag TRIUX, Elekta Oy, Finland) at a sampling rate of 1000 Hz.

MEG recordings were obtained during Xenon-induced anaesthesia at a concentration of 1.3 MAC-awake (42% Xe/O₂). Prior to the induction of anaesthesia, participants and the attending nurse or clinical observer were informed about the start of gas administration. MEG data collection was initiated simultaneously with the anesthesiologist beginning gas delivery, marking the onset of the experiment. Throughout the session, responsiveness was monitored using the auditory continuous performance task (ACPT). Participants wore MEG-compatible headphones that delivered binaural auditory tones at fixed stereo amplitude with frequencies of either 1 kHz or 3 kHz. The tones were presented at random intervals

ranging between 2 and 4 seconds. Participants were directed to respond promptly by pressing buttons on two handheld devices, using the left button to indicate low-frequency tones and the right button for high-frequency tones. The accuracy of responses in the ACPT was used as a measure of responsiveness, where a correct response was scored as 100, and a failure to respond or an incorrect response (rarely occurring) was scored as 0.

A concentration of 42% Xe/O₂ was chosen to induce a loss of responsiveness in most participants, as supported by previous research [68]. Higher concentrations were avoided since the study was conducted outside a hospital setting, necessitating strict adherence to safety protocols as outlined in the ethics approval. The Xenon concentration was manually adjusted to reach the target equilibrium and maintained at that level until the anesthesiologist or clinical observer deemed it unsafe to proceed. At this point, the gas administration was terminated, and a washout phase with 100% O₂ was initiated.

To ensure the reliability of the MEG data, artifact removal and signal preprocessing were performed. This process included notch filtering to eliminate power line noise and additional steps to address artifacts, such as those caused by eye movements. These measures were essential to improve the quality of the recordings and reduce interference from non-neuronal sources, facilitating accurate analysis. For source reconstruction, an atlas-guided approach employing the linearly constrained minimum variance (LCMV) beamformer method was utilized [37, 69]. To mitigate the depth bias typically associated with this technique, the beamformer weights were adjusted through normalization [70]. Given that MEG predominantly captures signals from superficial brain regions, the analysis was confined to the gray matter of the cerebral cortex. Specifically, it examined 78 voxels, each representing the source voxel with the highest power within one of 78 brain regions defined by the AAL atlas in the cerebral cortex [41].

4.2 Jansen-Rit neural mass model

The canonical Jansen-Rit neural mass model (NMM) [38] was used in this study to represent the 78 cortical structures of the brain at a macroscopic scale. This model has been extensively utilized in prior research [37, 71–74] and is particularly suitable for simulating source-level MEG signals. **Fig 1a** depicts the schematic of the NMM, which consists of pyramidal neurons, excitatory interneurons, and inhibitory interneurons.

The pyramidal population receives input μ and sends signals to both the excitatory and inhibitory populations. These populations, in turn, provide feedback to the pyramidal neurons, with excitatory neurons delivering positive feedback and inhibitory neurons contributing negative feedback. The model represents the dynamics of each population by their mean membrane potential v_n , which evolves over time due to cumulative post-synaptic membrane potentials v_{mn} , mediated by synaptic connections. Each synapse is characterized by a connection strength parameter α_{mn} . In this context, m denotes the pre-synaptic neuronal population and n refers to the post-synaptic neuronal population.

The post-synaptic membrane potentials are defined as

$$v_{mn}(t) = \alpha_{mn} \int_0^t h_{mn}(t-t')g(v_m(t')) dt', \quad (1)$$

where the post-synaptic response kernel $h_{ba}(t)$ is defined as

$$h_{mn}(t) = \eta(t) \frac{t}{\tau_{mn}} \exp\left(-\frac{t}{\tau_{mn}}\right), \quad (2)$$

and $\eta(\cdot)$ is Heaviside step function. The integral can be expressed as coupled first-order differential equations

$$\begin{aligned} \frac{dv_{mn}}{dt} &= z_{mn}, \\ \frac{dz_{mn}}{dt} &= \alpha_{mn}g(v_m) - \frac{2}{\tau_{mn}}z_{mn} - \frac{1}{\tau_{mn}^2}v_{mn}, \end{aligned} \quad (3)$$

where τ_{mn} is the synaptic time constant, and α_{mn} is the connection strength. The nonlinear firing rate function $g(v_m)$ has various forms and this study used a sigmoid function as suggested by some previous studies [37, 72, 73]

$$g(v_m) = \frac{1}{2} \left(\operatorname{erf} \left(\frac{v_m - v_0}{\sqrt{2}\varsigma} \right) + 1 \right), \quad (4)$$

where v_0 and ς represent the mean and variance of firing thresholds, respectively [71, 75, 76]. The pyramidal membrane potential is modeled as all contributing signals

$$v_p(t) = \mu(t) + v_{ip}(t) + v_{ep}(t), \quad (5)$$

which is corresponding to the recorded source-level MEG signals.

The model parameter vector is

$$\boldsymbol{\theta} = [\mu, \alpha_{ip}, \alpha_{pi}, \alpha_{pe}, \alpha_{ep}]^\top, \quad (6)$$

while the state vector captures the fast-changing dynamics

$$\mathbf{x} = [v_{ip}, z_{ip}, v_{pi}, z_{pi}, v_{pe}, z_{pe}, v_{ep}, z_{ep}]^\top. \quad (7)$$

They are concatenated into an extended state vector

$$\boldsymbol{\xi} = [\mathbf{x}^\top, \boldsymbol{\theta}^\top]^\top. \quad (8)$$

The continuous-time system is defined by the following equation

$$\dot{\boldsymbol{\xi}} = \mathbf{A}\boldsymbol{\xi} + \mathbf{B}\boldsymbol{\xi} \circ g(\mathbf{C}\boldsymbol{\xi}), \quad (9)$$

where $\circ$ represents element-wise multiplication. To estimate the parameters, the model is discretized and incorporates a noise term $\mathbf{w}_t$ accounting for process noise and modelling error

$$\boldsymbol{\xi}_{t+1} = \mathbf{A}_\delta \boldsymbol{\xi}_t + \mathbf{B}_\delta \boldsymbol{\xi}_t \circ g(\mathbf{C}_\delta \boldsymbol{\xi}_t) + \mathbf{w}_t. \quad (10)$$

Here, $\mathbf{A}$, $\mathbf{B}$, and $\mathbf{C}$ are defined in Supplementary Material 1.1.

The measurement model links the observed MEG time series to the averaged membrane potential of pyramidal population

$$y_t = \mathbf{H}\boldsymbol{\xi}_t + v_t. \quad (11)$$

Here, $\mathbf{H}$ is the measurement matrix, and v_t is Gaussian white noise representing measurement noise. The matrix $\mathbf{H}$ computes the pyramidal membrane potential as specified in Eq. (5).

4.3 Whole-cortex model

The coupling between cortical regions is modeled by connecting the output firing activity of the pyramidal population in region a to the input of the pyramidal population in region b via a post-synaptic response kernel. Pyramidal populations integrate post-synaptic membrane potentials induced by firing rates of all connected cortical regions. The parameter w_{ab} represents the connectivity strength between region a and region b , capturing inter-regional interactions rather than local synaptic dynamics. This hierarchical organization allows for a biologically plausible representation of regional interactions.

For a network comprising N cortical regions (where $N = 78$ in this study because there are 78 brain structures considered in the whole-cortex model), the neural mass model (NMM) for a single region b is defined by its state vector

$$\mathbf{x}^b = [\mu^b, u^b, v_{ip}^b, z_{ip}^b, v_{pi}^b, z_{pi}^b, v_{pe}^b, z_{pe}^b, v_{ep}^b, z_{ep}^b]^\top, \quad (12)$$

where v and z denote the mean membrane potential of a particular type of neuronal population and its time derivative, respectively. The input μ^b captures the summation of post-synaptic membrane potentials from all connected regions (including self-connection), and u^b represents its rate of change.

The temporal evolution of neural mass model states in region b is defined as

$$\begin{aligned} \frac{d\mu^b}{dt} &= u^b, & \frac{du^b}{dt} &= \sum_{b=1}^N w_{ab}g(\mu^a + v_{ep}^a + v_{ip}^a) - \frac{2}{\tau_d}u^b - \frac{1}{\tau_d^2}\mu^b, \\ \frac{dv_{ip}^b}{dt} &= z_{ip}^b, & \frac{dz_{ip}^b}{dt} &= \alpha_{ip}^b g(v_{pi}^b) - \frac{2}{\tau_{ip}}z_{ip}^b - \frac{1}{\tau_{ip}^2}v_{ip}^b, \\ \frac{dv_{pi}^b}{dt} &= z_{pi}^b, & \frac{dz_{pi}^b}{dt} &= \alpha_{pi}^b g(v_{ip}^b + v_{ep}^b + \mu^b) - \frac{2}{\tau_{pi}}z_{pi}^b - \frac{1}{\tau_{pi}^2}v_{pi}^b, \\ \frac{dv_{pe}^b}{dt} &= z_{pe}^b, & \frac{dz_{pe}^b}{dt} &= \alpha_{pe}^b g(v_{ip}^b + v_{ep}^b + \mu^b) - \frac{2}{\tau_{pe}}z_{pe}^b - \frac{1}{\tau_{pe}^2}v_{pe}^b, \\ \frac{dv_{ep}^b}{dt} &= z_{ep}^b, & \frac{dz_{ep}^b}{dt} &= \alpha_{ep}^b g(v_{pe}^b) - \frac{2}{\tau_{ep}}z_{ep}^b - \frac{1}{\tau_{ep}^2}v_{ep}^b. \end{aligned} \quad (13)$$

Here, the parameters α and τ represent the connection strength and time constant, respectively, for local synaptic dynamics, while w_{ab} quantifies inter-regional connectivity strength. Inputs from region a modulate the activity of region b , as reflected in the term $\sum_{b=1}^N w_{ab}g(\mu^a + v_{ep}^a + v_{ip}^a)$.

The entire cortical network, comprising N regions, is represented by the concatenated state vector

$$\mathbf{X} = [\mathbf{x}^1, \mathbf{x}^2, \dots, \mathbf{x}^N]^\top. \quad (14)$$

The dynamics of the full network are captured by

$$\dot{\mathbf{X}} = f(\mathbf{X}), \quad (15)$$

where f defines the system of equations mapping $\mathbb{R}^{10N}$ to $\mathbb{R}^{10N}$, as specified by Eq. (13).

This formulation allows for the modeling of both local neural dynamics and large-scale cortical interactions, providing a biologically grounded framework for simulating brain activity.

4.4 Parameter estimation from data

The parameter estimation contains two steps. The first step involves applying the semi-analytical Kalman filter that was developed in “NeuroProcImager” [37] to infer the parameters in each neural mass model from MEG data. This method provides unbiased estimates of both state vectors and parameters by minimizing the mean square error, assuming the underlying states follow a Gaussian distribution. The inhibitory connection parameter α_{ip} was fixed to a constant value during the filtering process, as Xenon is known to have minimal impact on GABAergic activity [77]. This fixed value was derived from earlier studies [71]. To initialize the Kalman filter, the *a posteriori* state estimate $\hat{\mathbf{x}}_0^+$ and covariance matrix $\hat{\mathbf{P}}_0^+$ at $t = 0$ were determined based on the mean and covariance of simulated data corresponding to the resting state. Recognizing that the initial filter configuration might not perfectly align with the MEG data, the first five seconds of the recordings were excluded from the analysis. This step ensured that the filter had sufficient time to stabilize and produce reliable estimates. Small constant values ($5 \mu V$) were assigned to the model noise covariance $\mathbf{Q}$ to prevent full convergence of the filter and ensure continuous influence from new observations. Measurement noise was set to $1 \mu V$, following the recommendations of prior research [37, 72]. The semi-analytical Kalman filter was applied to each source time series to estimate time-varying regional NMM parameters ($\hat{\alpha}_{mn}, \hat{\mu}$) and state variables ($\hat{v}_{mn}, \hat{z}_{mn}$).

To determine the effective connectivity between regions (i.e., w_{ab}), the input μ to region b was computed as the summation of post-synaptic membrane potentials caused by firing rates from other regions

$$\mu^b(t) = \sum_{a=1}^N w_{ab} \int_0^t h_{ab}(t-t') g(v_p^a(t')) dt', \quad (16)$$

where the kernel $h_{ab}(t)$ is defined as

$$h_{ab}(t) = \eta(t) \frac{t}{\tau_d} \exp\left(-\frac{t}{\tau_d}\right), \quad (17)$$

where τ_d is the decay time constant for inter-regional synaptic connections [78]. The estimation of w_{ab} was carried out using multivariate linear regression on data segmented into one-second intervals. This temporal resolution is supported by neurophysiological evidence, as inter-regional interactions are known to integrate information over relatively longer time scales compared to local neuronal dynamics. Such an approach is consistent with established methodologies in the field [79–82]. This multivariate linear regression was also adopted to handle the computational demands of the whole-cortex model, which has a high dimensionality (780 state variables and 6396 parameters), making Kalman filters computationally expensive and impractical. Specifically, let $\mathbf{M}$ represent the matrix of estimated μ for all regions, $\mathbf{Y}$ the matrix with each column containing the convolution of the v_p estimates with the post-synaptic response kernel, $\mathbf{W}$ the effective connectivity coefficients, and $\mathbf{E}$ the intercept matrix which can explain signals from the thalamus. The linear regression model is expressed as

$$\mathbf{M} = \mathbf{Y}\mathbf{W} + \mathbf{E}. \quad (18)$$

The maximum likelihood estimator for $\mathbf{W}$ is

$$\hat{\mathbf{W}} = (\mathbf{Y}^\top \mathbf{Y})^{-1} \mathbf{Y}^\top \mathbf{M}. \quad (19)$$

Connectivity matrices $\mathbf{W}$ were computed for each 1-second time window, enabling the derivation of time-varying connectivity patterns across MEG recordings. This strategy effectively balances computational efficiency and estimation accuracy, avoiding the prohibitive memory and processing requirements of Kalman filtering in large-scale models.

The inference framework was validated by examining the prediction error of the Kalman filter, which followed an approximately normal distribution with a mean close to zero (Fig S2). The effective connectivity estimates obtained from the multivariate regression model demonstrated a strong correlation with the observed data, achieving minimum $R^2 \geq 0.89$. This approach successfully combined the precision of Kalman filtering for local parameters with the efficiency of linear regression for inter-regional connectivity, making it a robust solution for whole-cortex modeling.

4.5 Local stability near the fixed points for whole-cortex model

The equilibrium points of the whole-cortex model, denoted by $\mathbf{X}^*$, were determined by setting $\dot{\mathbf{X}} = 0$ in Eq. (15) and solving the resulting equations. To identify equilibrium points near the model's estimated states, the solver utilizes these estimates as initial conditions for the numerical computation of the solution. To study the behavior of the system near equilibrium points, the whole-cortex model was linearized, and the Jacobian matrix at the equilibrium point $\mathbf{X}^*$ was calculated.

The system comprises N cortical regions, each represented by a neural mass model of 10 dimensions. As a result, the Jacobian matrix $\mathbf{J} \in \mathbb{R}^{10N \times 10N}$ for the entire model is structured as follows

$$\mathbf{J} = \text{diag}(\mathbf{M}_1, \dots, \mathbf{M}_N) + \begin{bmatrix} & \mathbf{0}_{9,10N} & \\ \mathbf{\Omega}_{1,1} & \dots & \mathbf{\Omega}_{N,1} \\ & \mathbf{0}_{9,10N} & \\ \mathbf{\Omega}_{1,2} & \dots & \mathbf{\Omega}_{N,2} \\ \vdots & \ddots & \vdots \\ & \mathbf{0}_{9,10N} & \\ \mathbf{\Omega}_{1,N} & \dots & \mathbf{\Omega}_{N,N} \end{bmatrix}, \quad (20)$$

where $\mathbf{\Omega}_{a,b}$ captures the coupling between regions a and b , defined as

$$\mathbf{\Omega}_{a,b} = [w_{ba}\nu_1 \ 0 \ 0 \ w_{ba}\nu_1 \ w_{ba}\nu_1 \ 0 \ 0 \ 0 \ 0 \ 0], \quad (21)$$

with $\nu_1 = g'(\mu^b + v_{ip}^b + v_{ep}^b)$. The term $\mathbf{0}_{k,l}$ represents a matrix of zeros (size $k \times l$), and $\text{diag}(\mathbf{M}_1, \dots, \mathbf{M}_N)$ is the block diagonal matrix with components $\mathbf{M}_a \in \mathbb{R}^{10 \times 10}$, given by

$$\begin{bmatrix} & & \mathbf{0}_{5,5} & & & & & \mathbf{I}_{5,5} & & \\ -\frac{1}{\tau_{ip}^2} & \alpha_{ip}^a g'(v_{pi}^a) & 0 & 0 & 0 & \frac{-2}{\tau_{ip}} & 0 & 0 & 0 & 0 \\ \alpha_{pi}^a \nu_2 & \frac{-1}{\tau_{pi}^2} & 0 & \alpha_{pi}^a \nu_2 & \alpha_{pi}^a \nu_2 & 0 & \frac{-1}{\tau_{pi}} & 0 & 0 & 0 \\ \alpha_{pe}^a \nu_2 & 0 & \frac{-1}{\tau_{pe}^2} & \alpha_{pe}^a \nu_2 & \alpha_{pe}^a \nu_2 & 0 & 0 & \frac{-2}{\tau_{pe}} & 0 & 0 \\ 0 & 0 & \alpha_{ep}^a g'(v_{pe}^a) & \frac{-1}{\tau_{ep}^2} & 0 & 0 & 0 & 0 & \frac{-2}{\tau_{ep}} & 0 \\ 0 & 0 & 0 & 0 & \frac{-1}{\tau_d^2} & 0 & 0 & 0 & 0 & \frac{-2}{\tau_d} \end{bmatrix}. \quad (22)$$

Here $\mathbf{I}_{k,k}$ is the identity matrix of size $k \times k$ and $\nu_2 = g'(\mu^a + v_{ip}^a + v_{ep}^a)$.

To assess linear stability of the model, the eigenvalues λ_k of $\mathbf{J}$ were computed by performing singular value decomposition

$$\mathbf{J} = \mathbf{U} \mathbf{\Lambda} \mathbf{U}^\top. \quad (23)$$

Here Λ is a diagonal matrix containing the eigenvalues and U is an orthonormal matrix containing eigenvectors (i.e., eigenmodes). The real part of each eigenvalue determines stability along the corresponding eigenvector. A negative real part indicates stability, meaning that small perturbations along the eigenvector decay over time, causing the system to return to equilibrium. Conversely, a positive real part implies instability, where small perturbations grow, driving the system away from equilibrium. A zero real part indicates neutral stability. In conclusion, the system is unstable even there is at least one eigenvalue with positive real part, while it is stable when all eigenvalues have negative real parts.

The count of unstable eigenvalues reflects the system's level of instability, indicating the number of eigenvector-defined directions in which the system is prone to diverge. In this study, the number of unstable eigenvalues was used to track shifts in cortical stability. In summary, linear stability analysis provides critical insights into a system's ability to withstand small disturbances. When applied to the study of loss of consciousness, this method helps elucidate how cortical dynamics evolve between stable and unstable states, offering a framework to understand the mechanisms driving transitions into unconscious states and relate NCCs to consciousness levels.

4.6 In-degree and out-degree centrality

In-degree centrality in the inter-regional connectivity matrix refers to the measure of the total weight of incoming connections that a brain region receives from other regions. Out-degree centrality represents the measure of the total weight of outgoing connections originating from a brain region. These centrality measures help identify regions that play significant roles in receiving or transmitting weighted connections, highlighting their importance in information integration and communication within the brain network.

4.7 Permutation tests

The foundational principles of permutation tests are extensively explained in the works of Nichols and Holmes [83, 84]. The procedure for performing a permutation test consists of the following steps: Begin with several observations under two separate conditions. Let N represent the total number of potential label permutations, and t_i indicate the test statistic corresponding to the i -th permutation. The permutation distribution is then formed by aggregating all t_i values across every possible permutation. Define the observed test statistic from the original experimental labels as T . Assuming the null hypothesis, each t_i has an equal likelihood of occurrence, enabling the computation of the p-value by determining the fraction of the permutation distribution that is at least as extreme as T . If this p-value falls below the significance level α , the null hypothesis H_0 is rejected at the α level.

As an illustration, a correlation analysis was performed to examine the relationship between responsiveness and intra-prefrontal connection strength, utilizing data from 15 participants. For each subject, a correlation coefficient was calculated, resulting in 15 individual values. The statistic of interest was defined as the average of these coefficients. Under the null hypothesis, which assumes no correlation between responsiveness and intra-prefrontal connection strength, relabeling was executed by randomly assigning a factor of either 1 or -1 to the correlation coefficients. The statistic was then recomputed for each relabeling. This procedure was repeated extensively (100000 times in this case) to construct the permutation distribution of the statistic. The proportion of the distribution with values as extreme as or more extreme than T was subsequently calculated to obtain the p-value. Finally, the p-value was compared against the significance threshold α to determine whether to reject the null hypothesis H_0 .

4.8 Multiple comparisons permutation tests

In our study, the challenge of multiple comparisons arises when simultaneously testing hypotheses across numerous voxels or connections in the human brain for multiple subjects. Specifically, statistical calculations are performed using data from each subject for every voxel or connection, generating a p-value corresponding to the null hypothesis for each voxel or connection. Controlling Type I errors collectively is essential to ensure that the probability of mistakenly identifying any voxel or connection as significant remains below the specified threshold α . To address this, we employ a testing procedure developed by Nichols and Holmes, which effectively manages Type I errors by providing adjusted p-values. Readers are encouraged to read [83].

To ensure the validity of an omnibus test under the assumption that all null hypotheses across voxels or connections are true, label exchangeability under the omnibus null hypothesis must be preserved. This condition is crucial for any summary statistic derived from voxel- or connection-level analyses, such as the maximum statistic. The critical threshold for significance is obtained by evaluating the distribution of the maximum statistic across the entire volume of interest. Instead of calculating permutation distributions for individual voxels or connections, a permutation-based approach is used to generate the distribution of the maximal statistic. A voxel or connection is deemed significant if its test statistic surpasses the $j + 1$ -th largest value in this permutation-derived distribution, where $j = \lceil \alpha N \rceil$ and N is the total number of permutations. The corrected p-value for each voxel or connection is determined by calculating the fraction of the permutation distribution of maximum statistics that are equal to or greater than the observed statistic. This approach provides a practical and robust means of adjusting for multiple comparisons across the entire dataset, ensuring control of the family-wise error rate.

For instance, in Subsection 2.1, we identify brain structures where the time-varying in-degree centrality significantly correlates with responsiveness. We conduct a correlation analysis between in-degree centrality and responsiveness for each brain structure and subject, resulting in an $n \times m$ correlation coefficient matrix. Here n denotes the number of subjects and m represents the number of brain structures. The t-statistic for each brain structure is computed using the correlation coefficients from the n subjects, yielding a $1 \times m$ t-statistic vector. This vector summarizes the correlation information across subjects.

The null hypothesis for each brain structure assumes no correlation between time-varying in-degree centrality and responsiveness. To test this hypothesis, we use a permutation approach by randomly permuting the correlation coefficient matrix while maintaining the null hypothesis. Each element is randomly multiplied by either 1 or -1 . The t-statistic vector is recalculated for the permuted matrix, and the maximum and minimum values are recorded. Repeating this permutation process N times generates permutation distributions for the maxima and minima. For each brain structure, the null is rejected if the observed t-statistic exceeds the $(100 - \alpha/2)$ th percentile of the maximum value distribution or falls below the $(\alpha/2)$ th percentile of the minimum value distribution.

Data Availability

The source-level MEG data will be made publicly accessible upon the publication of the manuscript.

Code Availability

The MATLAB code for the whole-cortex model, parameter estimation, and dynamic cortical stability analysis is accessible in the GitHub repository NeuroProcImager-Pro (<https://github.com/yundumbledore/NeuroProcImager-Pro>).

Ethical Statement

The data used in this study was collected in accordance with Alfred Hospital HREC approval number 260/12.

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