Sub-Second Fluctuation between Top-Down and Bottom-Up Modes Distinguishes Diverse Human Brain States

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Abstract

Information continuously flows between regions of the human brain, exhibiting distinct patterns that dynamically shift across states of consciousness, cognitive modes, and neuropsychiatric conditions. In this study, we introduce Relative Phase Analysis (RPA), a method that leverages phase-lead/lag relationships to reveal the real-time dynamics of dominant directional patterns and their rapid transitions. We demonstrate that the human brain switches on a sub-second timescale between a top-down mode–where anterior regions drive posterior activity–and a bottom-up mode, characterized by reverse directionality. These dynamics are most pronounced during full consciousness and gradually become less distinct as awareness diminishes. Furthermore, we find from simultaneous EEG–fMRI recordings that the top-down mode is expressed when higher-order cognitive networks are more active while the bottom-up mode is expressed when sensory systems are more active. Moreover, comparisons of an attention deficit hyperactivity disorder (ADHD) inattentive cohort with typically developing individuals reveal distinct imbalances in these transition dynamics, highlighting the potential of RPA as a diagnostic biomarker. Complementing our empirical findings, a coupled-oscillator model of the structural brain network recapitulates these emergent patterns, suggesting that such directional modes and transitions may arise naturally from inter-regional neural interactions. Altogether, this study provides a framework for understanding whole-brain dynamics in real-time and identifies sub-second fluctuations in top-down versus bottom-up directionality as a fundamental mechanism underlying human information processing.

Keywords: Reletive Phase Dynamics, Sub-Second Fluctuation, Internal-External Directionality Fluctuation, Human Brain State

1 Introduction

Information continuously flows between distinct regions of the human brain [1–12], forming characteristic patterns that dynamically reconfigure across states of consciousness [1, 4, 5], cognitive modes [3, 10, 11], and neuropsychiatric conditions [13–16], and understanding these patterns is essential for unraveling the neural mechanisms underlying the multifaceted nature of human behavior.

A key challenge in neuroscience is to reliably capture and interpret the directionality and flow of information across distributed brain regions. In this context, the conceptual distinction between top-down and bottom-up information flow has emerged as a pivotal framework for understanding inter-regional communication [3, 8–11, 17].

Top-down signals, emanating from higher-order cognitive regions, are thought to modulate sensory processing and guide goal-directed behavior, whereas bottom-up flows, originating in sensory cortices, underpin the encoding of environmental stimuli. Due to limitations in temporal resolution, neuroimaging studies have largely focused on functional networks biased toward these directional modalities, as observed in Blood Oxygen Level-Dependent (BOLD) activity patterns from functional magnetic resonance imaging (fMRI) [3, 17–21]. In contrast, electrophysiological investigations using electroencephalogram (EEG) and electrocorticography (ECoG)—with their superior temporal resolution—have more directly addressed the flow directionality and demonstrated its association with distinct cognitive processes [5, 7–11]. Yet, the dynamics governing the transitions between these directional modes remain largely enigmatic: How do these dominant patterns shift in real time? Moreover, can the transition dynamics observed in brain waves be systematically linked to functional networks derived from BOLD activity?

Traditional measures applied to electrocortical signals—such as traveling wave propagation metrics [8–11] and phase based indices [22, 23]–have provided valuable insights into specific aspects of inter-regional directionality. Numerous phase based indices quantify the probability that the phase of one signal consistently leads or lags another over defined time windows, thereby capturing asymmetric interactions in a time-averaged manner [5, 7, 23]. Similarly, traveling wave analyses, which track the propagation of neural mass activity within selected brain regions, have been linked to distinct cognitive functions, particularly in relation to bottom-up and top-down directionalities [9–11]. Despite their utility, these approaches are constrained by their reliance on time-averaging (in the case of phase-based measures) and their focus on preselected local regions (in traveling wave analyses), limiting our understanding of whole-brain dynamics in real-time.

Here, we introduce a new framework — the Relative Phase Analysis (RPA) — which focuses on the top-down and bottom-up modes and the transitions between them. By exploiting phase-lead/lag relationships in the brain waves, our approach provides a robust method to assess the real-time dynamics across the entire brain, revealing fine-temporal transitions of whole brain directionality patterns. We demonstrate that the human brain continually alternates between two dominant global modes on the scale of approximately 200 ms: a top-down mode, in which frontal regions lead posterior regions in phase, and a bottom-up mode, where posterior regions lead frontal regions. These modes exhibit distinct spatial and temporal profiles across different states of consciousness and cognitive conditions, as revealed by our analyses of diverse electrophysiological and neuroimaging datasets.

First, by applying RPA to EEG data obtained across various levels of consciousness during general anesthesia [24], we identified dominant modes of anterior-to-posterior and posterior-to-anterior directionality between which the brain dynamically transitions. Notably, these characteristic modes and transitions are most pronounced during full consciousness, suggesting that they serve as neural signatures of conscious information processing. As participants lose consciousness, these patterns progressively diminish—yielding a more random profile—a phenomenon that we interpret as indicative of altered information processing.

Second, we examine the functional relevance of the phase dynamics using simultaneous EEG–fMRI data [25]. By correlating these dynamics with task-related BOLD signals, we found that the anterior-to-posterior mode is associated with activity in higher-order cognitive networks, such as the Default Mode Network (DMN) and Fronto-Parietal Network (FPN), whereas the posterior-to-anterior mode correlates with the activity of the Visual Network (VN) and Dorsal Attention Network (DAN). These results lead us to conclude that the anterior-to-posterior mode reflects top-down directionality, while the reverse represents bottom-up directionality, thereby linking EEG dynamic patterns with network-level BOLD activation.

Third, we examined group-level differences in mode transition dynamics using RPA by comparing typically developing individuals with a neuropsychiatric cohort, focusing on the attention deficit hyperactivity disorder (ADHD) inattentive subtype. Our analyses reveal distinct imbalances between reduced front-to-back (top-down) directionality and excessive back-to-front (bottom-up) directionality. This supports the theory that ADHD-inattentive symptoms are associated with a lack of top-down signaling and a failure to inhibit bottom-up processes [26]. Furthermore, the enhanced performance of the RPA-based individual diagnostic predictor compared to the conventional Theta/Beta Power Ratio (TBR) underscores its potential as a more effective EEG biomarker for the ADHD-inattentive subtype using resting-state data. These results emphasize the significance of findings identified through simultaneous EEG-fMRI data, as well as the validity of RPA applications for mental disorders at the cognitive level.

Finally, to further elucidate the mechanisms underlying these dynamic patterns, we simulated relative phase dynamics using a generalized coupled-oscillator model on a structural brain network [27, 28]. The simulations successfully reproduced our empirical findings, demonstrating that distinct directional modes and the transitions between them emerge inherently and spontaneously from interactions among neural masses across the brain network.

Collectively, our study introduces **Relative Phase Analysis** as a comprehensive, real-time framework for understanding whole-brain dynamics, providing new insights into hierarchical processing, brain state transitions, and neuropsychiatric conditions. We reveal that the fluctuating interplay between top-down and bottom-up processing is an intrinsic feature of large-scale brain dynamics, and a fundamental mechanism underlying human information processing. By applying RPA, we uncover levels of consciousness, external stimuli, and pathological conditions influence the delicate balance, paving the way for a deeper exploration of the fundamental mechanisms governing perception, cognition, and consciousness.

2 Results

2.1 Robustness of relative phase analysis

Throughout the manuscript, we focus on the alpha band (8–12 Hz), as it most clearly exhibits the transition dynamics observed in our study. Similar patterns emerge in other frequency bands—including lower beta (12–20 Hz), theta (4–8 Hz), higher beta (20–30 Hz), delta (1–4 Hz), and gamma (30–50 Hz)—albeit with a progressively

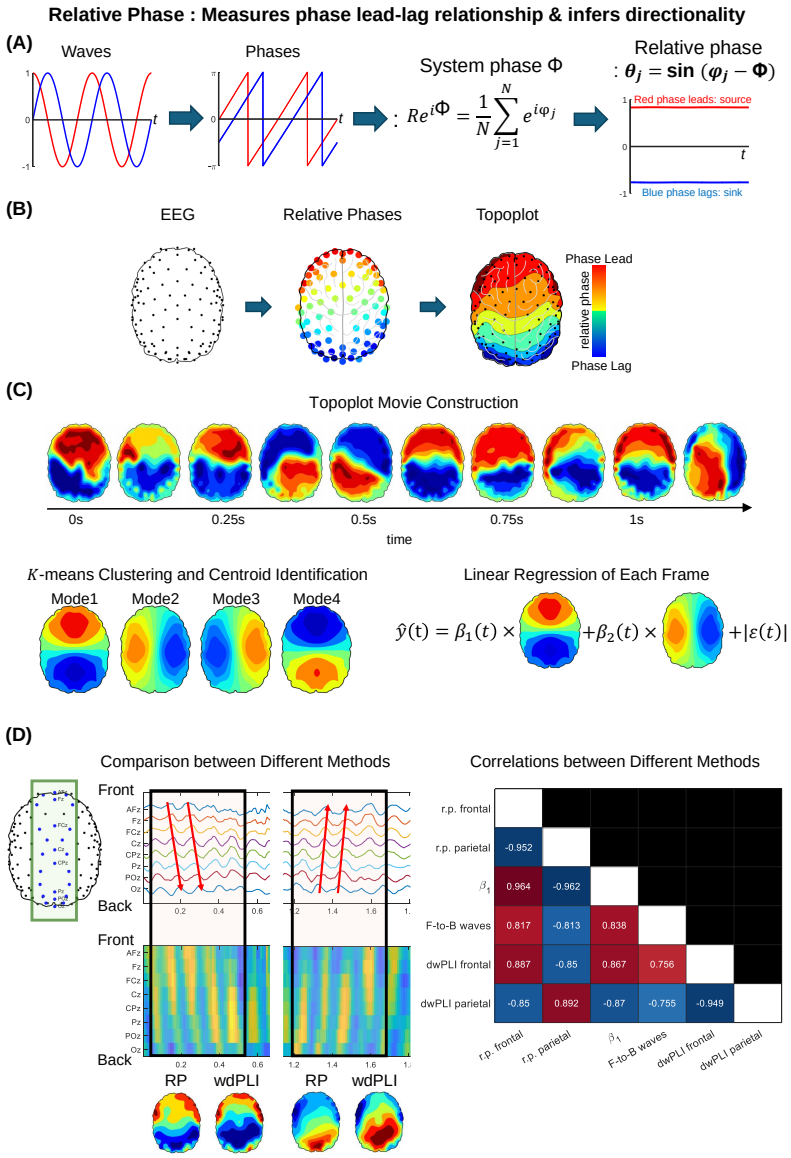

Fig. 1 Schematics of relative phase analysis. (A) After performing a Hilbert transform on EEG voltage time series to extract phase information, we calculate the global systems phase by averaging phases of all waves, and subtract them from the phases of each wave. Finally, we take sine of the differences and define the value as the relative phase. (B) After calculating the relative phase from each EEG channel, we spatially extrapolate to construct the topoplot of the relative phase at each time point. (C) By concatenating the topoplot of each time point, we construct the topoplot movie of each data set therefore revealing the dynamics of the relative phase. Then, we apply K-means clustering across the topoplot patterns of each time point to reveal dominant patterns of the topoplot. We also apply linear regression taking the centroids of the K-means clustering as the vector of regressors, where the topoplot of each time point t becomes the dependent variable $\hat{y}(t)$. (D) We compare the RP (relative phase) measure averaged within time windows against other measures such as wdPLI (weighted directional phase-lag index) and traveling wave measures.

reduced prominence of these dynamics (see Supplementary Information Section B for more detail).

We begin by validating the relative phase as a robust measure of directionality in brain activity, by comparing it with amplitude and phase-lag measures, as well as with measures that quantify traveling wave propagation. We will subsequently extend RPA to a real-time, whole-brain framework, thereby overcoming the spatial and temporal limitations of previous approaches.

Brain waves from each EEG channel are decomposed into amplitude and phase components over time using the Hilbert transform, with the phase reflecting the precise timing of a signal within its periodic cycle. We then computed the relative phase for each channel by subtracting the global mean phase (across all channels) at each time point. Next, we weighted the resulting phase by applying the sine function, mapping the values continuously from -1 to $+1$. In this framework, -1 corresponds to a 90° phase lag, $+1$ to a 90° phase lead, and 0 is obtained for phase differences of 0° or 180°. This weighting strategy is inspired by phase-based measures that mitigate the heightened sensitivity to noise—arising from factors such as volume conduction—near 0° and 180° differences in phase-lead/lag calculations (Figure 1) [22]. We hypothesize that the phase-lead/lag relationships serve as indicators of the directionality of information flow [5, 8–12, 23].

The eyes-closed resting state data from the general anesthesia dataset [24, 29], collected at the University of Michigan (UofM) using 128 electrode channels at a 500 Hz sampling rate, was employed for method comparison. Due to the computational demands imposed by this high-density, high-resolution data, we downsampled the dataset. To ensure that this reduction did not compromise critical information, we determined the optimal time scale for capturing relative phase dynamics (see Figure S7 in the Supplementary Information). We observed that the Shannon entropy of relative phase—computed over time windows of varying sizes—decreases as the window size increases across all frequency bands, indicating that the diversity of relative phase patterns diminishes with broader time averaging (We note that the Shannon entropy of relative phase was computed for each channel first then averaged over all channels). Notably, the alpha band (8–12 Hz) retains its Shannon entropy over longer time scales compared to other bands, up to approximately 100 ms (equivalent to a 10 Hz sampling rate), suggesting that 100 ms is a characteristic time scale for its relative phase patterns. Consequently, in our main analysis, we focus on the alpha wave's relative phase time series downsampled to 10 Hz to examine brain-state-dependent characteristics. We further note that increasing the downsampling rate to 50 Hz (yielding a time resolution of 20 ms) produces transition dynamics results that are highly consistent (see Supplementary Information Section B.7 for more detail).

The alpha-band filtered data were segmented into 2-second (or 10-second; see Supplementary Information Section B.1 for more detail) time windows, and key metrics were computed. Next, pairwise linear correlations were performed to assess relationships across brain states. Amplitude, derived via the Hilbert transform, was averaged across frontal and parietal regions. Phase-based directionality was quantified by calculating the weighted phase-lag index (wPLI) within each time window, which was

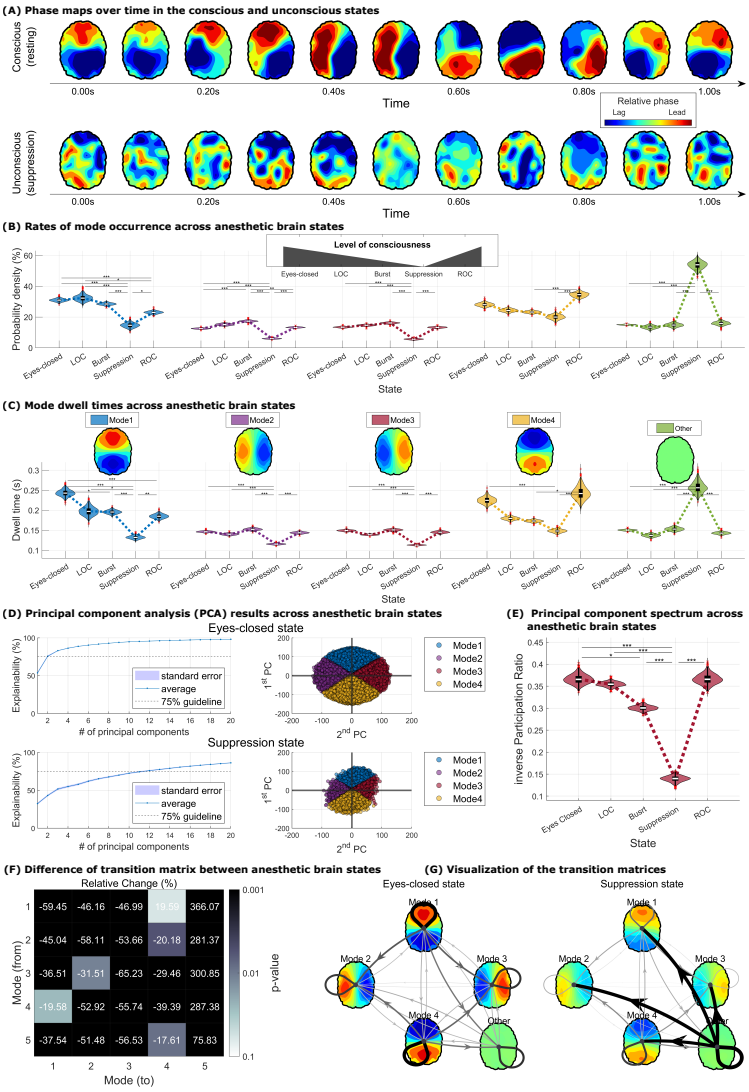

Fig. 2 Statistics of relative phase dynamics in the general anesthesia dataset. (A) Topographic maps of relative phase snapshots in the *eyes-closed* resting and *suppression* states. To address the limited number of observations, we perform 1,000 bootstrap resampling iterations (B, C, and E). (B) The probability density function varies across different levels of consciousness. In particular, modes 1 and 4 are related to the depth of consciousness, suggesting that the occurrence of these modes may serve as key markers for monitoring brain states. (C) The dwell time, which represents the duration spent in each mode, also shows distinct patterns across different brain states. (D) Explainability in principal component analysis (PCA) is defined by how the variance is distributed across each component. In the *eyes-closed* resting state, the first three principal components explain over 70% of the variance, whereas in the suppression state, at least twenty principal components are required to reach the same level. (E) The inverse Participation Ratio (iPR) decreases with the level of consciousness, indicating reduced heterogeneity in explainability across principal components. To highlight the difference between the *eyes-closed* and suppression states, we present (F) the relative change matrix, representing how the suppression state differs from the *eyes-closed* state, and present (G) the transition networks, respectively.

then time-averaged and subsequently grouped by frontal and parietal regions. Traveling wave propagation was analyzed using 2D FFT representations and phase gradients computed across selected electrodes traversing the midline of the brain, with the results averaged over time windows. Finally, the relative phase was calculated for all channels and averaged across time windows.

Relative phase showed a strong correlation with measures of information directionality in neural activity (Figure 1D) We found that the relative phase averaged over frontal regions shows a correlation of 0.887 with directional wPLI over frontal regions, and a correlation of 0.817 with frontal-to-posterior (F-P) traveling waves. Similarly, the relative phase averaged over parietal regions shows a correlation of 0.892 with directional wPLI over parietal regions, and a negative correlation of -0.813 with frontal-to-posterior traveling waves (all p-values < 0.001). Thus, the relative phase integrates two different approaches to reveal the directionality of inter-regional directionality. We also observed that the relative phase, traveling wave, and phase-based measures exhibit either no statistically significant correlations or only low correlations ($\rho \leq 0.304$) with amplitudes of the brain wave (see Supplementary Information Section B.1 for more detail), indicating that amplitude and phase dynamics contain distinct information [30].

2.2 Relative phase analysis across levels of consciousness

Monitoring the level of consciousness in general anesthesia is essential for ensuring patient safety and proper management. In this section, we investigate the relative phase dynamics in using the University of Michigan general anesthesia dataset [24, 29] to explore their relationship with consciousness levels. As each participant underwent general anesthesia through the administration of anesthetic agents (propofol followed by isoflurane), they gradually lost consciousness, progressing through distinct states: **eyes-closed resting state**, **loss of consciousness (LOC)**, **burst period**, **suppression period**, and **recovery of consciousness (ROC)**. The transitions between loss and recovery of consciousness were determined by the participant's ability to follow a verbal command to squeeze their hand. In essence, participants started in the resting state, then lost consciousness (LOC), entered deep anesthesia (burst and suppression periods), and finally regained consciousness (ROC). We note that the burst and suppression periods occur during the deepest stage of anesthesia, characterized by alternating bursts of brain activity (burst period) and suppressed activity (suppression period). (See Supplementary Information Section A.1 for the detailed anesthesia protocol.)

For each anesthesia state, we computed relative phase topographic patterns at each time point (Figures 1B and 1C; see Methods). Notably, the dynamics of relative phase patterns reveal distinct differences between conscious and unconscious states (Figure 2A). In the *eyes-closed* resting state, the front-to-back and back-to-front relative phase patterns repeat consistently over time. In contrast, the patterns become random and disorganized in the suppression state, the unconsciousness state occurring during the deepest anesthesia.

We further examined the relative phase properties, such as mode distribution and mode dwell time, to find the relationship between the relative phase and the level of

consciousness. We applied K-means to identify dominant phase dynamics (Figure 1C; see Methods). This analysis revealed four distinct relative phase topographic patterns: two dominant modes, characterized by front-to-back and back-to-front patterns (frontal area phase-leading parietal area and vice-versa), and two transient modes, defined by left-to-right and right-to-left patterns (left hemisphere phase-leading right hemisphere and vice-versa) (Figures 2B and 2C).

Occupancy rates and dwell times revealed that, in the resting state, front-to-back (mode 1) and back-to-front (mode 4) patterns were predominant, with higher occupancy rates and prolonged dwell times of approximately 200 milliseconds. In contrast, left-to-right (mode 2) and right-to-left (mode 3) patterns were more transient, exhibiting lower occupancy rates and shorter dwell times (Figures 2B and 2C). Transition matrix analysis further demonstrated that mode transitions predominantly occurred through the left-to-right or right-to-left patterns, serving as transition modes between dominant modes of front-to-back and back-to-front patterns (Figure 5C).

For every time series of relative phase topoplots, we can also apply linear regression taking the centroids of the K-means clustering as the vector of regressors, where the relative phase topoplot of each time point becomes the dependent variable $\hat{y}(t)$ (Figure 1C). we applied linear regression taking the first two centroids of the K-means clustering as the vectors of regressors: Here, the first vector is a centroid representing front-to-back pattern (negative of which represent back-to-front pattern), and the second vector is a centroid representing left-to-right (negative of which represent right-to-left pattern) (see the regression formula in Figure 1C). By observing how the coefficients for the first and second vector ($\beta_1(t)$ and $\beta_2(t)$ respectively) change over time, we can quantify the dominance of each modes, and also cluster topoplot from each time point t into the one of four modes: if $|\beta_1(t)| > |\beta_2(t)|$, the topoplot at time t is either in front-to-back mode (if $\beta_1(t) > 0$) or back-to-front mode ($\beta_1(t) < 0$); if $|\beta_1(t)| < |\beta_2(t)|$, the topoplot at time $t$is either in left-to-right mode (if $\beta_2(t) > 0$) or right-to-left mode ($\beta_2(t) < 0$). This linear regression approach is mathematically equivalent to principal component analysis (PCA), and the resulting clustering closely aligns with the K-means clustering results (see Supplementary Figure S6). This equivalence arises from the inherent relationship between K-means clustering and PCA, where each principal component closely corresponds to two symmetric modes identified by K-means clustering.

Front-to-back and back-to-front modes varied systematically across levels of consciousness (Figures 2B and 2C). Additionally, we introduced the category 'Other' to analyze the relative phase properties in greater detail. A topoplot at time point t is labeled as 'Other' when the regression residual $|\varepsilon(t)|$ exceeds the 85th percentile (top 15%) of all residuals across time points, indicating that the topoplot at t is not well characterized by $\beta_1(t)$ and $\beta_2(t)$. (Figures S8 and S9 in the Supplementary Information).

In summary, the occupancy rate and dwell time of front-to-back mode (mode 1) and back-to-front mode (mode 4) tended to decrease as consciousness diminished, then increased to levels comparable to the resting state upon recovery. The occupancy rate of mode 1 changed from 31.02% (resting) to 32.40% (LOC), 28.48% (Burst), 14.64% (Suppression), and 23.01% (ROC). Mode 4 shifted from 28.02% (resting) to

24.31% (LOC), 23.22% (Burst), 20.03% (Suppression), and 34.49% (ROC). Statistically significant differences in mode 1 occupancy rates were observed between resting and suppression states, resting and ROC states, LOC and suppression states, LOC and ROC states, burst and suppression states, and suppression and ROC states (one-way ANOVA test performed for all comparisons; see Methods; all p-values < 0.05). For mode 4, significant differences occurred between burst and ROC states, and suppression and ROC states (all p-values< 0.05).

Mode 1 dwell time changed from 242.7 ms (resting) to 197.4 ms (LOC), 195.5 ms (Burst), 132.2 ms (Suppression), and 185.5 ms (ROC). Mode 4 dwell time varied from 224.7 ms (resting) to 179.4 ms (LOC), 173.1 ms (Burst), 148.0 ms (Suppression), and 242.8 ms (ROC). Significant differences in mode 1 dwell time were found between resting and burst states, resting and suppression states, resting and ROC states, LOC and suppression states, burst and suppression states, and suppression and ROC states (all p-values < 0.05). For mode 4, significant differences were observed between resting and suppression states, LOC and suppression states, burst and suppression states, and suppression and ROC states (all p-values < 0.001).

Our findings from the regression model align with those obtained through principal component analysis (PCA). As shown in Figures 2D and 2E, the inverse participation ratio (iPR)–which reflects how many principal components are required to explain the given data–decreased as consciousness diminished. Specifically, iPR changed from 36.59% (resting) to 35.45% (LOC), 30.07% (Burst), and 13.95% (Suppression), before returning to 36.61% (ROC). Significant differences in iPR were observed between resting and burst states, resting and suppression states, LOC and suppression states, burst and suppression states, and suppression and ROC (all p-values < 0.05). These results confirm, using PCA, that relative phase patterns became more random as consciousness decreased.

Furthermore, we examined the transition properties among the modes. In addition to mode distribution and dwell time, transition patterns also differed between conscious and unconscious states (Figures 2F and 2G). Specifically, transition rates into the 'Other' mode were significantly higher in the suppression state compared to the eyes-closed state, indicating greater randomness in brain wave patterns. In contrast, transitions among modes 1, 2, 3, and 4 were generally reduced in the suppression state. In summary, our findings suggest that properties of the relative phase patterns, particularly the 'front-to-back' and 'back-to-front' modes, serve as reliable markers for distinguishing different states of consciousness.

2.3 Relative phase statistics on simultaneous fMRI-EEG data (checkerboard)

To further examine the functional significance of front-to-back and back-to-front phase modes, we compared their expression with the activity levels in well-established functional brain networks derived from fMRI BOLD signal.

We analyzed the relationship between EEG relative phase patterns and fMRI BOLD signals using the checkerboard task [25], which reliably activates the visual network (VN). The task consisted of alternating periods of resting (20 seconds) and

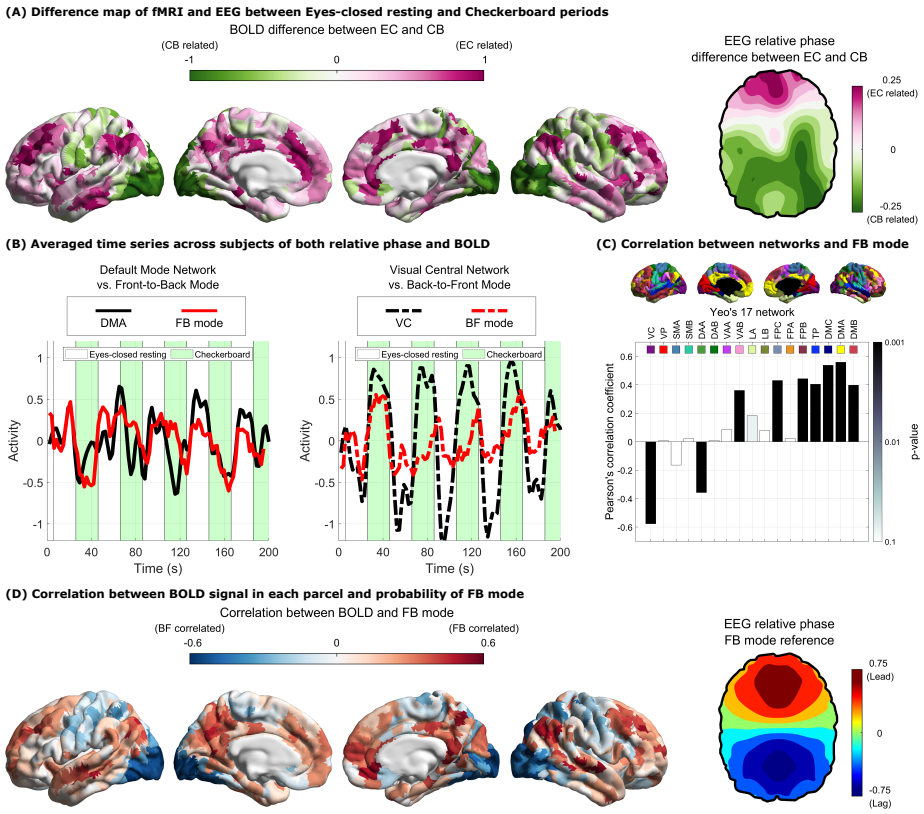

Fig. 3 Meaning of relative phase patterns using NKI simultaneous EEG-fMRI dataset. To examine the meaning of front-to-back and back-to-front EEG relative phase patterns, we compare the patterns with BOLD activity in a 12 Hz Checkerboard task. Mean BOLD and mean relative phase topographic map in (A) eyes-closed resting period, (B) checkerboard task period with 6s delay due to hemodynamic response. (C) Time series of β_1 and VisCent&DefualtA. We find β_1 is negatively correlated with the BOLD of the VisCent network and positively correlated with the BOLD of DefaultB network of Yeo's 17 networks. (D) Pearson's correlation coefficients between β_1 and all Yeo's 17 networks (VC: Visual Central (Visual A), CP: Visual Peripheral (Visual B), SMA: Somatomotor A, SMB: Somatomotor B, DAA: Dorsal Attention A, DAB: Dorsal Attention B, VAA: Salience / Ventral Attention A, VAB: Salience / Ventral Attention B, LA: Limbic A, LB: Limbic B, FPC: Control / Frontoparietal C, FPA: Control / Frontoparietal A, FPB: Control / Frontoparietal B, TP: Temporal Parietal, DMC: Default C, DMA: Default A, DMB: Default B). (E) Visualization of Pearson's correlation coefficients between β_1 and BOLD of Scheafer's 1000 parcellation.

flashing checkerboard stimulus (20 seconds, flashing with 12 Hz frequency). We confirmed that the visual network was activated during checkerboard stimuli periods and deactivated during rest periods. The difference in the BOLD activity between the rest and checkerboard periods are shown in Figure 3A (averaged across trials then across participants). To analyze the EEG relative phase differences between the periods, we also examined the difference of mean relative phase topographic map between rest and checkerboard periods (again, averaged across trials then across participants). We

found that the front-to-back patterns were more dominant in the resting state, whereas the back-to-front patterns appeared during the checkerboard periods (Figure 3A).

To more broadly determine the relationship between EEG relative phase patterns and fMRI BOLD signals, we compared each phase mode from EEG with activation of 17 canonical BOLD functional networks [31, 32]. We found a positive correlation between the occurrence of the front-to-back mode (coefficient $\beta_1(t)$ from the regression) and the activity of the Default Mode Network (DMN) (DMA, DMB, DMC; all $r > 0.5$, $p < 0.001$). Additionally, the back-to-front pattern (represented by the negative of coefficient $\beta_1(t)$) showed a positive correlation with Visual Network (VN) activity (VC; $r = 0.58$, $p < 0.001$) (Figures 3B and 3C). These findings suggest that posterior-to-anterior directionality is associated with VN activation, whereas anterior-to-posterior directionality is linked to DMN activation. This pattern was further validated through correlation mapping between front-to-back EEG relative phase patterns and BOLD signals across 1,000 parcels from the Schaefer parcellation (Figure 3D). Furthermore, the front-to-back pattern exhibits a high correlation not only with the DMN but also with other higher-order regions such as Frontal-Parietal Network (FPN) (FPC, and FPB), and TP at a significance level of p-value < 0.001 (Figure 3C). This suggests that the anterior-to-posterior directionality is associated not only with the DMN but also with higher-order regions in general. Based on these results, we define the front-to-back pattern as the **top-down mode**, representing information flow from higher-order cognitive anterior regions to lower-order sensory posterior regions. Conversely, we designate the back-to-front pattern as the **bottom-up mode**, representing information flows in the opposite direction.

2.4 Application of relative phase analysis: ADHD vs. Control

Using simultaneous EEG-fMRI data, we demonstrated that the fluctuations observed through Relative Phase Analysis (RPA) likely reflect activities and relationships of functional networks. To further validate the significance of the meaning of dominant modes and explore the potential of this approach at the cognitive level, We used relative phase dynamics to analyze resting-state EEG data from individuals with the ADHD inattentive subtype and typically developed controls. There are multiple neuroscientific approaches to understanding ADHD symptoms, with theories ranging from the neurotransmitter level to the network and cognitive levels [13, 33–35]. Among these, cognitive-level theories suggest that ADHD patients exhibit a lack of top-down signaling compared to control groups, along with poor communication between top-down and bottom-up modes [26, 36, 37]. This imbalance between top-down and bottom-up modes is believed to contribute to the inattentive symptoms observed in ADHD. As mentioned earlier, we demonstrated that the results of RPA fluctuates between top-down (front-to-back) and bottom-up (back-to-front) modes by correlating EEG relative phase results with simultaneous fMRI results on a matched time scale. Therefore, we apply relative phase measure to both the ADHD-inattentive type group and the control group to determine whether our findings align with previous research on ADHD inattention symptoms. This approach could demonstrate, at a cognitive level, that relative phase pattern reflects attentional processing as a feature of consciousness.

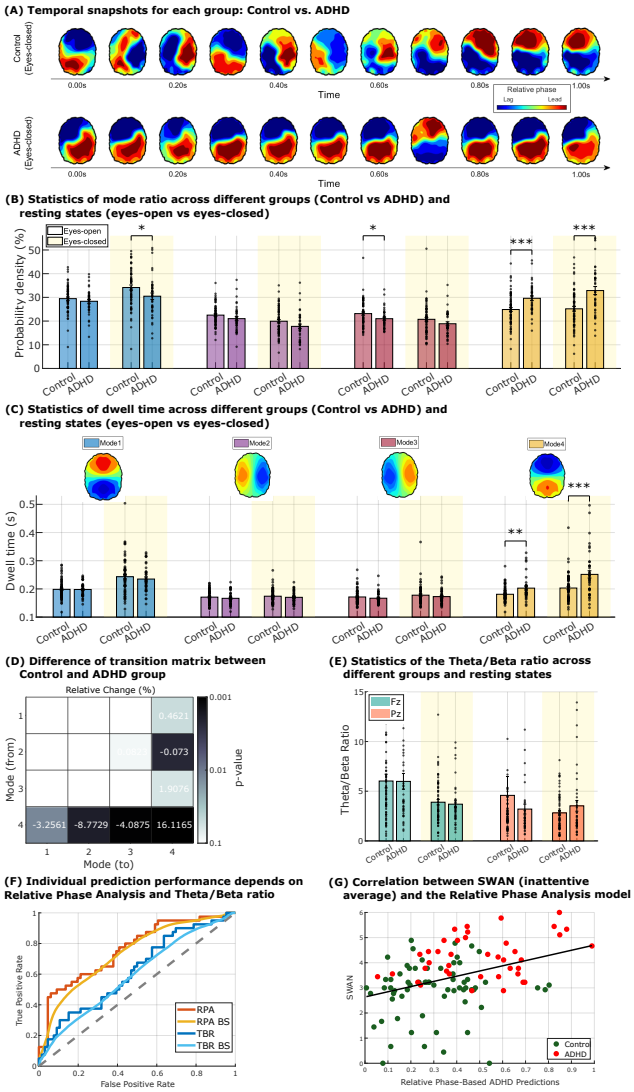

Fig. 4 Results of applying Relative Phase Analysis to the HBN (Healthy Brain Network) ADHD-inattentive Data: (A) Snapshot of relative phase topographic maps for the control group and the ADHD-inattentive group (*eyes-closed* state). (B) Probability density functions in the control and ADHD-inattentive groups. No background indicates the eyes-open state, while the yellow background indicates the *eyes-closed* state. Asterisks denote significance levels from the two-sample t-test: $*\ \ p \leq 0.05$, $**\ \ p \leq 0.01$, and $***\ \ p \leq 0.001$. (C) Dwell time for both the control and ADHD-inattentive group. (D) The difference matrix between the transition matrices of the control and the ADHD-inattentive group (*eyes-closed* state). The relative change was calculated by subtracting the mean transition rate of the control group from that of the ADHD group. The result was then normalized by the control group's mean and expressed as a percentage by multiplying by 100. (E) Theta/Beta ratio for the Fz and Pz channels in both the control and ADHD group. The green bar represents the Fz channel, while the orange bar shows the results from the Pz channel. (F) The Receiver Operating Characteristic (ROC) curves for individual prediction results from the Relative Phase Analysis and the Theta/Beta ratio. (G) The correlation result between the SWAN inattentive average score and the diagnostic predictions values using the Relative Phase logistic regression model.

Moreover, we aim to investigate the potential of relative phase dynamics as a biomarker for diagnosing the ADHD-inattentive subtype. Currently, the Theta/Beta Ratio (TBR) is the only EEG biomarker officially approved by the U.S. Food and Drug Administration (FDA) for ADHD diagnosis. However, this method has shown considerable variability in results and is most effective in distinguishing the ADHD combined type, which is characterized by high levels of both inattentive and hyperactive-impulsive symptoms [38, 39]. Therefore, by comparing conventional measures, we seek to determine whether relative phase analysis (RPA) can serve as a reliable diagnostic tool for the ADHD-inattentive subtype.

We analyzed EEG resting-state data from the ADHD-inattentive and control groups in the Healthy Brain Network (HBN) data released by the Child Mind Institute [40]. Following the same methodology as before, we conducted 4-means clustering and calculated both the mode occupancy rate and the dwell time in each of the four modes. The topological dynamics in the eyes-closed resting state derived from relative phase over time illustrate the differences between the ADHD and Control groups (Figure 4A). The Control group shows continuous changes at 0.1-second intervals, whereas the ADHD group tends to stay in the back-to-front (bottom-up) mode for longer periods. These topological dynamics alone suggest that the RPA displays an imbalanced pattern in the ADHD group.

Analysis of the mode distribution and mode dwell time quantitatively demonstrated these group differences (Figures 4B and 4C). In both eyes-closed and eyes-open resting states, the ADHD-inattentive subtype group exhibited significantly greater rates of mode occupancy and greater dwell times in mode 4 (back-to-front mode) compared to the control group. In the eyes-closed state, the differences between the two groups were 30.6% in mode distribution and 23.9% in dwell time, relative to the control group, and these differences were significant in both measures (two-sample t-test, $p < 0.001$). Furthermore, these results remained significant even after applying the more stringent False Discovery Rate (FDR) correction. Thus, the back-to-front mode could reliably distinguish the ADHD-inattentive group from the Control group. Furthermore, an analysis of probability density mode 1 (top-down) in the eyes-closed condition reveals that the ADHD group shows a significantly lower value than the control group at a 95% confidence level ($p = 0.036$, Figure 4C). This finding aligns with biased mode 4 (bottom-up), indicating a deficiency in top-down signaling of ADHD-inattentive group.

We also analyzed the between-mode transition matrix for each group, and computed the difference in between-mode transition probabilities for the ADHD group and Control group values (Figure 4D). We found that participants in the ADHD group exhibited greater mode 4 to mode 4 transitions (i.e. staying in mode 4), with a p-value < 0.001. This imbalance between mode 1 (front-to-back, top-down) and mode 4 (back-to-front, bottom-up), along with slower fluctuations, supports the current hypothesis regarding ADHD inattention symptoms.

To explore this further, we calculated the TBR using the same HBN dataset (Figure 4E). The TBR is usually calculated by obtaining power values from the Cz, Fz, and Pz channels to assess differences between the two groups. However, since the HBN dataset uses Cz as the reference channel, our study calculated solely on the TBR

values from the Fz and Pz channels. Previous research suggests that the differences between these two channels and the Cz channel are minimal [41]. Our analysis of the HBN data indicated no significant TBR differences between the control group and the ADHD-inattentive group, reaffirming findings from earlier studies [38, 39]. These results suggest that the relative phase pattern may be a more effective biomarker for the ADHD-inattentive subtype.

According to the analysis using Receiver Operating Characteristic (ROC) curves, the individual prediction performance of the model built with RPA was better than that of the TBR model (Figure 4F). For our model, we used logistic regression to determine the weights, with the dependent variable being the diagnostic outcome and the independent variables being mode occurrence of mode 4, dwell time of mode 4, and transition values from mode 4 to mode 4. We then used these weights to calculate the assessment score for each value. Similarly, for the TBR model, we used the results from the Fz and Pz channels to calculate the prediction score in the same manner. The performance of the RPA model was 0.76, and 0.73 when confirmed via bootstrap, whereas the performance of the TBR model was 0.62, and 0.59 with bootstrap.

Lastly, we examined the correlation between the RPA model's diagnostic prediction score and the average of Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale (SWAN) inattentive score [42]. The correlation coefficient R was 0.38 with significance at a p-value of 0.001. This result clearly indicates an association between the RPA model and behavioral measures, and the correlation could potentially be even stronger if we consider only those with an average SWAN inattentive score of 3 or higher (Figure 4G). While the SWAN score reduces the likelihood of false negatives when indicating ADHD, the RPA model reduces the potential for false positives. Notably, distinguishing the mixed group of control and ADHD subjects in the second quadrant (top-left) may be crucial, and further research is needed to investigate this aspect.

These analyses confirm that the relative phase dynamics are consistent with the existing hypothesis about ADHD-inattentive symptoms: a deficiency in top-down mode and an imbalance in communication between top-down and bottom-up modes. This finding strengthens our conclusion that the relative phase pattern can be linked to top-down and bottom-up directionalities in the brain, and highlights the importance of the relative phase pattern and its connection to ADHD-inattentive symptoms. Additionally, the comparison with the TBR measure indicates that RPA could serve as a biomarker for ADHD-inattentive subtype. In the future, developing more sophisticated AI models for individual predictions and investigating the relationship between the RPA model and other behavioral measures could enhance the potential of relative phase patterns for diagnosis and symptom reduction in clinical settings.

2.5 Simulation with Kuramoto model with generalized coupling function

Finally, to elucidate the mechanism underlying the mode fluctuations, we ran simulations of relative phase dynamics using a Kuramoto model, a well-known canonical coupled oscillator model frequently used to model large-scale cortical dynamics. Specifically, we utilized a Kuramoto model with a generalized coupling function that includes

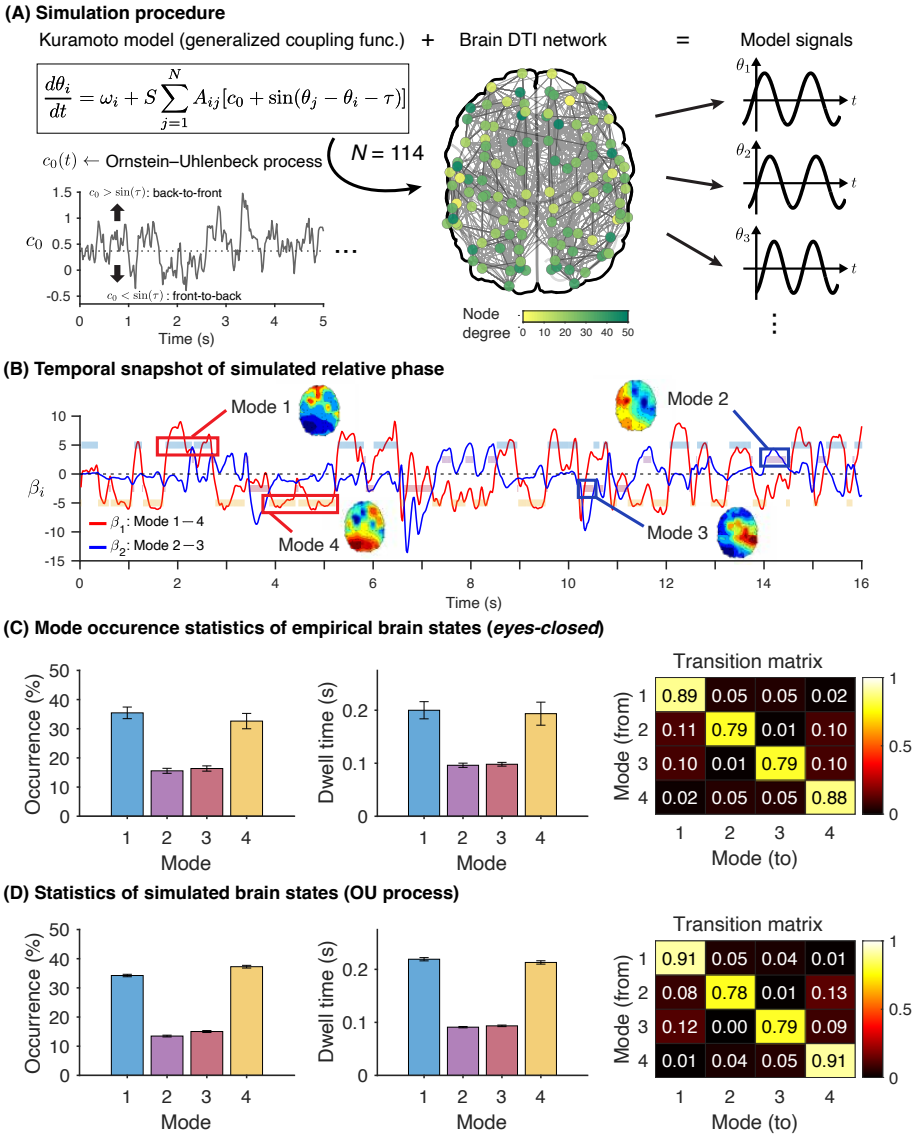

Fig. 5 Simulation of relative phase dynamics using a coupled oscillator model. (A) Schematic of the simulation process using Kuramoto model with generalized coupling function on a Lausanne brain network. c_0 parameter in the model evolves according to dynamics with either a single attractor or three attractors (see Methods for details). Horizontal dotted lines indicate fixed points in two types of processes. The model generates phase signals for each brain region ($N = 114$). For all simulations, $S = 0.25$ and $\beta = 0.167\pi$ were used. (B) Snapshot of relative phase topographic map from model-generated signals. (C) Empirical and simulated mode distributions in the University of Michigan general anesthesia dataset in the conscious state (eyes-closed resting state). Simulation is done with a single-attractor (middle) or three-attractor (right) stochastic process in c_0 parameter. (D) Empirical dwell time for each mode in the conscious state (eyes-closed resting state). (E) Empirical and simulated transition matrices among the four brain states.

a constant term (c_0), which results in a more realistic first order approximation of many coupling functions obtained from the phase reduction method [27, 28, 43]. This term is also naturally derived from a control parameter that represents an intermediary between the diffusive and direct coupling schemes in limit-cycle oscillators [44, 45]. Prior theoretical work has shown that inclusion of this parameter in the coupling function results in a rich repertoire of phase dynamics, especially relevant to the transitions between two distinct and dominant modes in the brain: one in which high-degree cortical regions phase-lag the network becoming sink of the directionality, and one in which the hub regions phase-lead the network and becoming source of the directionality [45]. Motivated by this finding, we hypothesized that the relative phase dynamics can be simulated with random fluctuations in this c_0 parameter, which is linked to the phase-lead/lag relationship of the higher-degree regions and the resulting front-to-back/back-to-front directionality (see Supplementary Figure S25 for more details). We simulated the Kuramoto model on a human structural cortical network with $N = 114$ regions [46], with each node generating a phase signal according to the dynamics of the model (Figure 5A). The fluctuations in c_0 were modelled with the Ornstein-Uhlenbeck (OU) process. Using grid search, we then estimated the parameters of the stochastic process that best match the empirical mode statistics, focusing on the UofM general anesthesia data (conscious, eyes-closed).

By applying the same procedure for the empirical data, we obtained the regression weights for each time point (β_1 and β_2) specifying the mode distribution over different brain states. Example temporal snapshots of simulated topographic plot for each mode is illustrated in Figure 5B. In particular, we found that mode 1 was indeed associated with high-degree nodes phase-lagging relative to the system, while mode 4 showed the opposite effect where high-degree nodes were phase-leading (Supplementary Figure S25D). This was reflected as significant correlations between the averaged relative phase and the anterior-posterior coordinates of the brain regions (Supplementary Figure S25E), consistent with the regression weights specifying back-to-front directionality (β_1). More specifically, when the brain state occupied mode 1, the correlation was negative ($r = -0.249$, $p = 0.00752$) such that the more anterior regions tended to phase-lead the system (Supplementary Figure S25E, middle). In contrast, the correlation was positive ($r = 0.255$, $p = 0.00608$) during mode 4, in which the more posterior regions tended to phase-lead the system (Supplementary Figure S25E, right).

By inspecting the statistics of the simulated mode occurrences and dwell time, we further found that the Kuramoto model captured the key characteristics of the empirical data in Figure 5C. As explained earlier, the empirical mode fluctuations during conscious resting state exhibited a pattern where modes 1 and 4 occurred more dominantly than modes 2 and 3 (Figure 5C, left). This pattern is also reflected in the dwell time distribution, in which modes 1 and 4 are occupied for a longer period of time than modes 2 and 3 on average (Figure 5C, middle). From the transition probability matrix (Figure 5C, right), the brain states tended to stay in the same mode (high transition rates along the diagonal), while modes 2 and 3 served as the transient states between modes 1 and 4. (For example, mode 2 or 3 was more likely to transition into mode 1 or 4 than transitioning into 3 or 2.) These characteristics were well reflected

in the simulated relative phase dynamics in Figure 5D. That is, the simulated modes fluctuations showed the dominance of modes 1 and 4 compared to modes 2 and 3 in terms of both occurrence rate and dwell time (Figure 5C, left and middle). The simulated transition probability matrix (Figure 5D, right) also highlighted the key tendency reflected in the empirical data, wherein the transitions between the modes 2 and 3 were near zero and instead they were transiently visited from 1 and 4.

Overall, these results illustrate that a canonical model of coupled oscillators, such as the Kuramoto model equipped with a simple stochastic process in just one parameter, can replicate the key characteristics of the relative phase dynamics in the human brain. The model simulations may also point to the universality of the relative phase dynamics observed in the human brain network. We note that the OU process is not the only stochastic process that can replicate the empirical data; we found that other processes, involving more than one stable fixed point, were also able to capture the data for a specific range of parameters (Supplementary Figures S26D and S26E). These findings raise the possibility that the observed top-down and bottom-up modes could be understood as the attractor states in a network of coupled brain regions.

3 Discussion

What are the dominant modes of directionality at the whole-brain level? What are the real-time transition dynamics between these modes? We addressed these questions by establishing relative phase as a robust, versatile, and clinically relevant measure of brain dynamics. Leveraging RPA, we found that: (i) the anterior-to-posterior (top-down) versus posterior-to-anterior (bottom-up) directional patterns are fundamental modes of human brain dynamics, with the brain rapidly fluctuating between these two states on a sub-second scale; (ii) these dynamic properties are most pronounced during full consciousness and diminish as consciousness fades; (iii) the directional modes are associated with the BOLD activity of corresponding functional networks (anterior-to-posterior moode with DMN and FPN, posterior-to-anterior mode with VN); (iv) developing individuals and those with ADHD exhibit group-level differences in their relative-phase profiles and dynamics; and (v) a generalized coupled-oscillator brain network model reproduces the observed mode transition dynamics.

Relative Phase Analysis Reveals a Real-Time, Whole-Brain Dynamics of Sub-Second Anterior-Posterior Directionality Fluctuations

Relative phase analysis (RPA) provides a real-time measure in quantifying phase dynamics, enhancing our ability to investigate large-scale neural interactions beyond previous methods. Unlike time-window-based phase-lag measures or region-specific traveling-wave analyses, RPA offers continuous tracking of neural phase relationships across the whole cerebral cortex. As demonstrated in the Results section, the method can still incorporate time-window averaging and region-specific calculations to examine long-term and spatially localized dynamics. However, its real-time nature offers a significant advantage for investigating fine temporal dynamics. Additionally, RPA

holds promise for neurofeedback applications, where the ability to monitor real-time neural dynamics is crucial.

Leveraging RPA, we identified sub-second transitions between dominant top-down and bottom-up directional modes. Prior studies suggest that such fluctuations, or more generally, the alternation between internally and externally biased processing states, occur across multiple spatial and temporal scales [17]. This oscillatory balance has even been proposed as a fundamental signature of human brain information processing across multiple levels of organization [17]. Event-related-potential (ERP) studies from EEG and ECoG indicate that the brain's response to external stimuli occurs within sub-second timescales, suggesting that bottom-up vs. top-down switching may operate within a similar temporal window. Our findings confirm this, demonstrating that these switching occurs approximately every 200 ms, spanning the whole brain in a dynamic interplay.

Crucially, we observed that these fluctuations are not solely stimulus-driven but also emerge spontaneously during resting states, suggesting an intrinsic top-down vs. bottom-up modulation independent of external input. This finding highlights a fundamental, self-organizing mechanism of cortical dynamics. For our future studies, we aim to leverage RPA in ERP paradigms, exploring its potential for ERD analysis and its role in cognitive function. Additionally, we observed that both top-down and bottom-up directionalities extend across all frequency bands up to 50 Hz. Future investigations will examine whether the balance between top-down and bottom-up processing varies across frequency bands in response to different stimuli, potentially uncovering frequency-dependent mechanisms of neural information flow [9, 47, 48].

Sub-Second Anterior-Posterior Directionality Fluctuations Link to BOLD Activity Dynamics and Distinguish Diverse States of Consciousness and ADHD

Our relative phase analysis may offer a new approach for assessing consciousness levels in clinical settings. Distinguishing brain states across different levels of consciousness remains a fundamental challenge, particularly in clinical applications such as general anesthesia. While phase- and amplitude-based measures have shown partial success in identifying consciousness levels, they do not fully capture all aspects of anesthesia. For instance, the amplitude dynamics of burst states during anesthesia closely resemble those of resting states, making differentiation difficult for some conventional measures. In contrast, our analysis of the distribution of top-down and bottom-up modes effectively characterizes variations in consciousness levels and successfully detects the reduction in burst states. This finding further supports the measure's ability to quantify reductions in dominant directional modes, which we propose as a key mechanism underlying full consciousness. Notably, the decrease in dominant modes correlated with consciousness levels occurred also in the low beta band as well as the alpha band. Further exploration of how different anesthetic agents modulate mode distributions across frequency bands could provide deeper insights into comparative anesthetic mechanisms and their effects on neural dynamics [1, 4].

Simultaneous EEG–fMRI not only bridges brain wave activity with BOLD signals but also uncovers insights unattainable through a single modality. Here, we establish

a link between directional mode transitions in brain waves and corresponding functional network transitions in BOLD activity. Using a flashing checkerboard stimulus, a well-established paradigm for eliciting reliable BOLD activation patterns, we interpret anterior-to-posterior and posterior-to-anterior directionality as reflecting top-down and bottom-up processing, respectively. Future research will extend this analysis to EEG–fMRI data acquired with more nuanced and naturalistic stimuli, aiming to capture mode transition dynamics in more natural settings. Additionally, applying relative phase analysis (RPA) directly to BOLD time series may provide novel insights into the directional propagation of BOLD signals, complementing recent methodological advances. A systematic comparison and integration of RPA with established measures could ultimately lead to a more robust framework for inferring BOLD dynamics, overcoming the inherent temporal resolution limitations of fMRI.

Our RPA approach successfully distinguishes between the inattentive type ADHD group and the typically developed control group demonstrating high performance in individual diagnostic prediction. These findings suggest the potential validity of RPA as a new EEG biomarker for ADHD, supplementing the TBR measure which remains a topic of debate regarding its effectiveness in diagnosing ADHD. Furthermore, the observed increase in bottom-up mode and decrease in top-down mode aligns with previous theories suggesting that attention deficit symptoms are associated with weakened top-down inhibition of bottom-up processes [26]. Considering the existing gap between cognitive-level explanations of ADHD and brain imaging measures, our results support the role of RPA in elucidating the neuroscientific mechanisms underlying ADHD-inattentive symptoms. By identifying group-level differences in resting-state brain dynamics, our study connects with previous research showing that top-down inhibition is less active in ADHD individuals in the absence of cognitively demanding tasks [26, 49]. This suggests that RPA could serve as a neuroscientific approach within integrative models of ADHD, which incorporate cognition, emotion, and environmental factors [35, 50, 51]. Furthermore, the measure may offer the potential for developing more targeted biomarkers and interventions, as the validity of such interventions may be measured with the changes in the RPA. Therefore, we expect that applying RPA to ADHD and other neuro-disorders will provide valuable insights into their underlying mechanisms.

In this study, we primarily focused on validating the differences in top-down and bottom-up directionality across different groups, restricting the application of relative phase measures to the inattentive type of ADHD. This decision was influenced by the relevance of inattention symptoms to top-down mode activity and the sample size distribution within the HBN dataset. Additionally, to facilitate a clear comparison with the typically developed control group, we analyzed only adolescents aged 11 and older diagnosed solely with the inattentive subtype of ADHD. The age restriction is due to significant differences in EEG alpha spectrum peak that exist between individuals below and above the age of 10 [52]. In future studies, we aim to expand our analysis to hyperactive and combined types of ADHD, as well as comorbid conditions, to explore mode differences across these subgroups. The distinct findings among different groups will contribute to a deeper understanding of the underlying mechanisms of various neuro-symptoms.

Computational Modeling of Sub-Second Directionality Modulation Provides Predictive Insights

Our computational modeling work suggests that the dominant modes and the transitions between them can occur spontaneously in a network of interacting neural masses. Namely, the anterior-posterior directionality and posterior-anterior directionality naturally occur due to their underlying brain network structure. With the addition of the stochastic coupling term (c_0), the model exhibits the dominant modes as the attractors. In our modeling framework with coupled oscillators, the c_0 parameter naturally arose as the first order approximation of many realistic coupling functions in the phase-reduced Kuramoto model [27, 28, 53]. In particular, this parameter serves as an intermediary term bridging the direct and diffusive coupling schemes [44, 45], which are two commonly assumed forms of coupling between oscillators. In the brain, these are often associated with the two major forms of coupling: electrical and chemical coupling of synapses, respectively [54, 55]. In our model, higher values of c_0 (bottom-up mode) are related to the dominance of electric synapses in which neurons are coupled based on the difference in potentials through gap junctions, whereas lower values of c_0 (top-down mode) are related to chemical synapses in which the generated action potentials are largely independent of potential difference between neurons. Thus our framework predicts that the transitions among the dominant modes reflect the changing ratios of these two forms of coupling in the large-scale brain network, which remain to be investigated empirically. Another possible interpretation of our model is that the c_0 term reflects the relative dominance of external stimuli (sensory input) in the network, such that when c0 exceeds the sine function ($\sin(\tau)$; Supplementary Figure S25A), external stimuli are more influential on the network dynamics, making the brain more receptive and responsive to sensory information (bottom-up processing mode). Conversely, when c_0 is smaller than the sine function, intrinsic network dynamics are more influential, making the brain able to coordinate external sensory inputs with spontaneous internal brain rhythms—representing effective top-down moduation. Overall, our framework extends the previous theoretical proposals on the functional implications of having two co-existing forms of coupling in the oscillator system [44, 45, 54, 56, 57].

Limitations and Future Perspectives

Finally, we mention some of the limitations of the current study, which we aim to address in future work i) Our analyses focused on resting-state data and a very strong external stimulus of flashing checkerboard. Extending RPA to task-based paradigms will be necessary to study the relationship between directionality modes and cognitive processes such as attention and memory. Establishing links between RPA modes and specific behavioral or cognitive tasks will be in order for understanding the functional significance of top-down and bottom-up dynamics. For example, the seminal study by (Bonnefond and Jensen, 2012) has reported a clear lag in the alpha oscillation in the posterior regions prior to strong distractions during a working memory task. Our RPA framework is consistent with this finding and could interpret the result as an increase in top-down control (i.e., mode 1) when distractors are expected. Future studies could probe whether such task-induced effects are more clearly demarcated by

considering the global phase lead/lag relationship in the whole brain. ii) While RPA shows sensitivity to changes in consciousness, its clinical utility should be benchmarked against established metrics like the Bispectral index (BIS) and Patient State Index (PSI) from the monitoring apparatuses used in the clinical settings. iii) Expanding the application of RPA to diverse ADHD subtypes, comorbidity symptoms, as well as varying age and sex groups, is critical for generalizing its utility as a biomarker and understanding the heterogeneity of the disorder. Additionally, finding a more rigorous correlation between various phenotype data and RPA results will help identify what behavioral characteristics are influenced by the differences in RPA. iv) Our general-coupled oscillator model framework has many potentials to be refined, for example, by utilizing more biologically informative models such as Wilson-Cowan model to reveal more information of the biophysical mechanism and the mode transition dynamics. v) Lastly, in David Marr's levels of analysis where a model consist of computational, algorithmic, and implementational levels — each level corresponding to questions about what problems are addressed, how the problem is addressed algorithmically, and how the mechanism is biophysically implemented — our model is at the level of implementation. Only the expansion and combinations of our model with the algorithmic and computational levels will provide a complete picture of how the information is processed via the top-down and bottom-up switching in our brain with respect to the external world and internal model construction.

Conclusion

This study introduces RPA as a powerful and versatile tool for investigating the brain dynamics, offering new insights into brain state transitions, hierarchical processing, and neuropsychiatric conditions. Our findings demonstrate that the fluctuating interplay between top-down and bottom-up processing is an intrinsic property of large-scale brain dynamics, reinforcing a dynamical systems perspective in which the brain continuously reconfigures its information processing organization. Our study offers a new research avenue exploring how external stimuli, cognitive demands, and pathological conditions influence this delicate balance. By integrating RPA with experimental neuroscience, we can investigate how spontaneous directional fluctuations shape perception, cognition, and consciousness, ultimately advancing our understanding of the fundamental principles of neural computation.

4 Methods

4.1 Relative Phase Dynamics in EEG Signals

In electroencephalography (EEG), a participant wears a cap that has tens or hundreds of electrodes attached to it. These electrodes record the brain's electrical activity over time. A key challenge in neuroscience is to understand how the brain processes external and internal information. To address this problem, we try to investigate information flow from the electrical activity in the brain using the relative phase dynamics approach.

EEG signals can be decomposed into amplitude and phase components over time using the Hilbert transform [59]. The phase of each electrode reflects the specific timing of its signal within a periodic waveform. To determine the directionality of information flow, we use the relative phase, which is derived by subtracting the global mean phase from the phase of each electrode [5, 7]. In the following equations, θ_j represents the signal phase of jth electrode, and Θ denotes the system's mean phase.

$$Re^{i\Theta} = \frac{1}{N}\sum_{j=1}^{N} e^{i\theta_j} \quad , \tag{1}$$

$$\sin\phi_j = \sin\left(\theta_j - \Theta\right) \quad . \tag{2}$$

Here, Eq. (1) represents the global mean phase and Eq. (2) represents the relative phase. Eq. (1) defines the system's phase denoted as Θ, which represents the global mean phase of the system at each time point, capturing the brain's overall phase state. In Eq. (2), we subtract the system's phase from each signal's phase, and define it as relative phase ϕ_j. When the relative phase is a positive value, it means that the signal from an electrode leads the global mean phase, whereas a negative value indicates that it lags the global mean phase. To increase the accuracy of the relative phase estimation, we take the sine of ϕ_j. This transformation allows us to obtain continuous relative phase values ranging from -1 to 1, utilizing only the values from the imaginary axis [22]. Using this approach, we can reliably estimate whether ϕ_j is relatively phase-leading or lagging at each time point.

4.2 *K*-means Clustering of the Relative Phase Patterns

The relative phase in the brain shows distinct patterns over time, reflecting different brain states. We found that the dynamics of the relative phase patterns show different aspects depending on the brain states. Interestingly, these patterns are not random in conscious states but follow specific dynamics. The K-means clustering algorithm finds dominant patterns as centroids by iteration in a given dataset [60, 61]. We performed K-means clustering to find dominant patterns in the relative phase dynamics.

K-means clustering divides the given data into K clusters, a parameter that must be predetermined. To determine the optimal K for resting state brain patterns, we evaluate the clustering performance using the Davies-Bouldin Index (DBI) [62]. The DBI reflects clustering quality, with higher values when the average distance between the same cluster is greater than the average distance between different clusters, otherwise lower values. After examining the DBI values across varying K values, we found that the optimal number of clusters for the brain's resting state is $K = 4$ (see Figure S5 in the Supplementary Information).

In the main text, we analyzed differences between different groups or brain states. To investigate these differences, we identified universal relative phase patterns based on resting state data. We derived four centroids using K-means clustering from two datasets: the concatenated resting state recordings of 18 subjects from the University of Michigan (UofM), and the concatenated resting state recordings of the Healthy Brain Network (HBN) control group (66 subjects), respectively. We excluded the NKI dataset due to noise introduced by simultaneous fMRI-EEG recordings. Despite analyzing

different datasets, we found that the same four centroids emerged consistently: i) front-leading/back-lagging pattern (mode 1), ii) left-leading/right-lagging pattern (mode 2), iii) right-leading/left-lagging pattern (mode 3), iv) back-leading/front-lagging pattern (mode 4) (see Figure S6 in the Supplementary Information). Therefore, we analyzed relative phase dynamics using these four centroids as standard.

4.3 Multiple Linear Regression using the Universal Centroids

The K-means clustering algorithm assigns every time frame to one of the four modes, even if some ambiguous frames do not closely resemble any mode. This limitation introduces ambiguity, as frames that fall between distinct patterns are still forced into one cluster. To address this issue, we performed multiple linear regression with the universal centroids [63]. Unlike K-means, which provides binary assignments, multiple linear regression assigns continuous weights to each mode for every time frame, representing the contribution of each pattern more accurately.

$$\hat{\mathbf{y}}(t) = \beta_1(t) \cdot \boldsymbol{X}_1 + \beta_2(t) \cdot \boldsymbol{X}_2 + \boldsymbol{\varepsilon}(t) \quad , \tag{3}$$

where $\hat{\mathbf{y}}$ is the relative phase pattern at a given time t, $\boldsymbol{X}_1$ and $\boldsymbol{X}_2$ are regressors based on the universal centroids that indicate front-leading/back-lagging (averaged with mode 1 and reverse mode 4) and left-leading/right-lagging patterns (averaged with mode 2 and reverse mode 3), respectively (see Supplementary Information Section B.3 for detail). β_1 and β_2 represent the coefficients of explanation using each regressor. ε represents residuals that cannot be explained by the superposition of $\boldsymbol{X}_1$ and $\boldsymbol{X}_2$. As a result, the coefficients are given for each time frame.

Quantifying brain states is challenging because both the relative phase time series and traditional measurements are calculated for each channel. Conventional approaches often reduce the dimension of the time series by averaging the measurements across channels, even though this approach may overlook spatially specific brain activity. In contrast, our approach preserves spatial information by focusing on temporal patterns without averaging over channels. In summary, we can obtain three distinct coefficient time series (i.e. β_1, β_2, and $|\boldsymbol{\varepsilon}|$) using multiple linear regression with the universal centroids.

4.4 Statistics over Brain States

By applying multiple linear regression and comparing whether $|\beta_1|$ is larger than $|\beta_2|$, we can obtain an index for each time frame. This index indicates the similarity to specific modes; i) mode 1 (front-leading/back-lagging, i.e. positive sign of β_1), ii) mode 2 (left-leading/right-lagging, i.e. positive sign of β_2), iii) mode 3 (right-leading/left-lagging, i.e. negative sign of β_2), iv) mode 4 (back-leading/front-lagging, i.e. negative sign of β_1). Using these indices, we can construct a probability density function to calculate the mode distribution over different brain states. In addition, by weighting each time frame with its corresponding regression coefficient, we can better distinguish the brain states (see Supplimentary Information Section B.7). To get the information intuitively comparing with unweighted version, we normalize the statistics with the mean of $\sqrt{\beta_1^2 + \beta_2^2}$ in baseline (eyes-closed resting state) to reasonably compare across

different brain states in Figures S18 and S20. This weighted approach enhances the effects of clear patterns and reduces the effects of ambiguous patterns. In the following analyses of EEG relative phase patterns, we find that the mode distribution can distinguish different brain states.

Furthermore, we can examine the dwell time for each mode. The dwell time refers to the time spent in a mode before transitioning to another. The mode time series changes noisily at the boundary of each mode. By investigating the average dwell time distribution across each mode, we can reduce the impact of these boundary effects and obtain a more accurate characterization of brain states. In addition, we can also define the weighted dwell time by multiplying the coefficients of multiple linear regression.

For the general anesthesia dataset, where sample sizes varied significantly across states (resting = 90, LOC = 15, Burst = 30, Suppression = 30, ROC = 45), we applied bootstrap resampling 1,000 times per state and compared the resampled means. To compare mode occurrences, dwell times, and iPR across different states, we performed one-way ANOVA for each mode. For each resampling iteration, confidence intervals were computed, and p-values were estimated as the proportion of bootstrap samples in which the confidence interval did not contain zero. To account for multiple comparisons, p-values were adjusted using the Bonferroni-Holm method. For the typically developed vs. ADHD dataset, where the sample sizes were sufficiently large and the difference less pronounced (typically developed = 66, ADHD = 40), we conducted statistical analyses without resampling. We performed a two-sample t-test to compare mode occurrences and dwell times. We refer to the Supplementary Information Section A for details on sample sizes.

4.5 Principal Component Analysis (PCA) of Relative Phase Dynamics

Principal component analysis (PCA) is a linear dimensionality reduction technique that finds the dominant axes of variation from a given dataset [64, 65]. By applying PCA, we can obtain the principal components, with each component explaining a proportion of the total variance along its corresponding axis. The inverse Participation Ratio (iPR) quantifies the heterogeneity of a given distribution by measuring how many principal components significantly contribute to the overall variance [66, 67]. We can use the iPR to find an effective number of the principal axes across different brain states and quantify the differences by comparing them.

The relationship between linear regression, K-means clustering, and PCA is well established [68]. (Ding and He, 2004) demonstrated that the cluster centroid space of the continuous solution of the K-means clustering algorithm spans the first $K-1$ principal directions. Despite this theoretical equivalence, we applied all three methods to check the consistency of our results. This provides robust validation by cross-checking the findings obtained through each technique.

4.6 EEG Data & Preprocessing

In this section, we describe the dataset and preprocessing pipeline (For details, see the dataset description in Supplementary Information A). We used three types of

datasets: 1) general anesthesia EEG data (UofM, University of Michigan) to find dominant relative phase patterns in the sub-second time scale because anesthesia is an obvious stimulus to weaken consciousness; 2) checkerboard task of simultaneous EEG-fMRI data (NKI, Nathan Kline Institute) to examine the meaning of the relative phase patterns as compared with functional networks based on fMRI BOLD signals; 3) ADHD/Control EEG data (HBN, Healthy Brain Network) to suggest that the relative phase approach can be applied in detecting neurodevelopmental disorders. For the preprocessing procedure, we used the EEGLAB package in MATLAB [69]. The EEG signal was processed as follows: 1) notch filtered at 60 Hz to remove power line noise, 2) bad channels were detected and removed using the `trimOutlier.m` function, and 3) band-pass filtered across six frequency bands (delta: 1-4 Hz, theta: 4-8 Hz, alpha: 8-12 Hz, low beta: 12-20 Hz, high beta: 20-30 Hz, gamma: 30-50 Hz). For the fMRI BOLD signal, we downloaded the preprocessed data from the website [25, 70].

4.7 fMRI Data & Preprocessing

In fMRI BOLD signals, we use the preprocessed data served by the reference site [25, 70, 71] (`func_pp_filter_gsr_sm0.mni152.3mm.nii.gz`). Briefly, the structural preprocessing included skull-stripping, tissue segmentation (gray matter, white matter, cerebrospinal fluid), and registration to the MNI152 template. The functional preprocessing included slice timing, motion correction, boundary-based co-registration, nuisance regression (Friston's 24 head motion parameters, white matter, cerebrospinal fluid, and global signal), band-pass filter (0.01-0.1 Hz) and linear and quadric detrending. For the more detailed description, we explain it in Supplementary Information Section A.

4.8 Other Measures

To validate that the relative phase approach is analogous and related to other measures, we compared it with key metrics such as amplitude and phase-lag measures. Additionally, we compared relative phase with measures that quantify traveling wave propagation to demonstrate that our measure captures the directionality of activity. To accomplish this, we applied the relative phase and other measures to the EEG data collected from the University of Michigan and looked at how the relationships between measures change across different states.

For each state, we segmented the alpha-band filtered signal into non-overlapping epochs of 2 seconds (see Figures S2, S3, and S4 for results of 0.5, 5, and 10 second time windows). The measures were then computed over these data segments. Finally, pairwise linear correlations were calculated for the time series of the measures. These correlation values were Fisher Z-transformed and averaged across subjects. P-values were calculated from these values and corrected for multiple comparisons using the Bonferroni method.

4.8.1 Amplitude

To calculate the amplitude, we applied the Hilbert transform to the segmented signals and averaged the instantaneous amplitude over each window. The amplitude time

series for each channel was then averaged across the frontal and parietal regions. For the frontal region, we selected 14 channels corresponding to the electrodes Fpz, Fp1-2, AF3-4, AF7-8, Fz, F1-4, and F7-8. Similarly, for the parietal region, we considered the electrodes Pz, P1-8, POz, PO3-4, and PO7-8.

4.8.2 Phase Lag Index

As a measure of functional connectivity, we used the weighted phase-lag index (wPLI), which takes into account the strength of the phase difference between signals and is robust to volume conduction and uncorrelated noise sources [22]. The wPLI ranges from 0 (random phase lead/lag) to 1 (consistent phase lead/lag). After obtaining the wPLI matrix for all channel pairs, we averaged the values for the frontal, parietal, and fronto-parietal regions. Additionally, we defined a directional connectivity measure using the signed wPLI, averaging over the frontal and parietal channels.

4.8.3 Traveling Wave Propagation

We calculated two measures of traveling waves using three lines of electrodes spanning from the frontal to the occipital regions. These included one line of midline electrodes and two lines of electrodes positioned to the left and right of the midline, respectively. First, we quantified traveling wave propagation using 2D fast Fourier transform (FFT) representations of the time-by-channel data matrix [10]. The spectral peaks in the first and fourth quadrants of the 2D FFT spectra correspond to forward- or backward-propagating waves. We took the maximum value, P_{real}, over spatial frequencies in the temporal frequency domain, and repeated this procedure with shuffled electrodes to obtain a surrogate measure as P_{shuffled}. The amount of waves was then calculated in decibels [dB] as $10 \cdot \log_{10}(P_{\text{real}}/P_{\text{shuffled}})$, which represents waves relative to the null distribution. The forward- or backward-propagating waves were calculated for each electrode line, and then averaged. Additionally, we measured traveling wave propagation by calculating the phase gradient over the three lines of electrodes [8]. This involved computing the relative phase across the selected electrodes and fitting a polynomial surface to these values. For each time point, we extracted the y coefficient from the polynomial, which quantifies the phase gradient from the frontal to the occipital electrodes.

4.9 Simulation of relative phase dynamics with Kuramoto oscillators

To elucidate the mechanism behind the mode fluctuations, we ran simulations of relative phase dynamics using a Kuramoto model, a well-known canonical coupled oscillator model frequently used to model large-scale cortical dynamics [7, 24, 72–85]. Using the generated relative phase signals from the model on human cortical network, we constructed the spatially extrapolated topoplot to obtain regression coefficients (β_1 and β_2) that specify the mode distribution over different brain states, using the same procedure for the empirical EEG data. Specifically, we focused on modeling the general anesthesia EEG data (UofM, University of Michigan) to find the model parameters

that best match the empirical statistics of the brain states including mode occurrence and dwell time. Below, we describe the model and simulation procedure in more detail.

4.9.1 Structural connectivity data

The structural and function connectome data was collected from 70 healthy individuals on a 3T scanner [86]. We used a group-averaged structural network generated with a consensus approach [87] which preserve the edge length distribution in individual participants, described in detail elsewhere [46, 88, 89]. In particular, we used the network with 114 regions. The structural matrix was further binarized, yielding a binary adjacency matrix of size 114 by 114 specifying the connectivity between brain regions. This matrix was then used to specify the connection between nodes in the Kuramoto model, explained below.

4.9.2 Kuramoto model

To simulate the phase signals of individual regions on the brain network, we utilized a Kuramoto model with a generalized coupling function that includes a constant term (c_0), which results in a more realistic first order approximation of many coupling functions obtained from the phase reduction method [27, 28, 53]. The model is written as:

$$\frac{d\theta_i}{dt} = \omega_i + S \sum_{j=1}^{N} A_{ij} \left[c_0 + \sin\left(\theta_j - \theta_i - \tau\right)\right] \quad , \tag{4}$$

where θ_i is the phase of the oscillator i, ω_i is the intrinsic frequency of the oscillator, S is the global coupling strength, $\mathbf{A}$ is the binary adjacency matrix of the network, and τ is the phase shift term between two nodes capturing the transmission delay between regions. c_0 is a constant that results from the first-order approximation of the coupling function. Seen in another way, this term can be thought of as a natural consequence of incorporating diffusive coupling in limit cycle oscillators [29, 44, 45, 55]. For all of our simulations, we set $\omega = 10$ Hz for all nodes to focus on the alpha band frequency, and $\tau = 0.12\pi$, which approximately translates into the average time delay between brain regions.

4.9.3 Ornstein-Uhlenbeck (OU) and other stochastic processes in c_0

The previous study has shown that inclusion of the c_0 parameter in the coupling function of oscillators results in a rich repertoire of phase dynamics, especially relevant to the transitions between two distinct and dominant modes in the brain: one in which high-degree midline cortical regions phase-lag the network becoming sink of the directionality, and one in which they phase-lead the network and becoming source of the directionality [45]. To simulate the signals, we assumed that the brain exhibits random fluctuations in the c_0 parameter. The stochastic dynamics were specified with the Ornstein-Uhlenbeck (OU) process [90], a commonly adopted framework for implementing time-varying random noise [91–95]. Formally, the OU process for our variable of interest x_t ($= c_0$ at time t) is described as:

$$dx_t = -\psi\left(x_t - \mu\right) dt + \sigma dW_t \quad , \tag{5}$$

where ψ is the parameter controlling for the rate of drift toward the constant μ which specifies the mean of the process, and σ is the parameter controlling the variance of the Gaussian noise dW_t. While μ could be a free parameter, we set $\mu = \sin(\tau)$ for all simulations as this corresponds to the in-phase synchronous state.

To explore other potential random dynamics in c_0 that might account for the observed relative phase dynamics, we tested two additional stochastic processes involving pitchfork bifurcations. More specifically, the supercritical case was described by its normal form involving third-order term, with the variable centered at μ as follows:

$$dx_t = -\psi \left(r\left(x_t - \mu\right) - \left(x - \mu\right)^3 \right) dt + \sigma dW_t \quad , \tag{6}$$

where $r > 0$ is the parameter controlling the distance between the two stable fixed points (as shown in Supplementary Figure S26B). Note that the two stable fixed points appear only when $r > 0$ [96].

For the subcritical case, an additional fifth-order term was included to stabilize the dynamics as follows:

$$dx_t = -\psi \left(r\left(x_t - \mu\right) + \left(x - \mu\right)^3 - \left(x - \mu\right)^5 \right) dt + \sigma dW_t \quad , \tag{7}$$

where r is a parameter bounded between $-0.25 < r < 0$ to allow for two stable fixed points (Supplementary Fig. S26C). For all simulations, we chose $r = 0.1$ for the supercritical case and $r = -0.18$ for the subcritical case to allow for two stable fixed points on both sides of $\mu = \sin(c_0)$, namely, the attractors states for mode 1 and 4 (Supplementary Figure S25A).

4.9.4 Parameter estimation using grid search

To estimate the parameters of the stochastic processes, we ran simulations of Kuramoto oscillators with stochastic processes in c_0 for 60s with a time step of $\Delta t = 0.001$ (for a total of 60,000 time steps). This was repeated for 10 unique random seeds, and the resulting mode occurrences and dwell time were averaged. We used grid search to run simulations with the given values of ψ, σ (step size of 0.5), and the coupling strength S (step size of 0.1), and selected the set of parameters which exhibited the minimum mean absolute error from the empirical mode occurrences and dwell times.

Data availability

The EEG dataset for the general anesthesia presented in this article are not publicly available. Requests to access these datasets should be directed to J.-Y.M. The simultaneous EEG-fMRI dataset with the checkerboard task, and ADHD vs. typically developed EEG dataset are publicly available: for more details, please refer to the references (Telesford et al., 2023) and (Alexander et al., 2017), respectively.

Code availability

Code for models, simulations and analyses is available at https://github.com/youngjai/RelativePhaseAnalysis [97].

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Author contributions

Y.P., Y.C., H.K., J.-Y.M. designed the study, and Y.K., J.H.W., H.C., T.X., U.L., S.-J.H., C.J.H. provided input and revisions. Y.P., H.K., J.-Y.M. developed the pipeline of the relative phase analysis. Y.P., Y.C., H.K., Y.K., J.-Y.M. developed and implemented the data analysis. J.H.W., J.-Y.M. developed and conducted the numerical simulations. Y.C., Y.K., H.C. performed the statistical analysis. G.A.M., T.X., U.L., S.-J.H. provided datasets. Y.P., Y.C., Y.K., J.H.W., J.-Y.M. wrote the manuscript, which was revised by H.K., H.C., U.L., S.-J.H., C.J.H.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information This manuscript is accompanied by supplementary material, containing additional texts and figures.

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