

Disparity in temporal and spatial relationships between resting-state electrophysiological and fMRI signals

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Abstract

Resting-state brain networks (RSNs) have been widely applied in health and disease, but the interpretation of RSNs in terms of the underlying neural activity is unclear. To address this fundamental question, we conducted simultaneous recordings of whole-brain resting-state functional magnetic resonance imaging (rsfMRI) and electrophysiology signals in two separate brain regions of rats. Our data reveal that for both recording sites, spatial maps derived from band-specific local field potential (LFP) power can account for up to 90% of the spatial variability in RSNs derived from rsfMRI signals. Surprisingly, the time series of LFP band power can only explain to a maximum of 35% of the temporal variance of the local rsfMRI time course from the same site. In addition, regressing out time series of LFP power from rsfMRI signals has minimal impact on the spatial patterns of rsfMRI-based RSNs. This disparity in the spatial and temporal relationships between resting-state electrophysiology and rsfMRI signals suggests that electrophysiological activity alone does not fully explain the effects observed in the rsfMRI signal, implying the existence of an rsfMRI component contributed by “electrophysiology-invisible” signals. These findings offer a novel perspective on our understanding of RSN interpretation.

eLife assessment

This **important** study combines fMRI and electrophysiology in sedated and awake rats to show that LFPs strongly explain spatial correlations in resting-state fMRI but only weakly explain temporal variability. The authors propose that other, electrophysiology-invisible mechanisms contribute to the fMRI signal. The evidence supporting the separation of spatial and temporal correlations is **convincing**, and the authors consider alternative potential factors that could account for the differences in spatial and temporal correlation that were observed. This work will be of interest to researchers who study the mechanisms behind resting-state fMRI.

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Introduction

Sophisticated brain function requires coordinated activities from separate brain regions, collectively forming functional brain networks. Functional brain networks in humans and animals are predominantly studied using the method of resting-state functional magnetic resonance imaging (rsfMRI), which measures the synchronization of brain-wide spontaneous blood-oxygen-level dependent (BOLD) signals. These networks are commonly referred to as resting-state brain networks (RSNs).

Despite the widespread application of BOLD-derived RSNs in both health and disease contexts, their relationship to the underlying neural activity remains incompletely understood. This is a fundamental issue, as the BOLD signal is known to indirectly reflect neural activity through accompanying hemodynamic and metabolic changes, a mechanism known as neurovascular coupling (NVC). While tight NVC has been repeatedly demonstrated when neural activities are evoked by explicit external stimulation (Goense and Logothetis, 2008 [↗](#); Logothetis et al., 2001 [↗](#); Nemoto et al., 2004 [↗](#)), this relationship in the resting state remains elusive. There is considerable evidence indicating that the spatial patterns of most RSNs effectively mirror established functional systems and activation patterns observed during various tasks (Biswal et al., 1995 [↗](#); Glasser et al., 2016 [↗](#); Hampson et al., 2002 [↗](#); Lowe et al., 1998 [↗](#); Smith et al., 2009 [↗](#)), as well as patterns of brain structural networks (Andrews-Hanna et al., 2010 [↗](#); Greicius et al., 2009 [↗](#); Lowe et al., 2008 [↗](#)). In addition, alterations in RSNs have been documented in several brain disorders, aligning with neuropathophysiological changes (Buckner et al., 2009 [↗](#)). This collective body of evidence suggests a robust neural basis for RSNs. However, it is notable that despite these findings, the predictive power of resting-state electrophysiological signals for corresponding rsfMRI time series is often relatively low (Mateo et al., 2017 [↗](#); Scholvinck et al., 2010 [↗](#); Winder et al., 2017 [↗](#)), and some studies have even demonstrated a disconnection between neural activity and hemodynamic signals under specific conditions (Maier et al., 2008 [↗](#); Zhang et al., 2019 [↗](#)). Moreover, various studies have reported divergent electrophysiological correlates of the rsfMRI signal across a broad spectrum of LFP bands, spanning from infraslow signals (Hiltunen et al., 2014 [↗](#); Pan et al., 2013 [↗](#)) and low-frequency delta/sub-delta band signals (He et al., 2008 [↗](#); Lu et al., 2007 [↗](#)) to high-frequency gamma band signals (Bastos et al., 2015 [↗](#); Foster et al., 2015 [↗](#); Keller et al., 2013 [↗](#); Mukamel et al., 2005 [↗](#); Nir et al., 2008 [↗](#); Magri et al., 2012 [↗](#)), as well as spiking activity (Mukamel et al., 2005 [↗](#)). These findings suggest that the rsfMRI signal may reflect diverse aspects of neural activity. Taken together, how RSNs and rsfMRI relate to spontaneous neural activity remains unclear (Laufs et al., 2003 [↗](#); Liu et al., 2011 [↗](#); Mantini et al., 2007 [↗](#)), highlighting a significant gap in our understanding of functional brain networks.

To address this critical issue, we systematically investigated the role of electrophysiological activity in determining specific spatiotemporal patterns of BOLD-based RSNs. In conjunction with whole-brain rsfMRI, we simultaneously recorded electrophysiology signals in the primary motor cortex (M1) and anterior cingulate cortex (ACC) in rats under light sedation and wakefulness. These brain regions were chosen due to their distinct roles in sensorimotor function and integrative cognition, respectively. Our data show that in both light-sedation and awake states, the spatial patterns of RSNs derived from gamma band power closely resemble BOLD-derived RSNs for both the M1 and ACC, and lower frequency band-derived RSNs exhibit inversed spatial patterns, both indicating strong neural underpinning of RSNs. However, the temporal profiles of band-limited LFP powers at both recording sites exhibit considerably lower temporal correlations with the corresponding local BOLD time courses. Moreover, regressing out the gamma band power or powers of all LFP bands has only limited effects on the spatial patterns of BOLD-derived RSNs, collectively suggesting LFP powers contribute only partially to the local rsfMRI signal. This

disparity in spatial and temporal relationships between resting-state BOLD and electrophysiology signals implies that there might be an electrophysiology-invisible component of brain activity that significantly influences the rsfMRI signal and RSNs.

Results

To systematically analyze the spatiotemporal relationship between resting-state electrophysiology and fMRI signals, we conducted simultaneous recordings of whole-brain rsfMRI and electrophysiology signals in the M1 and ACC in rats under both light-sedation and awake states (Fig. 1A). The accuracy of electrode placement in the M1 and ACC was confirmed using T2-weighted structural images (Fig. S1). Raw electrophysiology data were initially preprocessed to remove MR artifacts using a template regression approach (Tu and Zhang, 2022). Subsequently, the LFP was extracted by bandpass filtering preprocessed electrophysiology data within the frequency range of 0.1 - 300 Hz. An illustration of denoised LFP is depicted in Fig. 1A and Fig. S2. Band-specific LFP power was computed using a conventional LFP band definition (delta: 1–4 Hz, theta: 4–7 Hz, alpha: 7–13 Hz, beta: 13–30 Hz, gamma: 40–100 Hz). Figs. 1B–C illustrate the cross correlations between LFP power and BOLD signal in the M1 across the LFP spectrum (Fig. 1B, 1-Hz band interval) and for individual LFP bands (Fig. 1C). These data demonstrate that gamma band power is positively correlated with the BOLD signal, while lower-frequency bands display negative peak correlations with the BOLD signal. Additionally, the lag of the BOLD signal is approximately 2 sec for all bands, consistent with the hemodynamic response function (HRF) delay previously reported in rodents (Scholvinck *et al.*, 2010; Winder *et al.*, 2017).

LFP and rsfMRI signals derive consistent RSN spatial patterns in lightly sedated rats.

We first examined the spatial relationship between brain-wide rsfMRI signals and frequency band-specific LFP powers in lightly sedated rats. For each recording site, its BOLD-derived RSN was obtained as the seedmap, calculated by voxel-wise correlating the regionally averaged BOLD time series of the seed (M1 in Fig. 1F and ACC in Fig. 2B) with BOLD time series of individual brain voxels. This seedmap conventionally represents the resting-state functional connectivity (RSFC) pattern for the seed region. To assess the extent to which this RSN could be obtained using the LFP signal recorded from the same location (M1 or ACC), we convolved the power of each LFP band with a rodent-specific HRF (Fig. 1D, (Tong *et al.*, 2019)) to generate the LFP band-predicted BOLD signal. Subsequently, we voxel-wise correlated this signal with the brain-wide rsfMRI signal, producing the LFP band-derived RSN map (Fig. 1E, Fig. 2A). Our findings revealed that the gamma band power-derived RSN map exhibited high spatial consistency with the corresponding BOLD-derived RSN map (i.e. seedmap). Specifically, for M1, the voxel-to-voxel Pearson correlation coefficient (CC) between the mean gamma-derived RSN map (Fig. 1E) and mean BOLD-derived RSN map (Fig. 1F) was 0.95 (Fig. 1K, $R^2 = 0.90$), indicating 90% of the variance in the M1 BOLD-derived RSN map could be explained by the gamma-derived map. Conversely, spatial maps generated by lower-frequency bands displayed inverse correlations with the M1 BOLD-derived RSN map, with a trend of increasingly negative spatial CC in lower-frequency bands (Figs. 1E–J, delta: CC = -0.78; theta: CC = -0.78; alpha: CC = -0.5; beta: CC = -0.34), consistent with the LFP-BOLD cross correlations for these bands shown in Fig. 1B–C. These relationships are repeatable in the ACC (Figs. 2A–G, delta: CC = -0.62; theta: CC = -0.3; alpha: CC = -0.12; beta: CC = 0.12; gamma: CC = 0.85). These results suggest that the spatial patterns of BOLD-based RSNs can be reliably obtained using band-specific LFP signals.

To confirm that these findings were not an artifact of specific frequency cutoffs we adopted for any LFP band, we repeated the analysis for all individual 1-Hz bands across the full LFP spectrum. Once again, we observed a gradual transition from negative to positive spatial correlations in LFP-

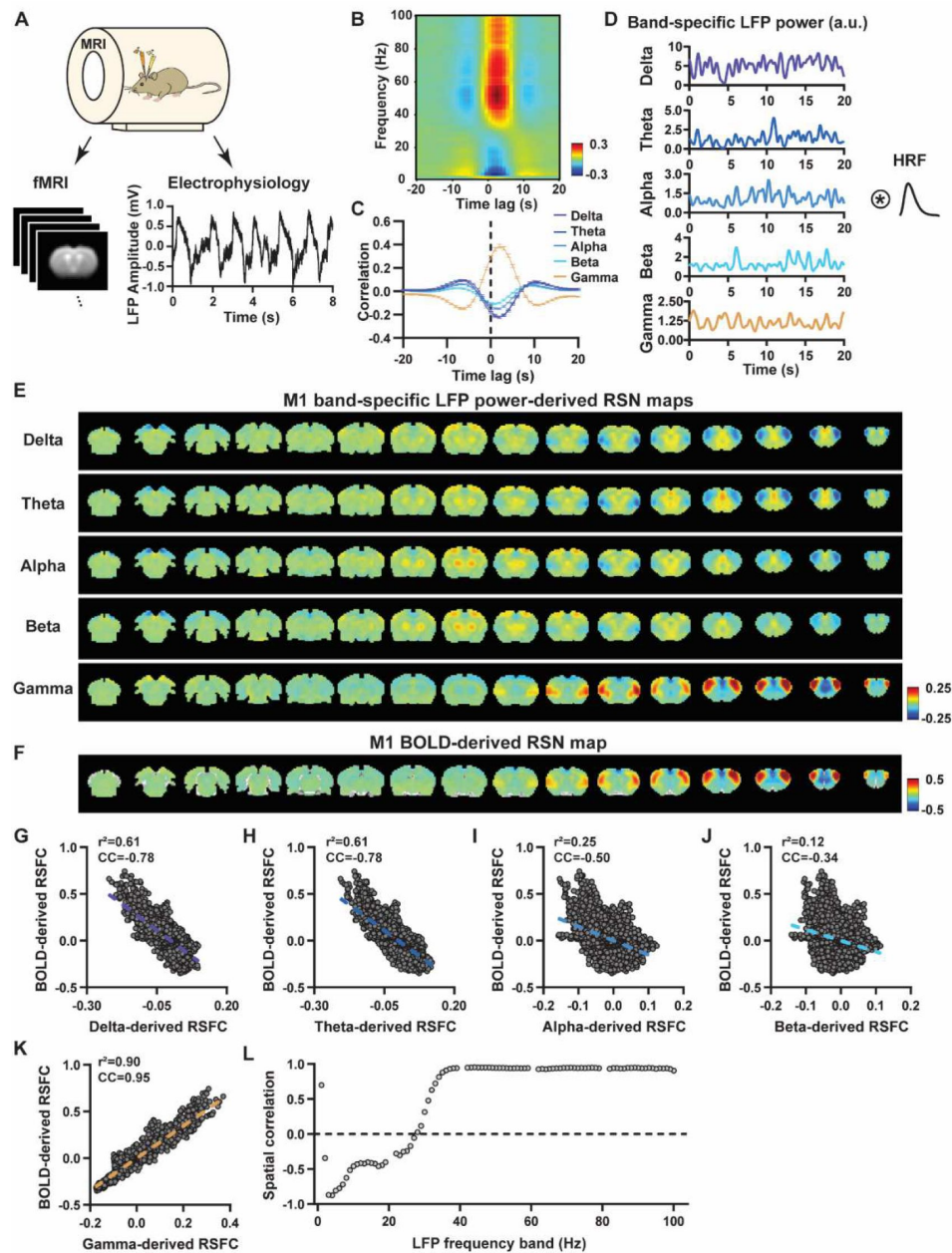


Figure 1.

Highly consistent RSN spatial patterns derived from LFP and rsfMRI signals in the M1 of lightly sedated rats.

A) Simultaneous acquisition setup for whole-brain rsfMRI and electrophysiology signals in the M1 and ACC. **B)** Cross correlations between the rsfMRI signal and LFP power in the M1 across the frequency range of 0.1–100 Hz (band interval: 1 Hz; lag range: -20 - 20 s). **C)** Cross correlations between the rsfMRI signal and powers of individual LFP bands in the M1. Error bars: SEM. **D)** Exemplar powers of individual LFP bands. Convoluting these powers with a rodent-specific hemodynamic response function (HRF) generates the corresponding LFP-predicted BOLD signals. **E)** M1 band-specific LFP power-derived RSN maps, obtained by voxel-wise correlating the LFP-predicted BOLD signal for each band with BOLD signals of all brain voxels. **F)** M1 BOLD-derived RSN map (i.e. M1 seedmap), obtained by voxelwise correlating the regionally averaged BOLD time course of the seed (i.e. M1) with BOLD time courses of all brain voxels. **G–K)** Spatial similarity between the M1 BOLD-derived RSN map and the M1 LFP-derived RSN map for each band, quantified by their voxel-to-voxel spatial correlations (G: delta, $CC = -0.78$; H: theta, $CC = -0.78$; I: alpha, $CC = -0.5$; J: beta, $CC = -0.34$; K: gamma, $CC = 0.95$). **L)** Spatial correlations between the M1 BOLD-derived RSN map and RSN maps derived by individual 1-Hz bands across the full LFP spectrum.

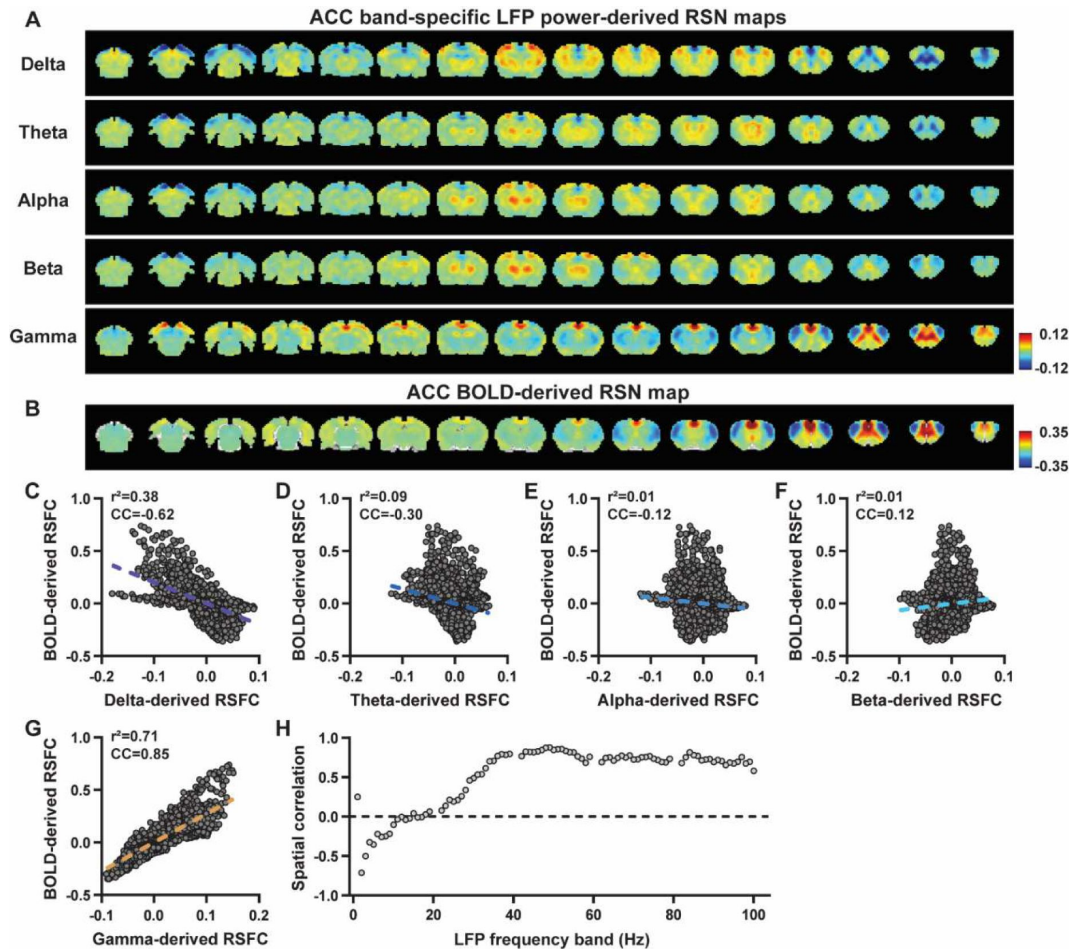


Figure 2.

Highly consistent RSN spatial patterns derived from LFP and rsfMRI signals in the ACC of lightly sedated rats.

A) ACC band-specific LFP power-derived RSN maps, obtained by voxel-wise correlating the LFP-predicted BOLD signal for each band with BOLD signals of all brain voxels. **B)** ACC BOLD-derived RSN map (i.e. ACC seedmap), obtained by voxel-wise correlating the regionally averaged BOLD time course of the seed (i.e. ACC) with BOLD time courses of all brain voxels. **C-G)** Spatial similarity between the ACC BOLD-derived RSN map and the ACC LFP-derived RSN map for each band, quantified by their voxel-to-voxel spatial correlations (C: delta, $CC = -0.62$; D: theta, $CC = -0.30$; E: alpha, $CC = -0.12$; F: beta, $CC = 0.12$; G: gamma, $CC = 0.85$). **H)** Spatial correlations between the ACC BOLD-derived RSN map and RSN maps derived by individual 1-Hz bands across the full LFP spectrum.

derived RSN maps with the corresponding BOLD-derived RSN maps as the LFP signal changed from low to high frequencies (**Fig. 1L** for M1; **Fig. 2H** for ACC). Additionally, as a control analysis, we temporally shuffled the gamma band power in the ACC, convolved it with the HRF and recalculated the correlation map (**Fig. S3**). As a result of this manipulation, the spatial pattern observed in **Fig. 2A** disappeared, suggesting that the observed LFP-derived spatial patterns were specifically related to the LFP signal, rather than an artifact of the HRF. We also confirmed that all our results are not sensitive to the rsfMRI data preprocessing step of global signal regression (**Figs. S4–S5**).

In summary, our data collectively indicate that BOLD-derived RSNs can be reliably replicated using LFP power from the same site in lightly sedated rats, underscoring the critical involvement of neural activity in RSN spatial patterns.

Temporal correlation between LFP power and local rsfMRI signal is significant but considerably weaker.

Given the high reliability of the gamma power in determining spatial patterns of BOLD based RSNs, it is logical to expect the HRF-convolved gamma power should reliably predict the rsfMRI time series from the same location. To test this hypothesis, we calculated temporal correlations between local rsfMRI time series and HRF-convolved LFP powers for individual scans at each recording site, and then averaged the resulting correlation values across scans. Surprisingly, we found that the local rsfMRI signal exhibited considerably weaker temporal correlations with LFP powers. In the M1, the LFP-BOLD temporal correlations gradually shifted from negative to positive as the LFP signal transitioned from low to high frequencies, mirroring the trend observed in spatial correlations (**Figs. 1E–K**). However, the absolute magnitude of these correlation coefficients was considerably lower, despite that they were all statistically significant (one sample t-tests, delta: CC = -0.20, $p = 2.1 \times 10^{-57}$; theta: CC = -0.19, $p = 7.1 \times 10^{-62}$; alpha: CC = -0.11, $p = 1.2 \times 10^{-42}$; beta: CC = -0.06, $p = 8.4 \times 10^{-15}$; gamma: CC = 0.37, $p = 2.1 \times 10^{-58}$, number of scans = 159). Similar results were observed in the ACC (one sample t-tests; delta: CC = -0.13, $p = 1.9 \times 10^{-28}$; theta: CC = -0.04, $p = 8.4 \times 10^{-7}$; alpha: CC = -0.03, $p = 6.0 \times 10^{-5}$; beta: CC = -0.01, $p = 0.1$; gamma: CC = 0.18, $p = 6.7 \times 10^{-42}$; number of scans = 172). Additionally, we confirmed that lower temporal correlations are not due to the HRF used (**Fig. S6**).

A notable difference in our calculation of spatial and temporal correlations may contribute to the disparity in their CC values. When computing spatial correlations, we first generated LFP- and BOLD-derived RSN maps for each scan, and then averaged these maps within each group before calculating spatial correlations using the averaged maps (**Figs. 1–2**). Conversely, for temporal correlations, we initially computed for correlation coefficients for individual scans, and then averaged the resulting correlation values across scans. This approach was chosen as averaging time courses first would diminish the actual signal due to the semi-random nature of spontaneous brain activities. Consequently, the variance in averaged RSN spatial maps might be lower than the variance in time series of individual scans, which can result in higher apparent spatial correlations than temporal correlations. To control this factor, we also computed spatial correlations between LFP- and BOLD-derived RSN maps for individual scans, and then averaged the corresponding correlations across scans. Similar to scan-wise temporal correlations, scanwise spatial correlations were significant for all LFP bands (one sample t-tests; in the M1, delta: CC = -0.37, $p = 4.9 \times 10^{-52}$; theta: CC = -0.39, $p = 3.9 \times 10^{-62}$; alpha: CC = -0.24, $p = 5.8 \times 10^{-37}$; beta: CC = -0.15, $p = 3.9 \times 10^{-15}$; gamma: CC = 0.58, $p = 1.0 \times 10^{-56}$; in the ACC, delta: CC = -0.26, $p = 2.6 \times 10^{-27}$; theta: CC = -0.09, $p = 1.7 \times 10^{-6}$; alpha: CC = -0.04, $p = 0.04$; beta: CC = 0.03, $p = 0.06$; gamma: CC = 0.33, $p = 5.4 \times 10^{-40}$). Comparisons of scan-wise spatial and temporal correlations (**Figs. 3A–B**) indicate that even after controlling for the variance level, the magnitude of spatial correlations remains appreciably higher than that of temporal correlations for all bands (paired t tests across

individual scans; in the M1, delta: $p = 1.01 \times 10^{-35}$; theta: $p = 3.74 \times 10^{-50}$; alpha: $p = 3.54 \times 10^{-25}$; beta: $p = 1.18 \times 10^{-12}$; gamma: $p = 7.02 \times 10^{-42}$; in the ACC, delta: $p = 6.73 \times 10^{-21}$; theta: $p = 5.75 \times 10^{-5}$; alpha: $p = 0.74$; beta: $p = 7.34 \times 10^{-5}$; gamma: $p = 3.43 \times 10^{-29}$).

Given that the gamma power-derived RSN map can explain ~90% of the spatial variance of the BOLD-derived RSN map (**Fig. 1K**, $R = 0.95$, $R^2 = 0.90$) when noise is diminished by averaging RSN maps across scans, we ask how much variance of the local BOLD time series the gamma power can explain without significant influence of noise. Although we cannot directly average rsfMRI/electrophysiology time courses across scans to reduce noise levels, we can estimate the true LFP-BOLD temporal correlation by quantitatively evaluating the effect of noise on correlation values. To achieve this aim, we utilized the difference between the spatial correlation of averaged M1 RSN maps (i.e. referred to as denoised data, $R = 0.95$, **Fig. 1K**) and that of unaveraged RSN maps (i.e. referred to as with-noise data, $R = 0.58$, **Fig. 3A**, gamma band power). Using this difference, we simulated two fixed signals with a true correlation of 0.95. By introducing varying levels of noise to the signals, we determined at what noise level the apparent correlation between the two signals became 0.58 (**Fig. 3C**). Specifically, in each trial, random noise at a defined contrast-noise-level (CNR) was added to the simulated signals, and this process was repeated 159 times (i.e. equal to the number of scans in our study) for a given CNR level. At each CNR level, the correlation was calculated based on either the averaged signals from all 159 trials (i.e. simulating denoised data, **Fig. 3C**), or the signals of individual trials (i.e. simulating with-noise data) before averaging resulting correlations across trials.

As anticipated, lower CNR values correspond to lower apparent trial-wise correlation values. Interestingly, we discovered that the trial-wise apparent correlation of 0.58, with the true correlation of 0.95, corresponds to the CNR of 1.3 (**Fig. 3D-E**), which aligns with the CNR of BOLD contrast reported in the literature (**Atkinson et al., 2008**). At this CNR level, we estimated that the true BOLD-LFP temporal correlation in the M1 should be approximately 0.59 ($R^2 = 0.35$, **Fig. 3F-G**), when the apparent correlation is 0.37 as measured by the gamma-BOLD temporal correlation in our real data (**Fig. 3A**). These findings indicate the temporal information provided by gamma power can only explain a minor portion (approximately 35%) of the temporal variance in the BOLD time series, even after accounting for the noise effect, which is in line with the reported correlation values between the cerebral blood volume (CBV) and fluctuations in GCaMP signal in head-fixed mice during periods of immobility ($R = 0.63$) (**Ma et al., 2016**). These results are also consistent with previous reports of relatively weak temporal correlations between gamma power and hemodynamic signals at rest obtained using different imaging modalities (**Scholvinck et al., 2010**; **Winder et al., 2017**). Furthermore, our simulation suggests that the difference in the number of data points (1200 in temporal correlation calculation vs. 6157 in spatial correlation calculation) has a negligible influence on correlation values (**Figs. 3D-G**).

Regressing out LFP powers has limited impact on RSN spatial patterns.

Given the lower predictive value of LFP power on the local rsfMRI signal, we investigated the extent to which the temporal information of LFP powers affects the RSN spatial patterns. The gamma-band power in the M1 (or ACC), after convolving with HRF, was linearly regressed out from rsfMRI signals of all brain voxels. As expected, the spatial patterns of gamma power-derived RSN maps observed in **Figs. 1E & 2A** disappeared after the regression (**Figs. 4A, 5A**). However, this regression process minimally altered M1/ACC BOLD-derived RSN maps (**Figs. 4B, 5B**). This result remained consistent when the powers of all LFP bands were voxel-wise regressed out from rsfMRI signals using soft regression (**Figs. 4C, 5C**). Soft regression was utilized to address the multicollinearity issue in the regression model resulting from potential correlations between LFP bands, as this method allows only unique components in five LFP bands to be regressed out.

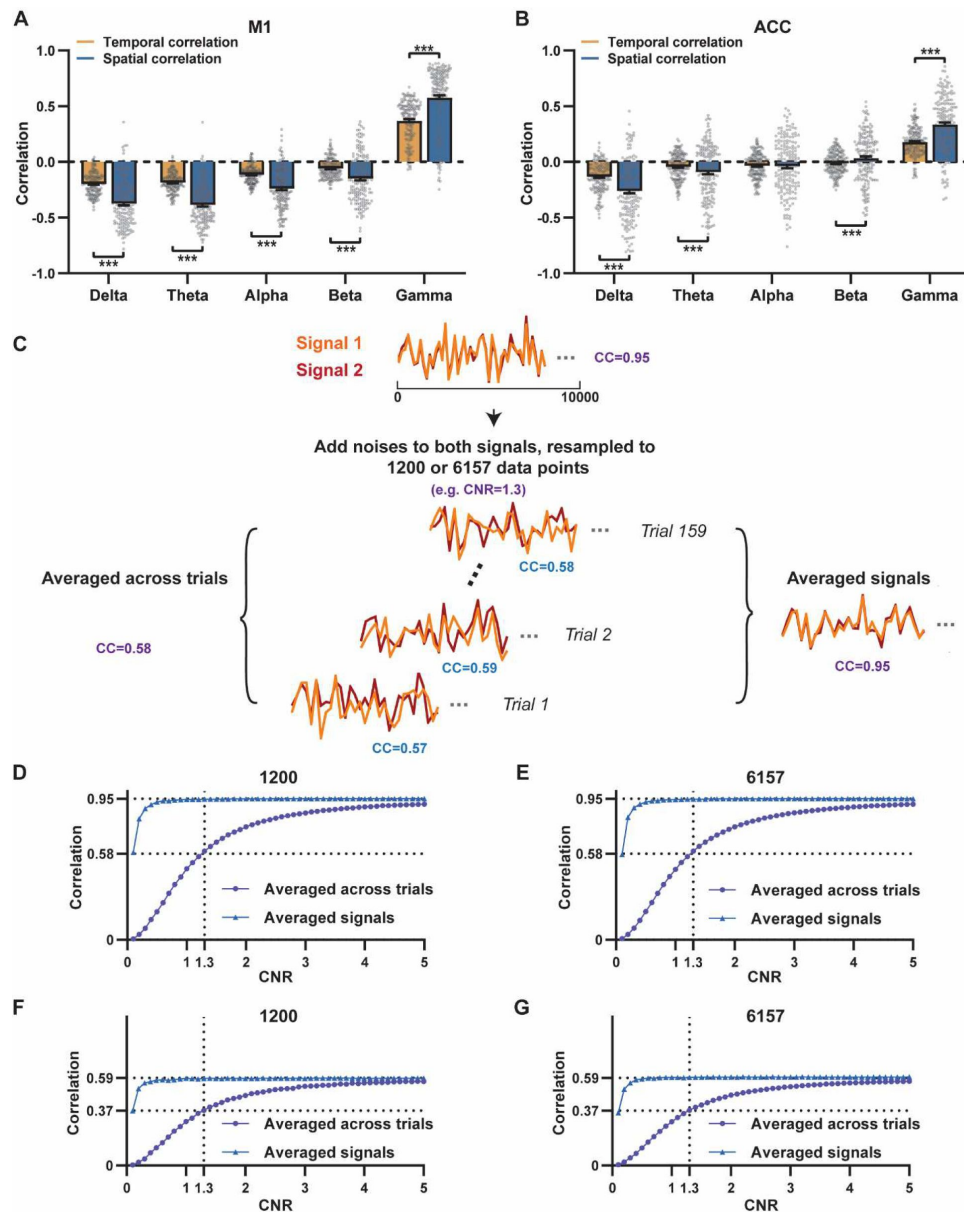


Figure 3.

Disparity in spatial and temporal correlations persists after controlling for the noise effect.

A, B) Comparison of scan-wise spatial and temporal correlations (paired t-tests across individual scans. ***: $p < 0.005$). **C-G**) Simulation to evaluate factors affecting apparent correlation values including contrast-to-noise ratio (CNR) and the number of data points; **C**) Two fixed signals with a true correlation coefficient of 0.95 are simulated (10000 data points) with random noise added at a given CNR level. This process is repeated 159 times (i.e. the number of scans in our study) for each CNR level. At each CNR, the CC is calculated based on either the averaged signals from all 159 trials (i.e. denoised data, triangle dots in D-G), or signals of individual trials (i.e. with-noise data, round dots in D-G) before averaging the resulting correlations across trials. **D**) Simulated signals resampled to 1200 data points (equal to the number of time points used to calculate temporal correlations). **E**) Simulated signals resampled to 6157 data points (equal to the number brain voxels used to calculate spatial correlations). Importantly, we can replicate the difference between true ($R = 0.95$) and apparent ($R = 0.58$) correlations obtained from denoised data and with-noise data, respectively, when $\text{CNR} = 1.3$. Therefore, we estimate that the CNR of our BOLD data is ~ 1.3 . **F, G**) The same process as C-E with the true correlation of 0.59. This true correlation value is obtained by iteratively setting different true correlation values and searching for the one that provides the trial-wise apparent correlation of 0.37, as measured by the gamma-BOLD temporal correlation in our real data (**Figs. 3A**), at $\text{CNR} = 1.3$. **F**) Simulated signals resampled to 1200 data points. **G**) Simulated signals resampled to 6157 data points.

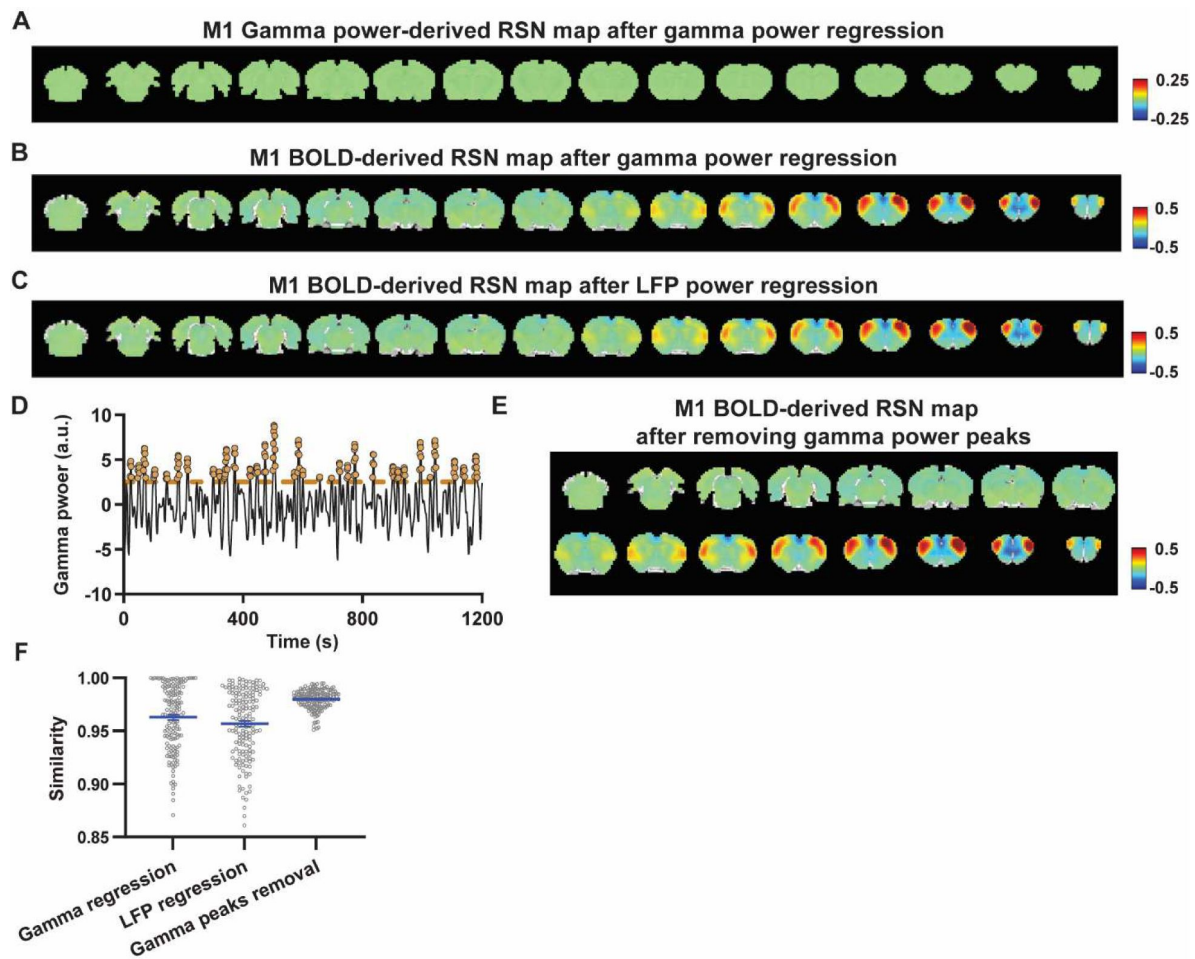


Figure 4.

Impact of removing the electrophysiology signal on M1 BOLD-derived RSN spatial patterns.

A) RSN map derived from gamma power after regressing out the HRF-convolved gamma power in the M1 from rsfMRI signals of all brain voxels. **B)** M1 BOLD-derived RSN map (i.e. M1 seedmap) after voxel-wise regression of the HRF-convolved gamma power from rsfMRI signals. **C)** M1 BOLD-derived RSN map after voxel-wise regression of all five LFP band powers from rsfMRI signals using soft regression. **D)** Peaks of HRF-convolved gamma power in one representative scan. **E)** M1 BOLD-derived RSN map after removing 15% of rsfMRI time points corresponding to gamma peaks. **F)** Spatial similarity of M1 BOLD-derived RSN maps before and after gamma power regression, regression of all LFP band powers, or gamma peak removal.

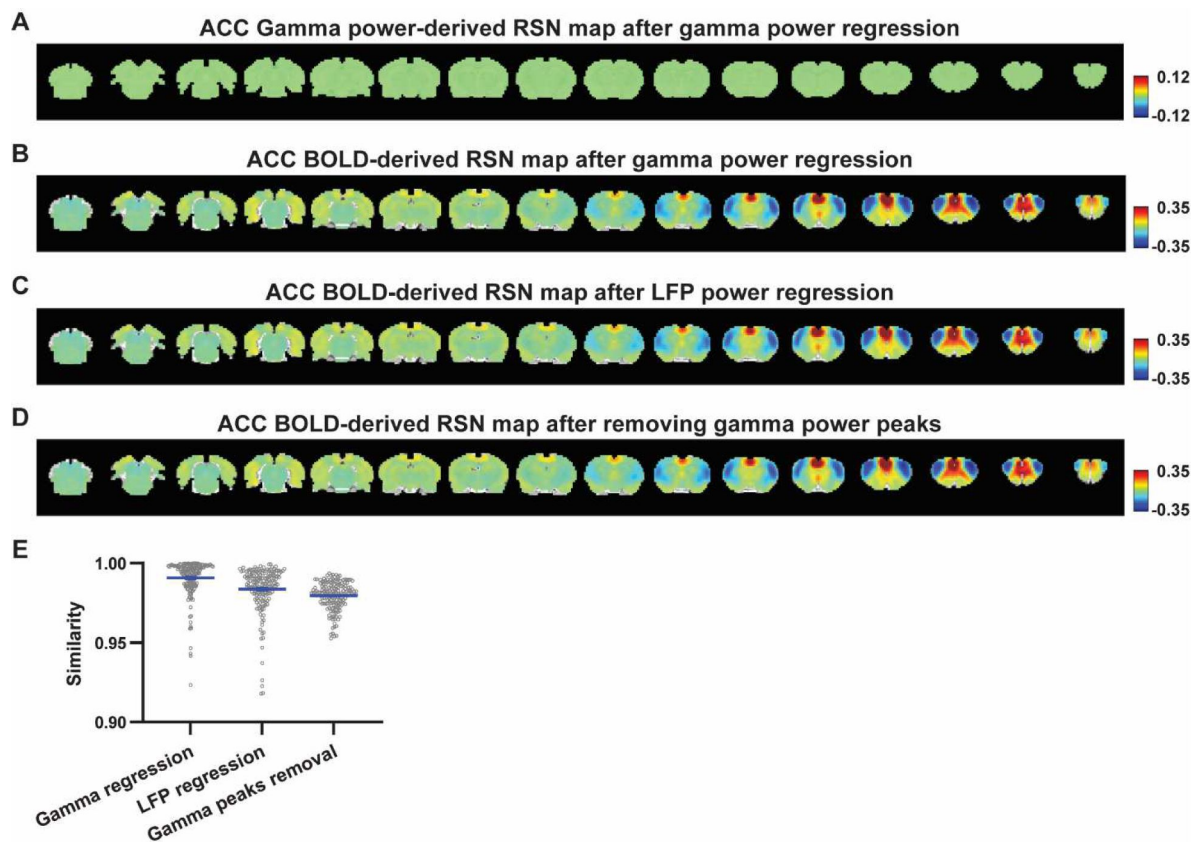


Figure 5.

Impact of removing the electrophysiology signal on ACC BOLD-derived RSN spatial patterns.

A) RSN map derived from gamma power after regressing out the HRF-convolved gamma power in the ACC from rsfMRI signals of all brain voxels. **B)** ACC BOLD-derived RSN map (i.e. ACC seedmap) after voxel-wise regression of the HRF-convolved gamma power from rsfMRI signals. **C)** ACC BOLD-derived RSN map after voxel-wise regression of all five LFP band powers from rsfMRI signals using soft regression. **D)** ACC BOLD-derived RSN map after removing 15% of rsfMRI time points corresponding to gamma peaks. **E)** Spatial similarity of ACC BOLD-derived RSN maps before and after gamma power regression, regression of all LFP band powers, or gamma peak removal.

To investigate whether the regression process is disproportionately dominated by time points with the largest LFP amplitude (i.e. outliers), we recalculated the M1/ACC BOLD-derived RSN maps after removing rsfMRI volumes corresponding to peaks in the M1/ACC gamma power (i.e. time points with the signal amplitude above the 85th percentile in HRF-convolved gamma power of each scan, **Figs. 4D, 4E** & **5D**). The spatial similarities between the BOLD-derived RSN maps before and after gamma power regression, all band power regression, or peak removal are summarized in **Figs. 4F** & **5E**, showing that the removal of gamma power has limited impact on the M1/ACC RSN maps.

To control for the potential nonlinear relationship between band-specific LFP powers and the rsfMRI signal, we calculated the mutual information between band-limited LFP powers and rsfMRI signals for all brain voxels (**Fig. S7**). The results show limited mutual information between any band-specific power and voxel-wise rsfMRI signals, indicating that the nonlinear component between BOLD and electrophysiological signals does not significantly influence RSN spatial patterns, which is consistent with the report that macroscopic resting-state brain dynamics are best described by linear models (Nozari et al., 2024). These data collectively indicate that the temporal fluctuations of LFP have limited effects on BOLD-derived RSN spatial patterns.

Disparity in temporal and spatial correlations persists across different physiological states.

To determine whether the disparity between temporal and spatial correlations of resting-state LFP and fMRI signals we observed is a specific phenomenon under anesthesia or can be generalized to different physiologic states, we repeated the experiment in awake rats. Despite that the physiological dynamics are substantially different, we still found higher spatial correlations between LFP-derived maps (**Fig. S8A**) and the BOLD-derived RSN map (**Fig. S8B**) in the M1. Also similar to what we showed in anesthetized rats (**Figs. 1** & **2**), correlation coefficients gradually changed from negative in low-frequency bands to positive in high-frequency bands, which were revealed both in conventionally defined bands (**Figs. S8C-G**) and 1-Hz bands (**Fig. S8H**). In the ACC, while spatial correlations in low-frequency bands were somewhat diminished, the overall pattern remained similar (**Fig. S9**). Similar to the results in **Fig. 3**, significant but weaker temporal correlations between the rsfMRI signal and HRF-convolved gamma band power were observed in awake rats (one sample t-tests; for M1, delta: CC = -0.05, $p = 2.3 \times 10^{-4}$; theta: CC = -0.06, $p = 4.7 \times 10^{-6}$; alpha: CC = -0.06, $p = 4.6 \times 10^{-5}$; beta: CC = -0.032, $p = 3.0 \times 10^{-3}$; gamma: CC = 0.04, $p = 0.02$; for ACC, delta: CC = 0.02, $p = 0.29$; theta: CC = 0.0009, $p = 0.96$; alpha: CC = -0.02, $p = 0.31$; beta: CC = 0.006, $p = 0.66$; gamma: CC = 0.10, $p = 9.52 \times 10^{-7}$; number of scans = 50). Scan-wise comparison between temporal and spatial correlations are shown in **Fig. S10**. Overall, both spatial and temporal correlations showed lower magnitudes in the awake state, likely due to increased variability from motion and other physiological fluctuations, as well as the smaller number of scans compared to the light sedation state (50 awake scans, 159 light-sedation scans for M1 and 172 light-sedation scans for ACC). Nonetheless, the consistent pattern of lower temporal but higher spatial correlations between gamma power and the rsfMRI signal supports the notion that this disparity is a general phenomenon across different physiological states.

The lack of significant alteration in BOLD-derived RSN maps after regressing out gammaband power or powers of all LFP bands in both ACC and M1 of awake rats (**Fig. S11**) further reinforces our earlier findings. These results indicate that the major findings observed in lightly anesthetized rats, including the disparity between temporal and spatial correlations, can be replicated in unanesthetized rats. Therefore, it appears that these results are not specific to the effects of anesthesia but rather reflect fundamental aspects of the relationship between electrophysiological and hemodynamic signals in the brain across different physiological states.

Ongoing rsfMRI signal could be contributed by electrophysiology-invisible brain activities.

Our findings indicate that the LFP signal can capture RSN patterns that account for nearly all the spatial variance observed in BOLD-based seedmaps. However, the temporal dynamics of the LFP signal only explain a minor fraction of the local BOLD time series and have minimal impact on the spatial patterns of BOLD-based RSNs. To reconcile this apparent contradiction, we propose a theoretical model, described as follows:

Brain activity consists of components measurable by electrophysiology and others that are electrophysiology-invisible. In addition to the electrophysiology activity, electrophysiology invisible brain activities, such as those involving nNOS neurons and astrocytes, actively contribute to NVC and can exert a significant influence on the rsfMRI signal. During the resting state, these two components may not be synchronized, lowering temporal correlations between electrophysiology and rsfMRI signals. Another factor contributing to low LFP-BOLD temporal correlations could be neuromodulations from distal modulator nuclei (e.g. locus coeruleus and/or basal forebrain), which exert strong vasoactive effects but may not proportionately affect electrophysiology activity. Moreover, the signaling of electrophysiology activities and that of electrophysiology-invisible are both constrained by the same anatomical pathways. This allows the two signals to generate similar RSN spatial patterns in parallel measured by the BOLD signal, which can reflect both direct and indirect anatomical connectivity. The model is summarized in **Figs. 6** and **S12**, and further details will be discussed in the next section.

Discussion

BOLD-derived RSNs have been widely investigated in multiple species (**Damoiseaux et al., 2006**; **Lu et al., 2012**; **Mantini et al., 2011**) and have been applied in various physiological and pathological conditions. However, the neural mechanisms underlying RSNs and the rsfMRI signal remain incompletely understood. To shed more light on this issue, we conducted systematic analysis of simultaneously recorded electrophysiology and rsfMRI signals in both lightly anesthetized and awake animals. Our findings reveal that both electrophysiology and rsfMRI signals can generate highly consistent brain-wide RSN patterns. However, the temporal information of the LFP signal contributes only minimally to the local BOLD time series at the same recording site. These seemingly paradoxical findings, along with those reported in the literature, can potentially be reconciled by the theoretical model we propose, which suggests that RSNs may also arise from electrophysiology-invisible brain activities that play a significant role in NVC. Together, our data and model offer a new perspective for interpreting the neural basis underlying the resting-state BOLD signal.

The spatial correspondence between BOLD- and electrophysiology-derived RSNs has been repeatedly reported across various physiological states and species using different methods. Studies employing electroencephalography (EEG) or electrocorticography (ECoG) in humans have shown that RSNs derived from the power of multiple-site electrophysiological signals exhibit similar spatial patterns to classic BOLD-derived RSNs, such as the default-mode network (**Hacker et al., 2017**; **Kucyi et al., 2018**). This high spatial correspondence between rsfMRI and LFP signals can even be found at the columnar level (**Shi et al., 2017**). Similarly, simultaneous recordings of resting-state calcium and fMRI signals in awake rats have revealed highly consistent spatial patterns between calcium- and BOLD-associated RSNs (**Ma et al., 2022**). Moreover, voltage sensitive dye imaging in mice has unveiled comparable sensory-evoked and hemisphere-wide activity motifs represented in spontaneous activity in both lightly anesthetized and awake states (**Mohajerani et al., 2013**). Furthermore, in a more recent study by Vafai and colleagues, overlapping cortical networks were identified using both fMRI and calcium imaging modalities,

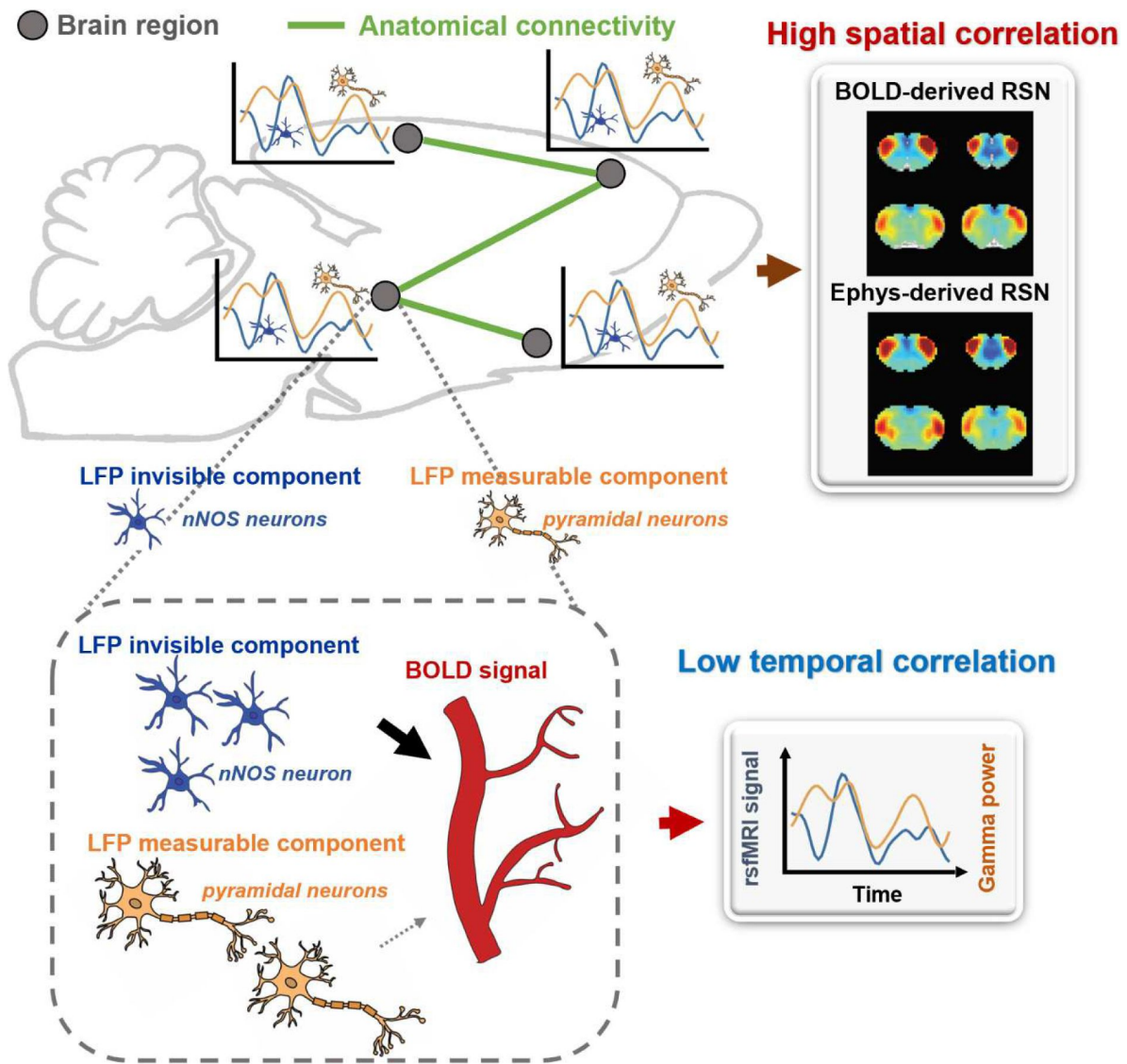


Figure 6.

A theoretic model that can explain the disparity in spatial and temporal correlations between resting-state electrophysiology and fMRI signals.

suggesting that networks observable in fMRI studies exhibit corresponding neural activity spatial patterns (Vafaii et al., 2024). These results align well with the notion that RSN spatial patterns are highly consistent with known functional systems and activation patterns observed in task-based studies (Biswal et al., 1995; Glasser et al., 2016; Hampson et al., 2002; Lowe et al., 1998; Smith et al., 2009), as well as patterns of structural networks (Andrews-Hanna et al., 2010; Greicius et al., 2009; Lowe et al., 2008). Taken together, previous studies and our data indicate that both electrophysiology and rsfMRI measurements can generate consistent RSN spatial patterns, strongly suggesting that the spatial structures of RSNs are dictated by neural activities.

Previous studies have also indicated that RSNs are likely constrained by axonal projections. For instance, consistent sensory-evoked and hemisphere-wide activity motifs in mice, as revealed using voltage-sensitive dye imaging, are defined by regional axonal projections (Mohajerani et al., 2013). Our previous work in awake rats further demonstrate spatial consistency between RSNs and anatomical connectivity patterns in thalamocortical networks (Liang et al., 2013). In the current study, we compared RSNs of M1 and ACC to their anatomical networks defined by the axonal projection patterns obtained from the Allen Brain Institute database (Fig. S13, (Oh et al., 2014)), illustrating that RSNs revealed by either the BOLD or LFP signal closely resemble the corresponding anatomical networks. It is important to note that RSNs measured by functional connectivity can reflect both direct and indirect connectivity and thus may not necessarily have identical spatial patterns as the corresponding anatomical networks (Honey et al., 2009).

In contrast to the seemingly strong LFP-BOLD relationship inferred from their high spatial correlations, we observed appreciably lower (yet significant) temporal correlations between the two signals from the same recording sites (M1 and ACC). Regressing out LFP powers has limited impact on RSN spatial patterns, reinforcing the notion that the contribution of temporal variations of the LFP signal to RSN spatial patterns is minor. These results are supported by previous research demonstrating weak but significant correlations between CBV changes and spontaneous gamma-band LFP or multiunit activity in awake, head-fixed mice (Winder et al., 2017). Importantly, persistent spontaneous fluctuations in CBV were observed even after blocking local neural spiking and glutamatergic input, as well as noradrenergic receptors, indicating that hemodynamic signal fluctuations may not dominantly reflect local ongoing electrophysiology activity (Winder et al., 2017). Comparably low temporal correlations between gamma-band power and the rsfMRI signal have been reported in monkeys (Scholvinck et al., 2010; Shmuel and Leopold, 2008). Additionally, data from our group show similarly low temporal correlations between spontaneous calcium peaks, a measure of neural spiking activity, and the rsfMRI signal in awake rats (Ma et al., 2022). Furthermore, Vafaii et al. revealed notable differences in functional connectivity strength measured by fMRI and calcium imaging, despite an overlapping spatial pattern of cortical networks identified by both modalities (Vafaii et al., 2024). These findings collectively suggest that while the temporal correlation between electrophysiology and rsfMRI signals is significant, the effect size of this correlation might be small. This result appears to remain consistent even for infraslow LFP activity (<1 Hz). Our data show that in the M1, the temporal correlation between infraslow LFP power and the rsfMRI signal was 0.08, while both derived consistent RSN spatial patterns (spatial correlation = 0.7), in line with the report that RSNs can be derived from infraslow LFP activity (Li et al., 2022). It is noteworthy that these results differ from two earlier studies in isoflurane-anesthetized rats, which found the LFP power in the primary somatosensory cortex was highly correlated with BOLD fluctuations (Liu et al., 2011; Pan et al., 2011). This discrepancy may be attributed to brain-wide synchronization during burst suppression in deeply anesthetized states in those studies.

Why would electrophysiology and rsfMRI signals exhibit unmatched spatial and temporal correlations? Our model offers one possible scenario that can reconcile this discrepancy. It hypothesizes that a portion of the rsfMRI signal is driven by electrophysiology invisible brain activities involved in NVC. LFP records various neural activities, such as synaptic potentials and

voltage-gated membrane fluctuations, reflecting the input and local neural processing of a particular brain region. However, electrophysiology cannot measure activities from certain cell populations, while electrophysiology invisible components can trigger vasoactive responses and significantly contribute to the rsfMRI signal. For instance, the electrical activity of nNOS neurons is not detectable by electrophysiology because the nNOS neuron population is very small, yet it strongly contributes to NVC. Chemogenetic or pharmacological stimulation of nNOS neurons causes vasodilation without detectable changes in LFP (Echagarruga et al., 2020). In addition, astrocytes, a type of glia cell, coordinate communication between neurons and blood vessels and play a crucial role in NVC. Astrocytes regulate vessel tone by releasing signaling molecules such as ATP, arachidonic acid metabolites and nitric oxide (Ladecola and Nedergaard, 2007; Mulligan and MacVicar, 2004; Murphy et al., 1993). Furthermore, astrocytes can alter the diameter of blood vessels by extending or retracting the endfeet wrapping around them (Mills et al., 2022; Niu et al., 2019). Optogenetic stimulation of astrocytes in transgenic mice without affecting neurons elicited a BOLD response, indicating that astrocyte activity alone can cause changes in the BOLD signal, independent of neuronal activity (Takata et al., 2018). Additionally, Uhlirova et al. conducted a study where they utilized optogenetic stimulation and two-photon imaging to investigate how the activation of different neuron types affects blood vessels in mice. They discovered that only the activation of inhibitory neurons led to vessel constriction, albeit with a negligible impact on LFP (Uhlirova et al., 2016). These studies collectively suggest electrophysiology-invisible activities can significantly drive the rsfMRI signal. Exclusively identifying all electrophysiology-invisible sources contributing to the rsfMRI signal is beyond the scope of this work. However, a key point is that as the resting state LFP and electrophysiology-invisible (and thus rsfMRI) signals reflect different components of brain activities, they can be minimally synchronized and display low temporal correlations. Another possible factor that can contribute to low BOLD-LFP temporal correlations is direct modulation of the vasculature from distant modulator nuclei (e.g. locus coeruleus and/or basal forebrain). Some neuromodulators, such as norepinephrine (NE) (Bekar et al., 2012; Kim et al., 2016) and acetylcholine (ACh) (Sato and Sato, 1995), have vasoconstrictive/vasodilatory effects that are spatially targeted in distributed brain regions, and thus can modulate brain-wide rsfMRI signals. However, these neural modulation effects may not be proportionately reflected from the electrophysiology signal, lowering BOLD-LFP temporal correlations (see a schematic diagram in Fig. S12). On the other hand, as the signaling of LFP- and electrophysiology-invisible components in functional networks is constrained by the same anatomical connectivity structure (Liu et al., 2018a; Liu et al., 2018b), the LFP- and BOLD-derived RSN spatial patterns can be highly similar and thus have high spatial correlations.

Our model can also potentially explain high spatial and temporal correlations when brain activation is evoked by external stimulation (Winder et al., 2017). At the evoked state, both LFP (and spiking activity) and electrophysiology-invisible components are temporally modulated by the same external stimulation paradigm, leading to both high temporal and high spatial correlations between fMRI and electrophysiology signals.

Potential pitfalls

Our proposed theoretic model represents just one potential explanation for the apparent discrepancy in temporal and spatial relationships between resting-state electrophysiology and BOLD signals. It is important to acknowledge that there may be other scenarios where a stronger temporal relationship between LFP and BOLD signals could manifest. For instance, recent research suggests that the relationship between LFP and rsfMRI signals may vary across different modes or instances (Cabral et al., 2023), which can be masked by correlations across the entire time series. Moreover, the 1-second temporal resolution employed in our study may obscure certain temporal correlations between LFPs and rsfMRI signals. Future investigations employing ultrafast fMRI imaging coupled with dynamic connectivity analysis could offer a more nuanced exploration of BOLD-LFP temporal correlations at higher temporal resolutions (Bolt et al., 2022; Thompson et al., 2014; Ma and Zhang, 2018).

In addition to LFP, various other features can be derived from electrophysiology signals and alternative methods for comparing electrophysiology and rsfMRI signals, such as rank correlation, warrant consideration. It is plausible that employing different features or comparison methods could yield a stronger BOLD-electrophysiology temporal relationship (Ma et al., 2016). In our current study we focused solely on band-limited LFP power as the primary feature in our analysis, given its prevalence in prior studies of LFP-rsfMRI correlates. More importantly, we demonstrate that band-specific LFP powers can yield spatial patterns nearly identical to those derived from rsfMRI signals, prompting a closer examination of the temporal relationship between these same features. Furthermore, since correlational analysis was used in studying the LFP-BOLD spatial relationship, we used the same analysis method when comparing their temporal relationship. Some other comparison methods such as rank correlation and transformation prior to comparison were also tested and results remain persistent (Fig. S14). These findings align with the notion that, compared to nonlinear models, linear models offer superior predictive value for the rsfMRI signal using LFP data, as comprehensively illustrated in (Nozari et al., 2024) (also see Fig. S7). Importantly, in this study, the predictive powers (represented by R^2) of various comparison methods tested all remain below 0.5 (Nozari et al., 2024), suggesting that while certain models may enhance the temporal relationship between LFP and BOLD signals, the improvement is likely modest. Further exploration involving the extraction of all possible features from electrophysiology signals and their examination in relation to the rsfMRI signal, as well as the exploration of alternative methods for comparing LFP and rsfMRI signals warrants more detailed analysis in future studies.

Summary

Our study demonstrates that BOLD-based RSNs can be reliably derived by the electrophysiology signal. Nonetheless, the weak BOLD-LFP temporal correlations suggest that the dominant contributors to these networks might be signals not captured by electrophysiology. This finding provides a novel interpretation of RSNs. Importantly, this new concept of RSN signaling does not in any way diminish the importance of BOLD-based RSNs or the rsfMRI method. In fact, it makes fMRI even more important than previously thought because it might provide a new signal that traditional electrophysiology measures cannot provide.

Methods and Materials

Animals

All experiments in the present study were approved by and conducted in accordance with guidelines from the Pennsylvania State University Institutional Animal Care and Use Committee (IACUC). Adult male Long-Evans rats weighing 300–500g were obtained from Charles River Laboratory (Wilmington, MA). Animals were housed in Plexiglas cages with food and water given ad libitum. The ambient temperature was maintained at 22–24°C under a 12h light :12h dark cycle.

Surgery

MR-compatible electrodes were implanted in animals with aseptic stereotaxic surgeries. The rat was briefly anesthetized with isoflurane before receiving intramuscular injections of ketamine (40 mg/kg) and xylazine (12 mg/kg). Baytril (2.5mg/kg) and long-acting buprenorphine (1.0mg/kg) were administered subcutaneously as antibiotics and analgesics, respectively. The animal was then endotracheal intubated and ventilated with oxygen using the PhysioSuite system (Kent Scientific Corporation). Body temperature was monitored and maintained at 37 °C with a warming pad placed underneath the animal (PhysioSuite, Kent Scientific Corporation). Heart rate and SpO₂ were continuously monitored using a pulse oximetry (MouseSTAT® Jr, Kent Scientific Corporation) throughout the surgery. After performing craniotomies over the right ACC (coordinates: anterior/posterior +1.5, medial/lateral +0.5, dorsal/ventral -2.8) and the left M1 (coordinates: anterior/posterior +3.2, medial/lateral -3, dorsal/ventral -2.8), two MR-compatible electrodes

(MRCM16LP, NeuroNexus Inc) were carefully implanted into the ACC and M1, respectively. The reference and grounding wires from each electrode were wired together and connected to one of the two silver wires placed in the cerebellum. This electrode, which is a silicon-based micromachined probe, is capable of recording the LFP activity within a broad frequency range, starting from 0.1 Hz. At last, the skull was sealed with dental cement. After surgery, the animal was returned to the home cage and allowed to recover for at least one week before any experiment.

Acclimation for awake imaging

Rats were restrained using a custom-designed restrainer during awake imaging sessions. To minimize stress and motion during the imaging process, animals underwent a 7-day acclimation procedure to the restrainer as well as the MRI environment and scanning noise. The duration of the acclimation procedure was gradually increased from 15 min on the first day to 60 min on days 4–7 days (i.e., 15 min on day 1, 30 min on day 2, 45 min on day 3, and 60 min on days 4–7). More details of the acclimation procedure can be found in previous publications from our laboratory (Liang et al., 2012 [DOI](#)) and other research groups (Bergmann et al., 2016 [DOI](#); Chang et al., 2016 [DOI](#)).

Simultaneous rsfMRI and electrophysiology recordings

All rsfMRI experiments were conducted on a 7T Bruker 70/30 BioSpec system running ParaVision 6.0.1 (Bruker, Billerica, MA) using a homemade single loop surface coil at the *high field MRI facility* at the Pennsylvania State University. During each fMRI session, T2*-weighted rsfMRI images covering the entire brain were obtained using an echo planar imaging sequence with the following parameters: repetition time (TR) = 1 s; echo time (TE) = 15 ms; field of view = 3.2×3.2 cm²; matrix size = 64×64 ; slice number = 20; slice thickness = 1 mm; volume number = 1200. Five to ten scans were repeated within each session. T2-weighted anatomical images were also acquired using a rapid acquisition with a relaxation enhancement (RARE) sequence with the following parameters: TR = 3000 ms; TE = 40 ms; field of view = 3.2×3.2 cm²; matrix size = 256×256 ; slice number = 20; slice thickness = 1 mm; repetition number = 6.

Six rats with two electrodes implanted in the ACC and M1 were imaged in both awake and lightly sedated states in separate fMRI sessions. Two additional rats with an electrode only implanted in the ACC were imaged in the light sedation state. For both states, animals were restrained throughout the imaging session. In the light sedation state, the animal was sedated with the combination of low-dose dexmedetomidine (initial bolus of 0.05 mg/kg followed by a constant infusion at the rate of 0.1 mg·kg⁻¹·h⁻¹) and low-dose isoflurane (0.3%). Artificial tears were applied to protect the animal's eyes from drying out. Body temperature was maintained at 37°C using warm air and was monitored using a rectal thermometer.

Before imaging, the implanted electrodes were connected to MR-compatible LP16CH headstages and a PZ5 neurodigitizer amplifier (Tucker Davis Technologies (TDT) Inc, Alachua, FL). Electrophysiology recording began 10 min before rsfMRI data acquisition and continued until the end of the imaging session using a TDT recording system and an RZ2 BioAmp Processor (TDT Inc, Alachua, FL). The raw, unfiltered electrophysiology signal was sampled at 24414 Hz and stored using the TDT Synapse software on a WS8 workstation.

rsfMRI and electrophysiology data preprocessing

All data preprocessing and analysis were performed using MATLAB (Mathworks, Natick, MA). First, the movement of each rsfMRI volume was estimated using the framewise displacement (FD). For the awake imaging data, volumes with FD > 0.1 mm and their adjacent preceding and following volumes were removed. If > 25% of volumes in a scan were scrubbed, the entire scan was excluded from further analysis. For rsfMRI data collected in the lightly sedated state, scans with any volume that had FD > 0.1 mm were removed from further analysis. Subsequently, data were preprocessed using the following steps: co-registration to a defined atlas, motion correction

(SPM12), spatial smoothing using a Gaussian kernel (FWHM = 0.75 mm), voxelwise nuisance regression with the regressors of motion parameters as well as signals from the white matter and ventricles, and the global brain signal, and, lastly, bandpass temporal filtering (0.01–0.1 Hz).

Raw electrophysiology data were preprocessed to remove the MR interference using a template regression method as previously described (Tu and Zhang, 2022). Briefly, the raw electrophysiology signal for each scan was first aligned to the corresponding rsfMRI scan, and segmented for each imaging slice based on the starting time of the scan. Next, an MRI interference template for each rsfMRI slice acquisition was obtained by averaging the electrophysiology data across all slices from all rsfMRI volumes. The template was further aligned to the electrophysiology data for each slice acquisition using cross correlation and was then linearly regressed out from the raw electrophysiology data. In addition, a series of notch filters for harmonics of the power supply (60 Hz and multiples of 60 Hz) and slice acquisition (20 Hz and multiples of 20 Hz) were applied to further denoise the data.

Data analysis

The LFP power was obtained by bandpass filtering preprocessed electrophysiology data in the frequency range of 0.1 - 300 Hz. Based on the conventional LFP band definition (delta: 1–4 Hz, theta: 4–7 Hz, alpha: 7–13 Hz, beta: 13–30 Hz, gamma: 40–100 Hz) (Lu et al., 2016; Zhang et al., 2020), the LFP band power was computed using the MATLAB function *spectrogram* with a window size of 1 s and a step size of 0.1 s. To investigate the relationship between the LFP and rsfMRI signals, the time course of band-specific LFP power was convolved with a hemodynamic response function (HRF, $p = [4 \ 4 \ 1 \ 1 \ 6 \ 0 \ 32]$ for function *spm_hrf*) to generate the corresponding LFP-predicted BOLD signal. The HRF used was specific to rodents with a shorter onset time and time-to-peak as a faster HRF was reported in rats relative to humans (Tong et al., 2019). The temporal relationship between the LFP and fMRI signals was quantified using the Pearson correlation between the HRF-convolved LFP band power and the regionally averaged rsfMRI time course from voxels surrounding the implanted electrode for each site. To examine the potential impact of HRF used, we calculated the BOLD gamma power correlation using different HRFs with various response delays, ranging from 2 sec to 8 sec with the increment of 0.25 sec, as well as different undershoot delays ranging from 2 sec to 12 sec with the increment of 0.5 sec (Fig. S6).

The LFP-derived spatial correlation maps for the M1 and ACC were respectively generated by computing voxel-wise Pearson correlations between each HRF-convolved LFP band power and brain-wide rsfMRI signals. The seedmaps for the M1 and ACC were respectively obtained by calculating the voxel-wise Pearson correlations between the regionally averaged rsfMRI time course for each seed and rsfMRI signals of all brain voxels.

To determine the contribution of LFP powers to BOLD-based RSFC, we removed LFP powers from voxel-wise fMRI signals and then recalculated RSNs. Given that the gamma signal might be the most related to the rsfMRI signal, the time course of gamma-band power (convolved with HRF) was linearly regressed out from rsfMRI signals of all brain voxels. To examine the potential contributions of other LFP bands, all five LFP band powers (each convolved with HRF) were “softly” removed from voxel-wise rsfMRI signals, meaning only the unique components in five bands were regressed out but the shared components were maintained. Specific details of soft regression can be found in (Griffanti et al., 2014). This method can avoid ‘over regression’ when multiple regressors are involved particularly when regressors are correlated between themselves. Lastly, we removed rsfMRI volumes corresponding to peaks in the M1/ACC gamma power. The seedmaps of M1 and ACC were recalculated and compared before and after removing the LFP signal.

Simulation

We simulated two fixed signals with the true Pearson correlation of 0.95. The first signal was generated using MATLAB function *rand* with 10000 data points. The second signal with a defined correlation with the first signal (i.e. 0.95) was obtained based on the equation below:

$$B = A * \text{Corr} + \sqrt{1 - \text{Corr}^2} * N(0,1)$$

in which A represents the first signal, Corr is the desired Pearson correlation coefficient, and N(0, 1) represents random values with the mean equal to 0 and standard deviation equal to 1. For each signal, random noise was added to achieve a contrast-to-noise ratio (CNR) ranging from 0.1 to 5 with the step size of 0.1. CNR was quantified by the standard deviation of the signal over the standard deviation of the noise. This process was repeated 159 times (equal to the # of scans in the present study). The noise-added signals were resampled to either 1200 or 6157 data points, which corresponded to the total number of time points used to calculate temporal correlations and total number of brain voxels used to calculate spatial correlations, respectively, in our study. Pearson correlations between the resampled signals either based on the averaged signals from all 159 trials or on individual trials were calculated.

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Conflict of interest:

The authors declare no competing financial interests.

Author Contributions:

N.Z. designed the research; W.T. performed animal experiments; W.T. performed data analysis; S.R.C. designed and made the restrainer for imaging experiments; W.T. and N.Z. wrote the paper; W.T., S.R.C. and N.Z. revised the paper; N.Z. acquired funding.

Additional Declarations:

The authors declare no competing interests.

Supplementary Figures

Figure S1.

Representative T2-weighted structural images confirming the electrode location in A) M1 and B) ACC.

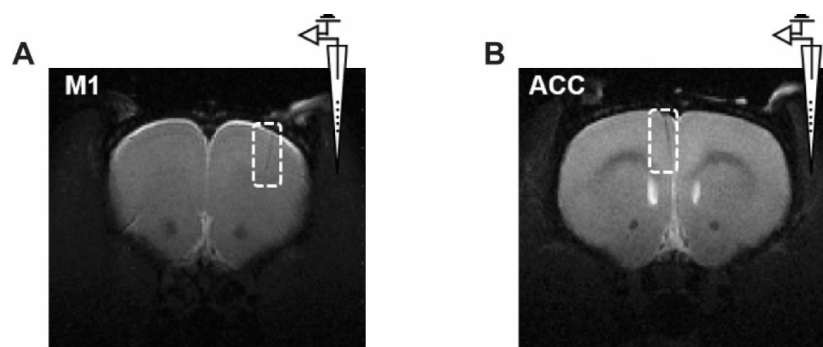
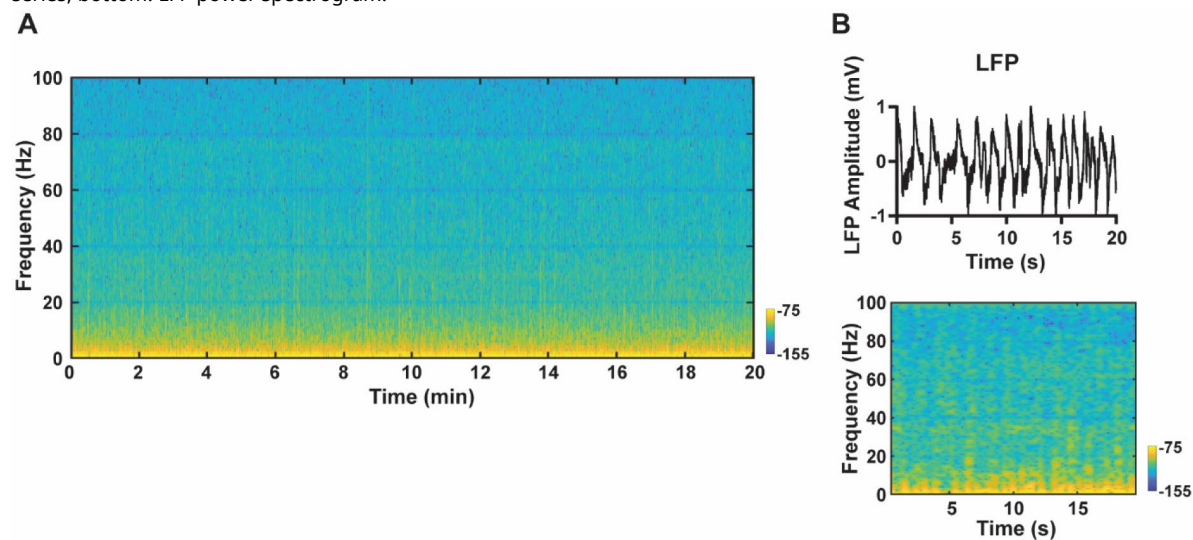


Figure S2.

Exemplar denoised LFP signal.

A) Exemplar LFP power spectrogram from one fMRI scan. **B)** A 'zoom-in' 20-sec segment of the LFP signal. Top: LFP time series; bottom: LFP power spectrogram.



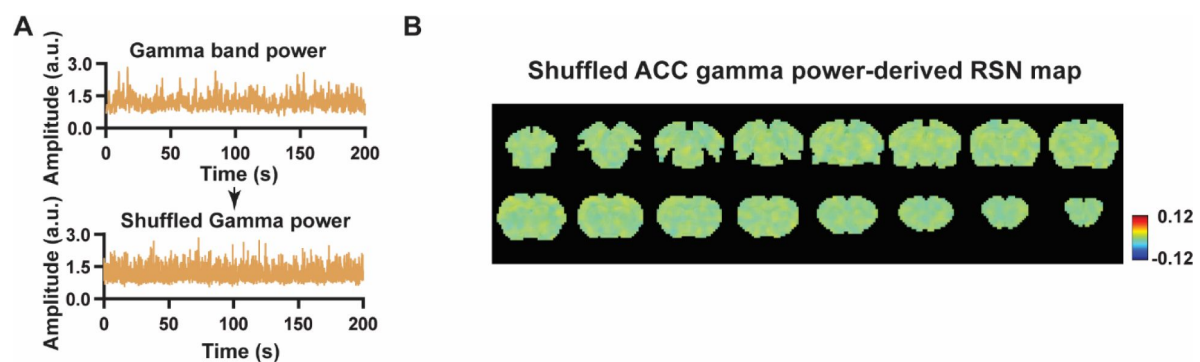


Figure S3.

Control analysis for LFP-derived spatial pattern.

A) Top: Example of gamma band power in the ACC; bottom: shuffled gamma band power. **B)** RSN map derived by shuffled gamma band power, obtained by voxel-wise correlating the shuffled gamma band power convolving with HRF to BOLD signals of all brain voxels.

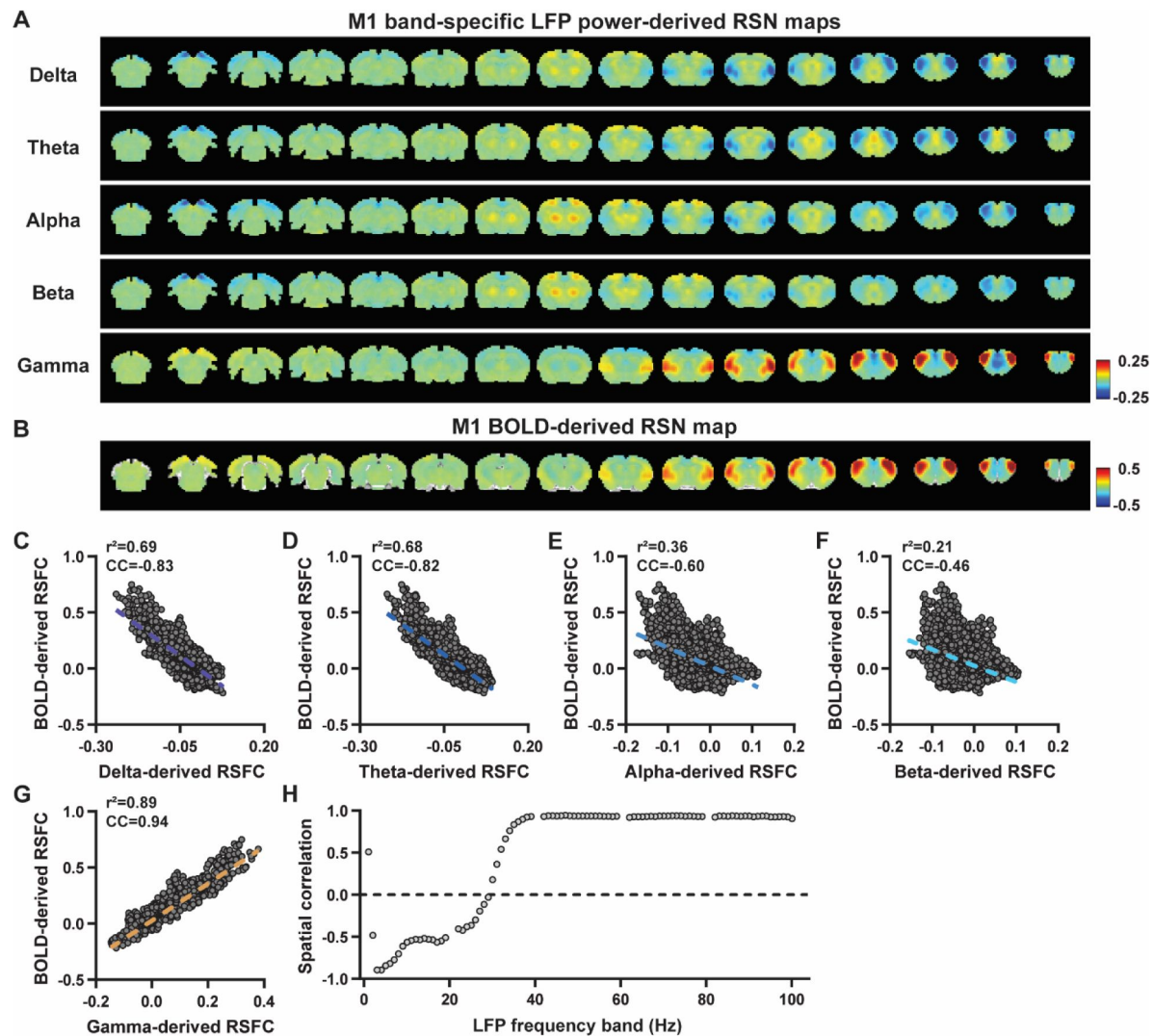


Figure S4.

Spatial relationship between M1 LFP-derived and M1 BOLD-derived RSNs without global signal regression in rsfMRI data preprocessing.

A) RSN maps derived by band-specific LFP powers in the M1. **B)** M1 BOLD-derived RSN map (i.e. M1 seedmap). **C-G)** Spatial similarity between the M1 BOLD-derived RSN map and the M1 LFP-derived RSN maps for individual bands, quantified by their voxel-to-voxel correlations (C: delta, $CC = -0.83$; D: theta, $CC = -0.82$; E: alpha, $CC = -0.6$; F: beta, $CC = -0.46$; G: gamma, $CC = 0.94$). **H)** Spatial correlations between the M1 BOLD-derived RSN map and RSN maps derived by all 1-Hz bands in the full LFP spectrum.

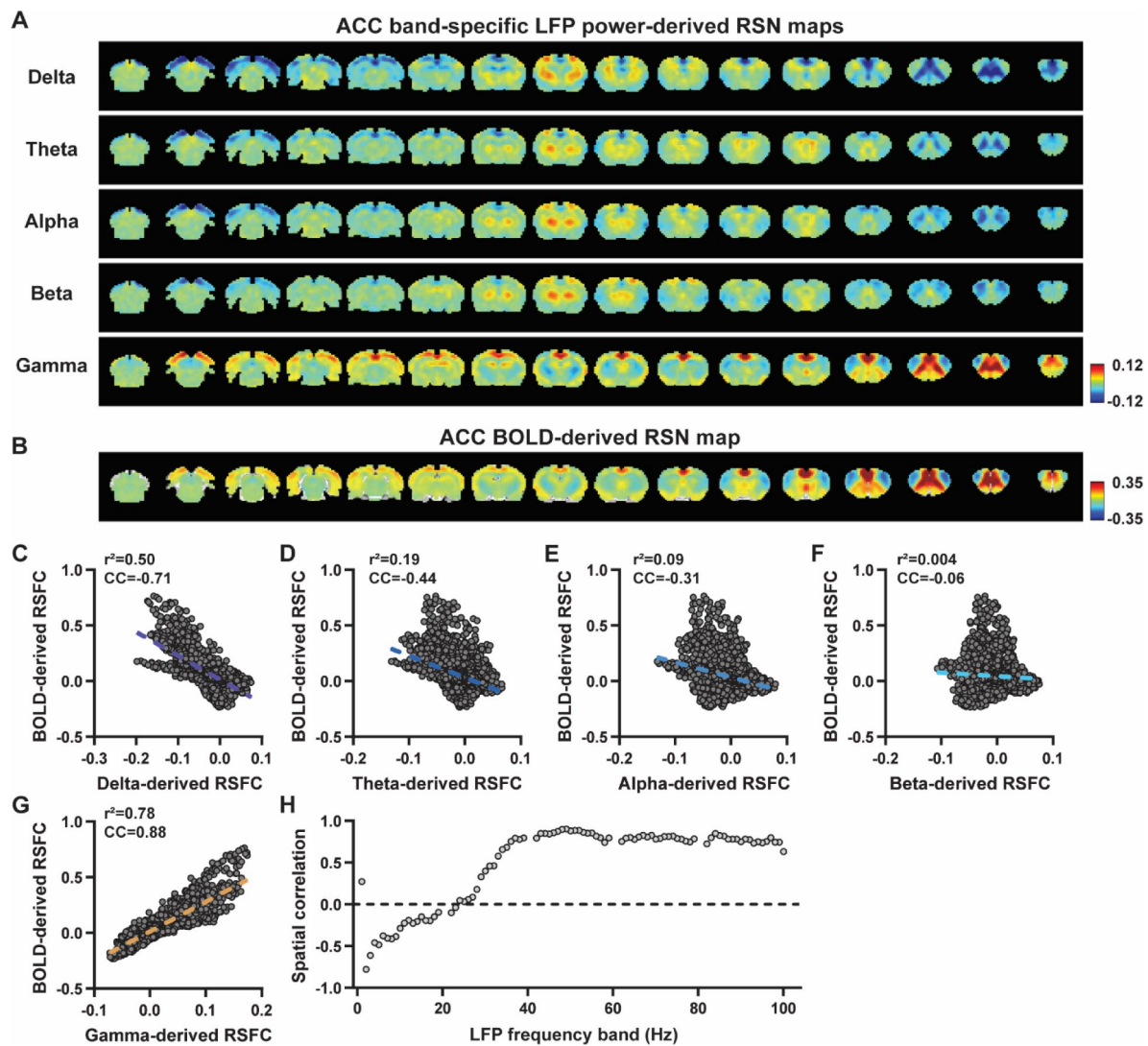


Figure S5.

Spatial relationship between ACC LFP-derived and ACC BOLD-derived RSNs without global signal regression in rsfMRI data preprocessing.

A) RSN maps derived by band-specific LFP powers in the ACC. **B)** ACC BOLD-derived RSN map (i.e. ACC seedmap). **CG)** Spatial similarity between the ACC BOLD-derived RSN map and the ACC LFP-derived RSN maps for individual bands, quantified by their voxel-to-voxel correlations (C: delta, $CC = -0.71$; D: theta, $CC = -0.44$; E: alpha, $CC = -0.31$; F: beta, $CC = -0.06$; G: gamma, $CC = 0.88$). **H)** Spatial correlations between the ACC BOLD-derived RSN map and RSN maps derived by all 1-Hz bands in the full LFP spectrum.

Figure S6.

BOLD-gamma power correlations in the two-dimensional space of HRF parameters.

The maximal correlation value is close to that obtained with the HRF used in the study.

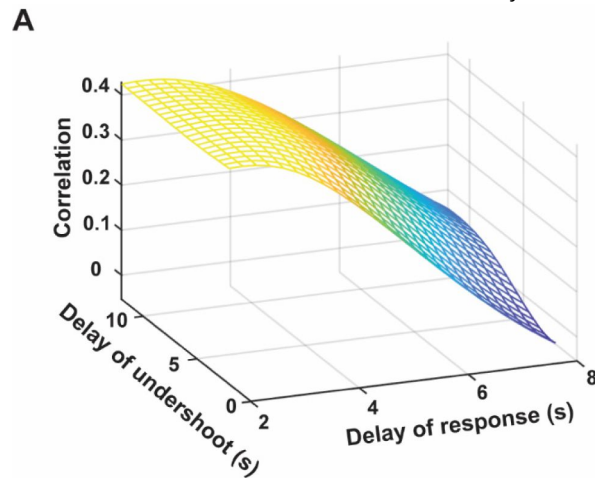
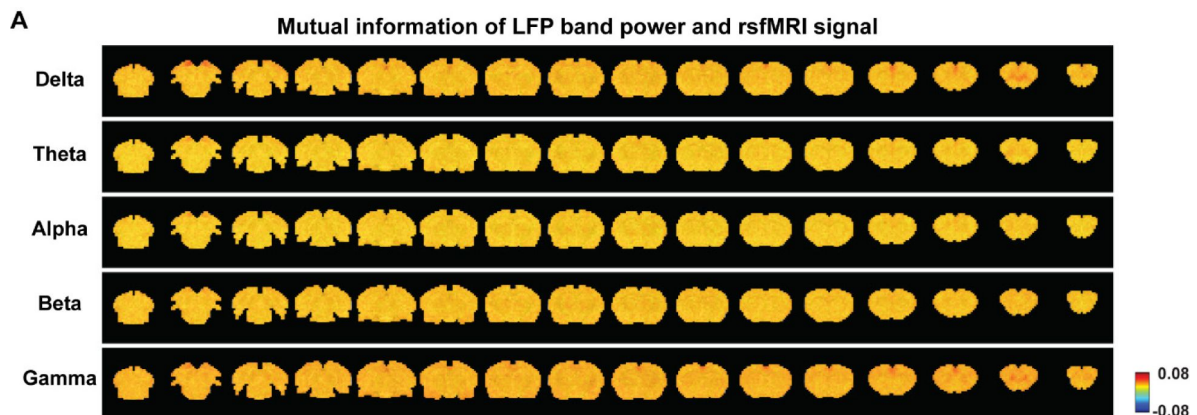


Figure S7.

Mutual information between band-limited LFP powers and brain-wide rsfMRI signals.



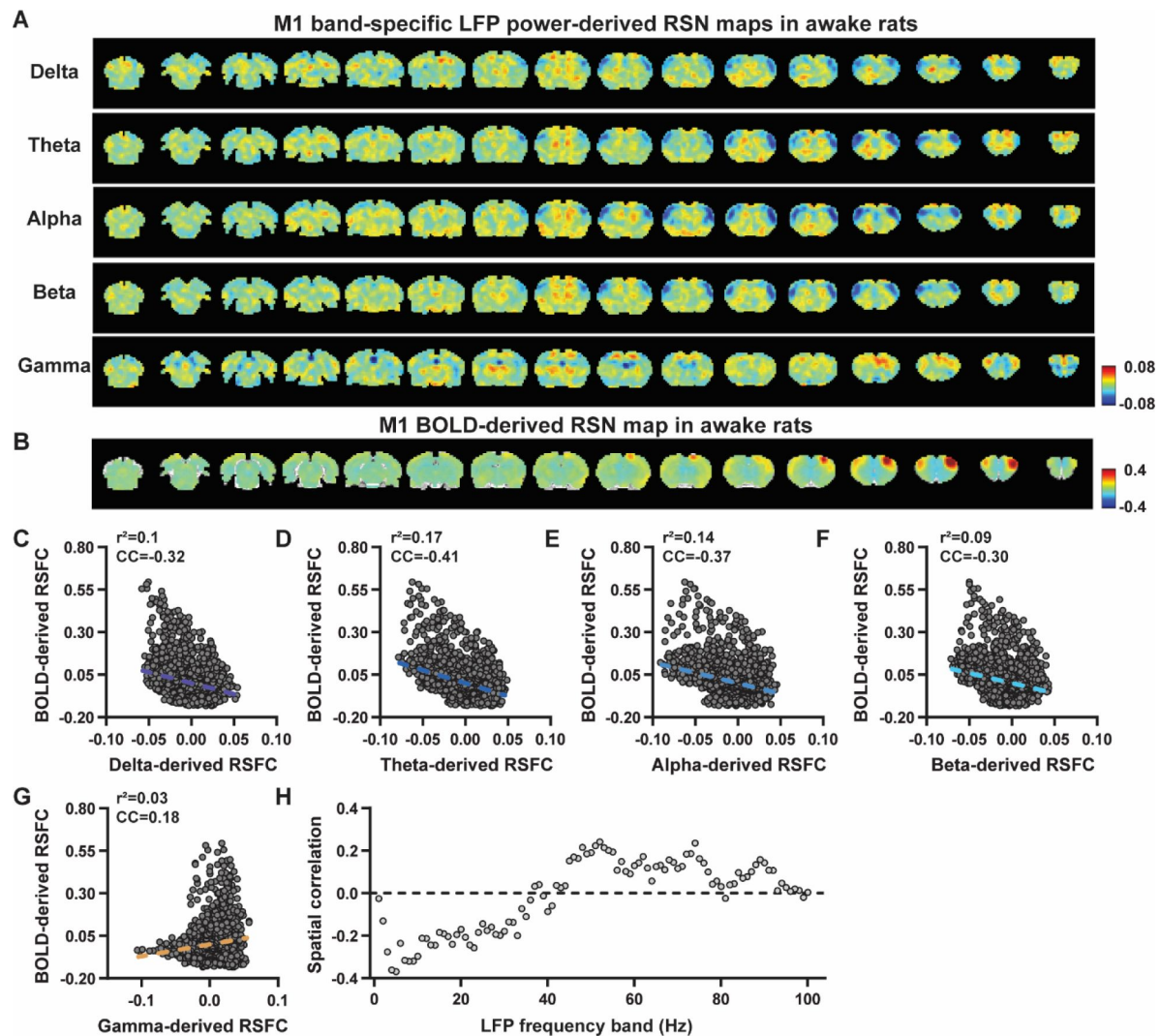


Figure S8.

Spatial correlations of M1 LFP-derived and BOLD-derived RSNs in awake animals.

A) RSN maps derived by band-specific LFP powers in the M1, obtained by voxel-wise correlating the LFP-predicted BOLD signal for each band with BOLD signals of all brain voxels. **B)** M1 BOLD-derived RSN map (i.e. M1 seedmap), obtained by voxel-wise correlating the regionally averaged BOLD time course of the seed (i.e. M1) with BOLD time courses of all brain voxels. **C-G)** Spatial similarity between the M1 BOLD-derived RSN map and M1 LFP-derived RSN maps of individual bands, quantified by their voxel-to-voxel spatial correlations (**C:** delta, CC = -0.32; **D:** theta, CC = -0.41; **E:** alpha, CC = -0.37; **F:** beta, CC = -0.30; **G:** gamma, CC = 0.18). **H)** Spatial correlations between the M1 BOLD-derived RSN map and RSN maps derived by individual 1-Hz bands across the full LFP spectrum.

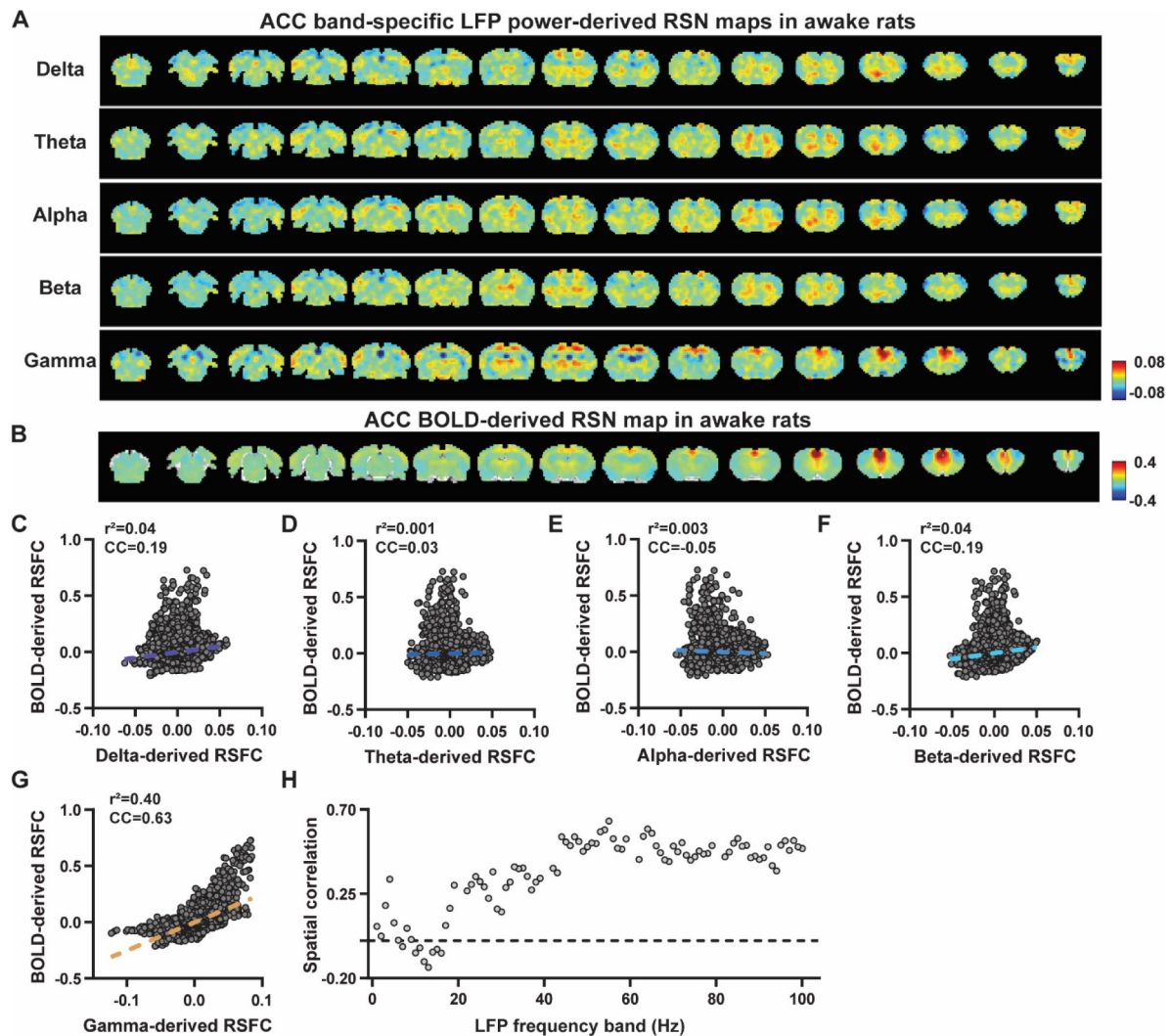


Figure S9.

Spatial correlations of ACC LFP-derived and BOLD-derived RSNs in awake animals.

A) RSN maps derived by band-specific LFP powers in the ACC, obtained by voxel-wise correlating the LFP-predicted BOLD signal for each band with BOLD signals of all brain voxels. **B)** ACC BOLD-derived RSN map (i.e. ACC seedmap), obtained by voxel-wise correlating the regionally averaged BOLD time course of the seed (i.e. ACC) with BOLD time courses of all brain voxels. **C-G)** Spatial similarity between the ACC BOLD-derived RSN map and ACC LFP-derived RSN maps of individual bands, quantified by their voxel-to-voxel spatial correlations (**C**: delta, $CC = -0.19$; **D**: theta, $CC = 0.03$; **E**: alpha, $CC = -0.05$; **F**: beta, $CC = 0.19$; **G**: gamma, $CC = 0.63$). **H)** Spatial correlations between the ACC BOLD-derived RSN map and RSN maps derived by all 1Hz bands across the full LFP spectrum.

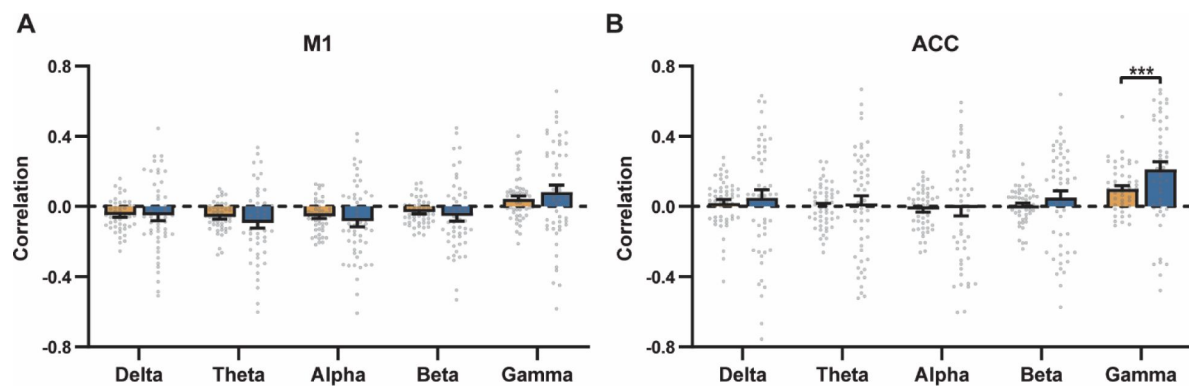


Figure S10.

Comparison of scan-wise spatial and temporal correlations

for **A)** M1 and **B)** ACC. Paired t tests across individual scans. # of scans = 50. ***: $p < 0.005$.

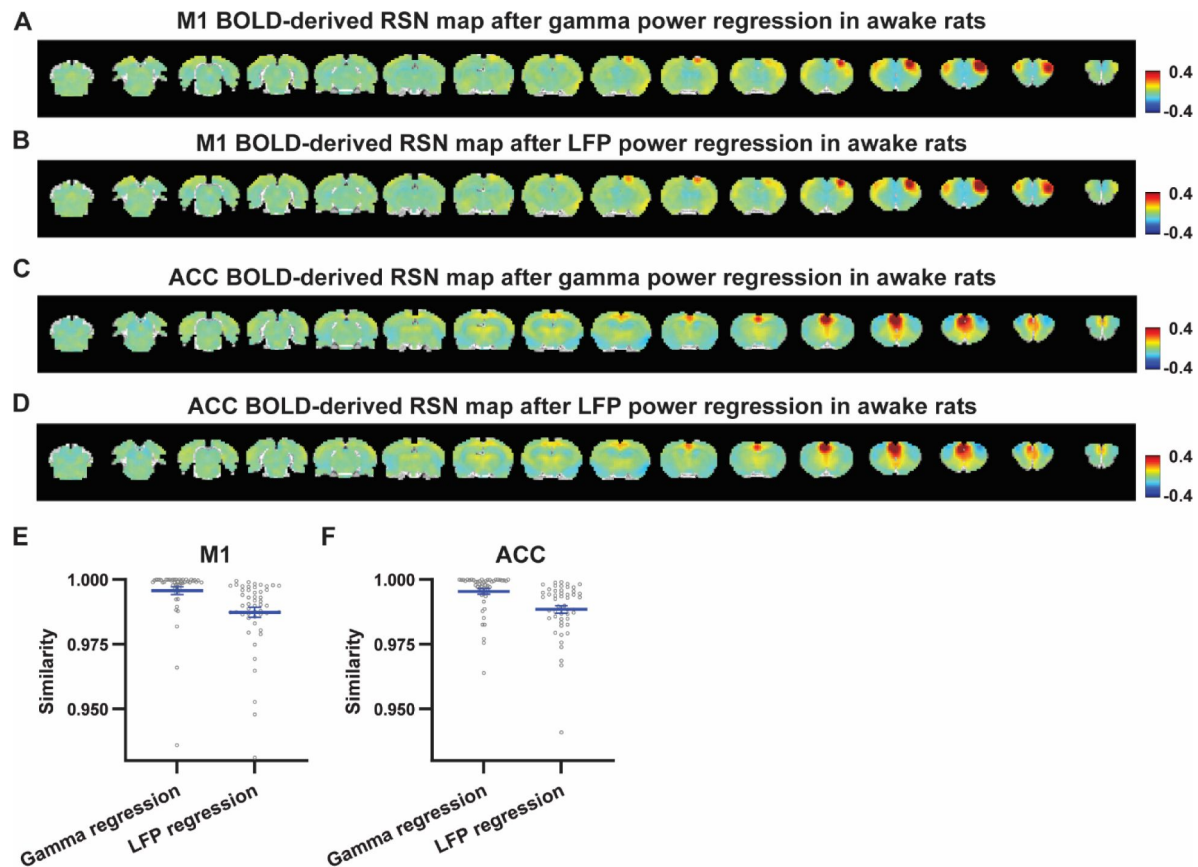


Figure S11.

Impact of removing electrophysiology signals on M1 and ACC RSN spatial patterns in awake animals.

A) M1 BOLD-derived RSN map (i.e. M1 seedmap) after the HRF-convolved gamma power in the M1 is voxel-wise regressed out from rsfMRI signals of all brain voxels. **B)** M1 BOLD-derived RSN map after powers of all five LFP bands are voxel-wise regressed out from rsfMRI signals of all brain voxels using soft regression. **C)** ACC BOLD-derived RSN map after the HRF-convolved gamma power in the ACC is voxel-wise regressed out from rsfMRI signals. **D)** ACC BOLD-derived RSN map after powers of all five LFP bands are voxelwise regressed out from rsfMRI signals using soft regression. **E)** Spatial similarity of M1 BOLD-derived RSN maps before and after gamma power regression or regression of powers of all LFP bands. **F)** Spatial similarity of ACC BOLD-derived RSN maps before and after gamma power regression or regression of powers of all LFP bands.

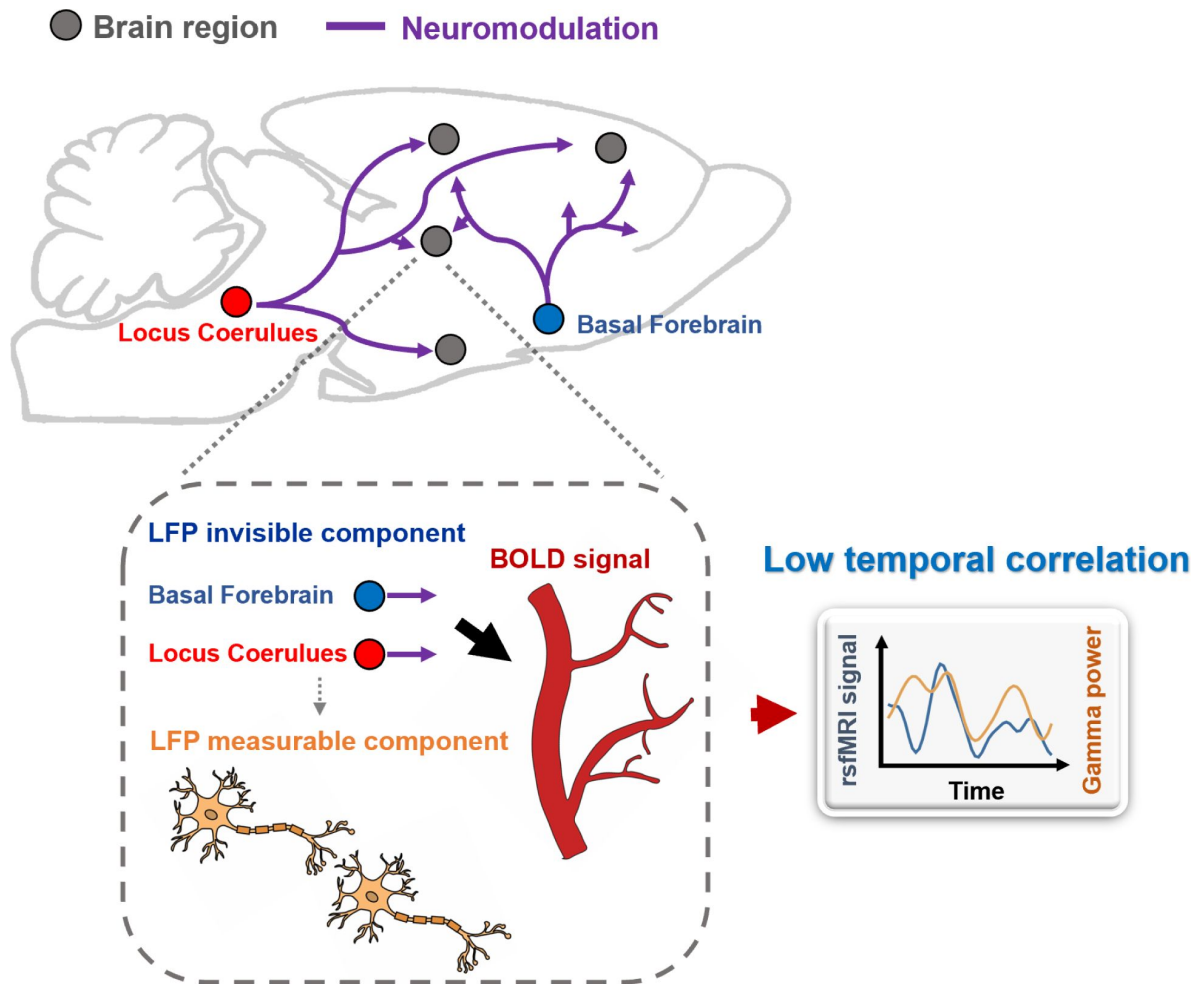


Figure S12.

Schematic diagram illustrating that distal neuromodulation, which have strong vasoactive effects, can contribute to low temporal correlations between electrophysiology and rsfMRI signals.

Figure S13.

Anatomical connectivity labeled by tracers.

Adopted from the Allen Brain Institute database (Oh et al., 2014 [link](#)).

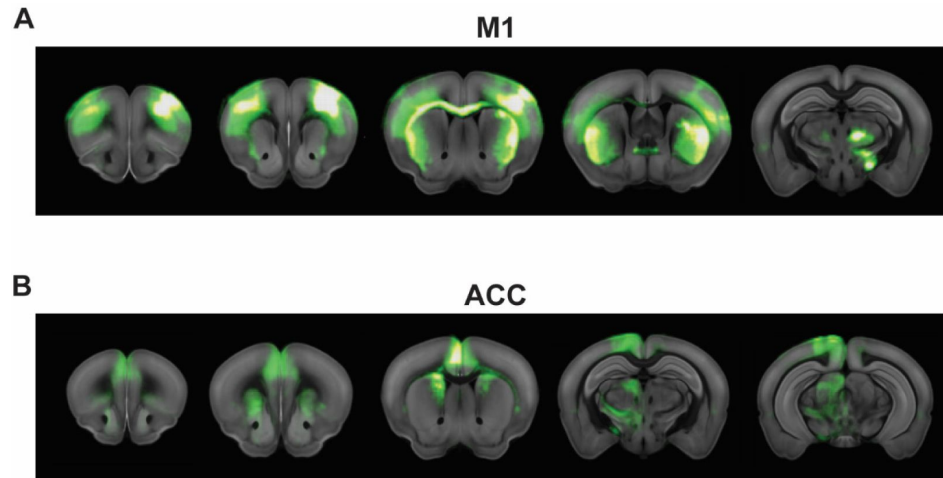
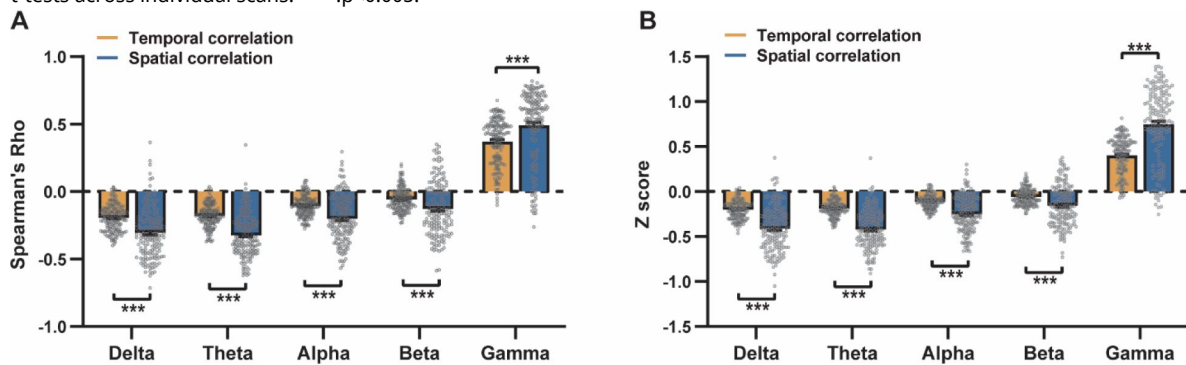


Figure S14.

Disparity in spatial and temporal relationships between resting-state LFP and BOLD signals quantified using alternative methods.

A) Spearman's rank correlation coefficient. **B)** z transformation prior to comparison of Pearson correlation coefficient. Paired t-tests across individual scans. ***: $p < 0.005$.



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Reviewer #1 (Public Review):

Tu et al investigated how LFPs recorded simultaneously with rsfMRI explain the spatiotemporal patterns of functional connectivity in sedated and awake rats. They find that connectivity maps generated from gamma band LFPs (from either area) explain very well the spatial correlations observed in rsfMRI signals, but that the temporal variance in rsfMRI data is more poorly explained by the same LFP signals. The authors excluded the effects of sedation in this effect by investigating rats in the awake state (a remarkable feat in the MRI scanner), where the findings generally replicate. The authors also performed a series of tests to assess multiple factors (including noise, outliers, etc., and nonlinearity of the data...) in their analysis.

This apparent paradox is then explained by a hypothetical model in which LFPs and neurovascular coupling are generated in some sense "in parallel" by different neuron types, some of which drive LFPs and are measured by ePhys, while others (nNOS, etc.) have an important role in neurovascular coupling but are less visible in Ephys data. Hence the discrepancy is explained by the spatial similarity of neural activity but the more "selective" LFPs picked up by Ephys account for the different temporal aspects observed.

This is a deep, outstanding study that harnesses multidisciplinary approaches (fMRI and ephys) for observing brain activity. The results are strongly supported by the comprehensive analyses done by the authors, that ruled out many potential sources for the observed findings. The study's impact is expected to be very large.

There are very few weaknesses in the work, but I'd point out that the 1-second temporal resolution may have masked significant temporal correlations between LFPs and spontaneous activity, for instance, as shown by Cabral et al *Nature Communications* 2023, and even in earlier QPP work from the Keilholz Lab. The synchronization of the LFPs may correlate more with one of these modes than the total signal. Perhaps a kind of "dynamic connectivity" analysis on the authors' data could test whether LFPs correlate better with the activity at specific intervals. However this could purely be discussed and left for future work, in my opinion.

<https://doi.org/10.7554/eLife.95680.2.sa2>

Reviewer #2 (Public Review):

The authors investigate the disparity between spatial extant and temporal variance of electrophysiological-fMRI correlations in a rodent model. They found high correspondence in

spatial extent but a disparity in temporal variance. From this, they propose a model of an electrophysiologically-invisible signal affecting temporal variance.

I remain skeptical about the "electrophysiologically invisible signal" model but the authors have done a much better job of both explaining it and hedging it in this version. Readers can decide for themselves.

The revision submitted by the authors substantially improves writing and methods.

<https://doi.org/10.7554/eLife.95680.2.sa1>

Author response:

The following is the authors' response to the original reviews.

eLife assessment

This important study combines fMRI and electrophysiology in sedated and awake rats to show that LFPs strongly explain spatial correlations in resting-state fMRI but only weakly explain temporal variability. They propose that other, electrophysiology-invisible mechanisms contribute to the fMRI signal. The evidence supporting the separation of spatial and temporal correlations is convincing, however, the support of electrophysiological-invisible mechanisms is incomplete, considering alternative potential factors that could account for the differences in spatial and temporal correlation that were observed. This work will be of interest to researchers who study the fundamental mechanisms behind resting-state fMRI.

We appreciate the encouraging comments. We added a section in discussion that thoroughly discussed the potential alternative factors that could account for the differences in spatial and temporal correlation that we observed.

Public Reviews:

Reviewer #1 (Public Review):

Tu et al investigated how LFPs recorded simultaneously with rsfMRI explain the spatiotemporal patterns of functional connectivity in sedated and awake rats. They find that connectivity maps generated from gamma band LFPs (from either area) explain very well the spatial correlations observed in rsfMRI signals, but that the temporal variance in rsfMRI data is more poorly explained by the same LFP signals. The authors excluded the effects of sedation in this effect by investigating rats in the awake state (a remarkable feat in the MRI scanner), where the findings generally replicate. The authors also performed a series of tests to assess multiple factors (including noise, outliers, and nonlinearity of the data) in their analysis.

This apparent paradox is then explained by a hypothetical model in which LFPs and neurovascular coupling are generated in some sense "in parallel" by different neuron types, some of which drive LFPs and are measured by ePhys, while others (nNOS, etc.) have an important role in neurovascular coupling but are less visible in Ephys data. Hence the discrepancy is explained by the spatial similarity of neural activity but the more "selective" LFPs picked up by Ephys account for the different temporal aspects observed.

This is a deep, outstanding study that harnesses multidisciplinary approaches (fMRI and ephys) for observing brain activity. The results are strongly supported by the

comprehensive analyses done by the authors, which ruled out many potential sources for the observed findings. The study's impact is expected to be very large.

Comment: There are very few weaknesses in the work, but I'd point out that the 1-second temporal resolution may have masked significant temporal correlations between

LFPs and spontaneous activity, for instance, as shown by Cabral et al Nature Communications 2023, and even in earlier QPP work from the Keilholz Lab. The synchronization of the LFPs may correlate more with one of these modes than the total signal. Perhaps a kind of "dynamic connectivity" analysis on the authors' data could test whether LFPs correlate better with the activity at specific intervals. However, this could purely be discussed and left for future work, in my opinion.

We appreciate this great point. Indeed, it is likely that LFP and rsfMRI signals are more strongly related during some modes/instances than others, and hence correlation across the entire time series may have masked this effect. In addition, we agree that 1-second temporal resolution may obscure some temporal correlations between LFPs and rsfMRI signal. The choice of 1-second temporal resolution was made to be consistent with the TR in our fMRI experiment, considering the slow hemodynamic response. Ultrafast fMRI imaging combined with dynamic connectivity analysis in a future study might enable more detailed examination of BOLD-LFP temporal correlations at higher temporal resolutions. We have added the following paragraph to the revised manuscript:

“Our proposed theoretic model represents just one potential explanation for the apparent discrepancy in temporal and spatial relationships between resting-state electrophysiology and BOLD signals. It is important to acknowledge that there may be other scenarios where a stronger temporal relationship between LFP and BOLD signals could manifest. For instance, recent research suggests that the relationship between LFP and rsfMRI signals may vary across different modes or instances (Cabral et al., 2023), which can be masked by correlations across the entire time series. Moreover, the 1-second temporal resolution employed in our study may obscure certain temporal correlations between LFPs and rsfMRI signals. Future investigations employing ultrafast fMRI imaging coupled with dynamic connectivity analysis could offer a more nuanced exploration of BOLD-LFP temporal correlations at higher temporal resolutions (Bolt et al., 2022; Cabral et al., 2023; Ma and Zhang, 2018; Thompson et al., 2014).”

Reviewer #2 (Public Review):

The authors address a question that is interesting and important to the sub-field of rsfMRI that examines electrophysiological correlates of rsfMRI. That is, while electrophysiology-produced correlation maps often appear similar to correlation maps produced from BOLD alone (as has been shown in many papers) is this actually coming from the same source of variance, or independent but spatially-correlated sources of variance? To address this, the authors recorded LFP signals in 2 areas (M1 and ACC) and compared the maps produced by correlating BOLD with them to maps produced by BOLD-BOLD correlations. They then attempt to remove various sources of variance and see the results.

The basic concept of the research is sound, though primarily of interest to the subset of rsfMRI researchers who use simultaneous electrophysiology. However, there are major problems in the writing, and also a major methodological problem.

Major problems with writing:

Comment 1: There is substantial literature on rats on site-specific LFP recording compared to rsfMRI, and much of it already examined removing part of the LFP and

examining rsfMRI, or vice versa. The authors do not cover it and consider their work on signal removal more novel than it is.

We have added more literature studies to the revised manuscript. It is important to note that while there exists a substantial body of literature on site-specific LFP recording coupled with rsfMRI, our paper makes a significant contribution by unveiling the disparity in temporal and spatial relationships between resting-state electrophysiological and fMRI signals. This goes beyond mere reporting of spatial/temporal correlations. Furthermore, our exploration of the impact of removing LFP on rsfMRI spatial patterns constitutes one among several analyses employed to demonstrate that the temporal fluctuations of LFP minimally affect BOLD-derived RSN spatial patterns. We wish to clarify that our intention is not to claim this aspect of our work is more novel than similar analyses conducted in previous studies (we apologize if our original manuscript conveyed that impression). Rather, the novelty lies in the objective of this analysis, which is to elucidate the disparity in temporal and spatial relationships between resting-state electrophysiological and fMRI signals—a crucial issue that has not been thoroughly addressed previously.

Comment 2: The conclusion of the existence of an "electrophysiology-invisible signal" is far too broad considering the limited scope of this study. There are many factors that can be extracted from LFP that are not used in this study (envelope, phase, infraslow frequencies under 0.1Hz, estimated MUA, etc.) and there are many ways of comparing it to the rsfMRI data that are not done in this study (rank correlation, transformation prior to comparison, clustering prior to comparison, etc.). The one non-linear method used, mutual information, is low sensitivity and does not cover every possible nonlinear interaction. Mutual information is also dependent upon the number of bins selected in the data. Previous studies (see 1) have seen similar results where fMRI and LFP were not fully commensurate but did not need to draw such broad conclusions.

First we would like to clarify that the existence of "electrophysiologyinvisible signal" is not necessarily a conclusion of the present study, per se, as described by the reviewer. As we stated in our manuscript, it is a proposed theoretical model. We fully acknowledge that this model represents just one potential explanation for the apparent discrepancy in temporal and spatial relationships between resting-state electrophysiology and BOLD signals. It is important to acknowledge that there may be other scenarios where a stronger temporal relationship between LFP and BOLD signals could manifest. This issue has been further clarified in the revised manuscript (see the section of Potential pitfalls).

We agree with the reviewer that not all factors that can be extracted from LFP are examined. In our current study we focused solely on band-limited LFP power as the primary feature in our analysis, given its prevalence in prior studies of LFP-rsfMRI correlates. More importantly, we demonstrate that band-specific LFP powers can yield spatial patterns nearly identical to those derived from rsfMRI signals, prompting a closer examination of the temporal relationship between these same features. Furthermore, since correlational analysis was used in studying the LFP-BOLD spatial relationship, we used the same analysis method when comparing their temporal relationship.

Extracting all possible features from the electrophysiology signal and examining their relationship with the rsfMRI signal or exploring all other types of ways of comparing LFP and rsfMRI signals goes beyond the scope of the current study. However, to address the reviewer's concern, we tried a couple of analysis methods suggested by the reviewer, and results remain persistent. Figure S14 shows the results from (A) the rank correlation and (B) z transformation prior to comparison. We added these new results to the revised manuscript.

Comment 3: The writing refers to the spatial extent of correlation with the LFP signal as "spatial variance." However, LFP was recorded from a very limited point and the variance

in the correlation map does not necessarily reflect underlying electrophysiological spatial distributions (e.g. Yu et al. Nat Commun. 2023 Mar 24;14(1):1651.)

The reviewer accurately pointed out that in our paper, “spatial variance” refers to the spatial variance of BOLD correlates with the LFP signal. Our objective is to assess the extent to which this spatial variance, which is derived from the neural activity captured by LFP in the M1 or ACC, corresponds to the BOLD-derived spatial patterns from the same regions. We acknowledge that this spatial variance may differ from the spatial map obtained by multi-site electrophysiology recordings. Nevertheless, numerous studies have consistently reported a high spatial correspondence between BOLD- and electrophysiology-derived RSNs using various methodologies across different physiological states in both humans and animals. For instance, research employing electroencephalography (EEG) or electrocorticography (ECoG) in humans demonstrates that RSNs derived from the power of multiple-site electrophysiological signals exhibit similar spatial patterns to classic BOLD-derived RSNs such as the default-mode network (Hacker et al., 2017; Kucyi et al., 2018). These studies well agree with our findings. Notably, the reference paper cited by the reviewer studies brain-wide changes during transitions between awake and various sleep stages, which is quite different from the brain states examined in our study.

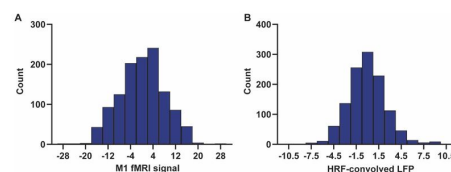
Major method problem:

Comment 4: Correlating LFP to fMRI is correlating two biological signals, with unknown but presumably not uniform distributions. However, correlating CC results from correlation maps is comparing uniform distributions. This is not a fair comparison, especially considering that the noise added is also uniform as it was created with the rand() function in MATLAB.

This is a good point. We examined the distributions of both LFP powers and fMRI signals. They both seem to follow a normal distribution. Below shows distributions of the two signals from a random scan. In addition, z transformation prior to comparison generated the same results (Fig. S14).

Author response image 1.

Exemplar distributions of A) the fMRI signal of M1, and B) HRF-convolved LFP power in M1.



Reviewer #1 (Recommendations For The Authors):

Comment 1: In the Discussion, a few more calcium imaging papers could be fruitfully discussed (e.g. Ma et al Resting-state hemodynamics are spatiotemporally coupled to synchronized and symmetric neural activity in excitatory neurons, PNAS 2016, or more recently Vafaii et al, Multimodal measures of spontaneous brain activity reveal both common and divergent patterns of cortical functional organization, Nat Comms 2024).

We appreciate this suggestion. We have added the following discussions to the revised manuscript:

“These findings indicate the temporal information provided by gamma power can only explain a minor portion (approximately 35%) of the temporal variance in the BOLD time series, even after accounting for the noise effect, which is in line with the reported correlation value between the cerebral blood volume and fluctuations in GCaMP signal in head-fixed mice during periods of immobility ($R = 0.63$) (Ma et al., 2016).”

“It is plausible that employing different features or comparison methods could yield a stronger BOLD-electrophysiology temporal relationship (Ma et al., 2016).”

“Furthermore, in a more recent study by Vafaii and colleagues, overlapping cortical networks were identified using both fMRI and calcium imaging modalities, suggesting that networks observable in fMRI studies exhibit corresponding neural activity spatial patterns (Vafaii et al., 2024).”

“Furthermore, Vafaii et. al. revealed notable differences in functional connectivity strength measured by fMRI and calcium imaging, despite an overlapping spatial pattern of cortical networks identified by both modalities (Vafaii et al., 2024).”

Comment 2: Similarly when discussing the "invisible" populations, perhaps Uhlirova et al eLife 2016 should be mentioned as some types of inhibitory processes may also be less clearly observed in LFPs but rather strongly contribute to NVC.

We appreciate the suggestion. We added the following sentences to the revised manuscript.

“Additionally, Uhlirova et al. conducted a study where they utilized optogenetic stimulation and two-photon imaging to investigate how the activation of different neuron types affects blood vessels in mice. They discovered that only the activation of inhibitory neurons led to vessel constriction, albeit with a negligible impact on LFP (Uhlirova et al., 2016).”

Reviewer #2 (Recommendations For The Authors):

Major problems with writing:

Comment 1: The authors need to review past work to better place their study in the context of the literature (some review articles: Lurie et al. Netw Neurosci. 2020 Feb 1;4(1):30-69. & Thompson et al. Neuroimage. 2018 Oct 15;180(Pt B):448-462.)

Here are some LFP and BOLD "resting state" papers focused on dynamic changes.

Many of these papers examine both spatial and temporal extents of correlations. Several of these papers use similar methods to the reviewed paper.

Also, many of these papers dispute the claim that correlations seen are

"electrophysiology invisible signal." Note that I am NOT saying that "electrophysiology invisible" correlations do not exist (it seems very likely some DO exist). However, the authors did not show that in the reviewed paper, and some of the correlations which they call an "electrophysiology invisible signal" probably would be visible if analyzed in a different manner.

Quite a few literature studies that the reviewer suggested were already included in the original manuscript. We have also added more literature studies to the revised manuscript. Again, we would like to emphasize that the novelty of our study centers on the discovery of the disparity in temporal and spatial relationships between resting-state electrophysiological and fMRI signals. See below our responses to individual literature studies listed.

In humans:

<https://pubmed.ncbi.nlm.nih.gov/38082179/> Predicts by using models the paper under review does not use here.

The following discussion was added to the revised manuscript:

“Some other comparison methods such as rank correlation and transformation prior to comparison were also tested and results remain persistent (Fig. S14). These findings align with the notion that, compared to nonlinear models, linear models offer superior predictive value for the rsfMRI signal using LFP data, as comprehensively illustrated in (Nozari et al., 2024) (also see Fig. S7). Importantly, in this study, the predictive powers (represented by R^2) of various comparison methods tested all remain below 0.5 (Nozari et al., 2024), suggesting that while certain models may enhance the temporal relationship between LFP and BOLD signals, the improvement is likely modest.”

In nonhuman primates: <https://pubmed.ncbi.nlm.nih.gov/34923136/> Most of the variance that could be creating resting state networks is in the <1 Hz band which the paper under review did not study

[We also examined infraslow LFP activity (< 1Hz) in our data. Consistent with the finding in the reference paper (Li et al., 2022), infraslow LFP power and the BOLD signal can derive consistent RSN spatial patterns (for M1, spatial correlation = 0.70), while the temporal correlation remains very low (temporal correlation = 0.08). These results and the reference paper were added to the revised manuscript.

<https://pubmed.ncbi.nlm.nih.gov/28461461/> Compares actual spread of LFP vs. spread of BOLD instead of just correlation between LFP and BOLD.

The following sentence has been added to the revised manuscript.

“This high spatial correspondence between rsfMRI and LFP signals can even be found at the columnar level (Shi et al., 2017).”

<https://pubmed.ncbi.nlm.nih.gov/24048850/> Comparison of small (from LFP) to large (from BOLD) spatial correlations in the context of temporal correlations.

In this study, researchers compared neurophysiological maps and fMRI maps of the inferior temporal cortex in macaques in response to visual images. They observed that the spatial correlation increased as the neurophysiological maps got greater levels of spatial smoothing. This suggests that fMRI can capture large-scale spatial information, but it may be limited in capturing fine details. Although interesting, this paper did not study the electrophysiology-fMRI relationship at the resting state and hence is not very relevant to our study.

<https://pubmed.ncbi.nlm.nih.gov/20439733/> Electrophysiology from a single site can correlate across nearly the entire cerebral cortex.

We have included the discussion of this paper in the original manuscript.

<https://pubmed.ncbi.nlm.nih.gov/18465799/> The original dynamic BOLD and LFP work from 2008 by Shmuel and Leopold included spatiotemporal dynamics.

We have included the discussion of this paper in the original manuscript.

In rodents:

<https://pubmed.ncbi.nlm.nih.gov/34296178/> Better electrophysiological correspondence was found using alternate methods the paper under review does not use.

This study investigates the electrophysiological correspondence in taskbased fMRI, while our study focused on resting state signals.

<https://pubmed.ncbi.nlm.nih.gov/31785420/> Electrophysiological basis of co-activation patterns, similar comparisons to the paper under review.

We have included the discussion of this paper in the original manuscript.

<https://pubmed.ncbi.nlm.nih.gov/29161352/> Cross-frequency coupling of LFP modulating the BOLD, perhaps more so than raw amplitudes.

This paper investigated the impact of AMPA microinjections in the VTA and found reduced ventral striatal functional connectivity, correlation between the delta band and BOLD signal, and phase–amplitude coupling of low-frequency LFP and high-frequency LFP, suggesting changes in low-frequency LFP might modulate the BOLD signal.

Consistent with our study, we also found that low-frequency LFP is negatively coupled with the BOLD signal, but we did not investigate changes in neurovascular coupling with disturbed neural activity using pharmacological methods, and hence, we did not discuss this paper in our study.

<https://pubmed.ncbi.nlm.nih.gov/24071524/> This paper did the same kind of tests comparing LFP-BOLD correlations to BOLD-BOLD correlations as the paper under review.

This study examined the neural mechanism underpinning dynamic restingstate fMRI, revealing a spatiotemporal coupling of infra-slow neural activity with a quasiperiodic pattern (QPP). While our current investigation centered on stationary restingstate functional connectivity, we acknowledge that dynamic analysis will provide additional value for investigating the relationship between LFP and rsfMRI signals. This warrants more investigation in a future study. This point has been added to the revised manuscript.

<https://pubmed.ncbi.nlm.nih.gov/24904325/> This paper found that different frequencies of electrophysiology (including ones not studied in the reviewed paper) contribute independently to the BOLD signal

This paper identified phase-amplitude coupling in rats anesthetized with isoflurane but not with dexmedetomidine, indicating that this coupling arises from a special type of neural activity pattern, burst-suppression, which was probably induced by high-dose isoflurane. They conjectured that high and low-frequency neural activities may independently or differentially influence the BOLD signal. Our study also examined the influence of various LFP frequency bands on the BOLD signal and found inversed LFP-BOLD relationship between low- and high-frequency LFP powers. We also added more results on the analysis of infraslow LFP signals. Regardless, since the reference study did not examine the spatial relationship of LFP and BOLD activities, we cannot comment on how it may provide insight into our results.

<https://pubmed.ncbi.nlm.nih.gov/26041826/> This paper found electrophysiological correlates within the BOLD signal when using BOLD analysis methods not used in the reviewed paper, and furthermore that some of these correlate with electrophysiological frequencies not studied in the reviewed paper (< 1 Hz).

We have added more results on the analysis of infraslow LFP signals and acknowledged the value of dynamic rsfMRI analysis in studies of BOLD/electrophysiology relationship.

I am not saying the authors need to use all these methods or even cite these papers. As I stated in their review, they merely need to (1) cite some of the most relevant for the proper context, the above list can maybe help (2) remove the claim of an "electrophysiology invisible signal" (3) use terms more commonly used in these papers for the extent of correlation with the electrode, other than "spatial variance."

We thank the reviewer again for providing a detailed list of reference studies. We have added the related discussion to the revised manuscript as described above.

Comment 2: The abstract entirely and much of the rest of the paper should be rewritten to be more reasonable. The authors would do well to review some of the past controversies in this area, e.g. Magri et al. J Neurosci. 2012 Jan 25;32(4):1395-407.

We have made significant revision to improve the writing of the paper. The reference paper has been added to the revised manuscript.

Comment 3: This should be re-written and the terminology used here should be chosen more carefully.

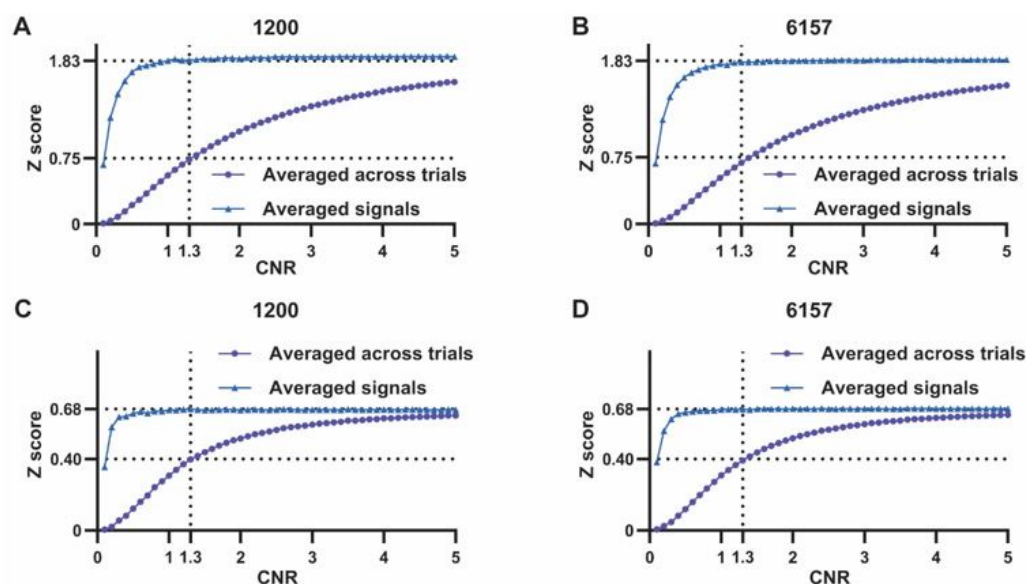
The writing of the manuscript has been improved with more careful choice of terminology.

Major method problem:

Comment 4: At a minimum, the authors should be transforming the uniform distribution of CC results to Z or T values and using randn() instead of rand() in MATLAB.

Below is the figure illustrating the simulation results by transforming CC values to Z score. Results obtained remain consistent.

Author response image 2.



Minor problems:

Comment 5: "MR-510 compatible electrodes (MRCM16LP, NeuroNexus Inc)"

Details of this type of electrode are not readily available. But for studies like this one, further information on materials is critical as this determines the frequency coverage, which is not even across all LFP frequencies for all materials. Most commercially prepared electrodes cannot record <1Hz accurately, and this study includes at least 0.11Hz in some of its analysis.

The type of electrode used in our current study is a silicon-based micromachined probe. These probes are fabricated using photolithographic techniques to pattern thin layers of conductive materials onto a silicon substrate. This probe is capable of recording the LFP activity within a broad frequency range, starting from 0.1Hz . We added this information to the revised manuscript.

Comment 6: Grounding to the cerebellum in theory would remove global conduction from the LFP but also global signal regression is done to the fMRI. Does the LFP-rsfMRI correlation change due to the regression or does only the rsfMRI-rsfMRI correlation change?

The results obtained with global signal regression were consistent with those obtained without it (see Figs. S4-S5), and therefore, we do not believe our results are affected by this preprocessing step.

Comment 7. Avoid colloquial language like "on the other hand" etc.

We used more appropriate language in the revised manuscript.

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<https://doi.org/10.7554/eLife.95680.2.sa0>