Report

Current Biology

BOLD fMRI Correlation Reflects Frequency-Specific Neuronal Correlation

Highlights

- Electrophysiological correlation structure predicts BOLD fMRI correlation structure
- BOLD fMRI and electrophysiology correlate on the single-subject level
- BOLD-electrophysiology correlation extends from 2 to 128 Hz
- Most predictive electrophysiological frequency varies with cortical connection

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In Brief

Brain-wide correlations of spontaneous BOLD fMRI signals are widely used to study large-scale neuronal interactions. Hipp and Siegel show that BOLD correlation in the human brain reflects the correlation of frequency-specific neuronal population activity.

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BOLD fMRI Correlation Reflects Frequency-Specific Neuronal Correlation

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SUMMARY

The brain-wide correlation of hemodynamic signals as measured with BOLD fMRI is widely studied as a proxy for integrative brain processes [1–3]. However, the relationship between hemodynamic correlation structure and neuronal correlation structure [4–6] remains elusive. We investigated this relation using BOLD fMRI and spatially co-registered, source-localized MEG in resting humans. We found that across the entire cortex BOLD correlation reflected the co-variation of frequency-specific neuronal activity. Resolving the relation between electrophysiological and hemodynamic correlation structures locally in cortico-cortical connection space, we found that this relation was subject specific and even persisted on the centimeter scale. At first sight, this relation was strongest in the alpha to beta frequency range (8–32 Hz). However, correcting for differences in signal-to-noise ratios across electrophysiological frequencies, we found that the relation extended over a broad frequency range from 2 to 128 Hz. Moreover, we found that the frequency with the tightest link to BOLD correlation varied across cortico-cortical space. For every cortico-cortical connection, we show which specific correlated oscillations were most related to BOLD correlations. Our work provides direct evidence for the neuronal origin of BOLD correlation structure. Moreover, our work suggests that, across the brain, BOLD correlation reflects correlation of different types of neuronal network processes and that frequency-specific electrophysiological correlation provides information about large-scale neuronal interactions complementary to BOLD fMRI.

RESULTS

Large-scale neuronal interactions are fundamental for normal brain function and altered in various neuropsychiatric diseases. The brain-wide correlation structure of spontaneous hemodynamic signals as measured with blood-oxygenation-level-dependent (BOLD) fMRI during rest is thought to provide a window into large-scale neuronal interactions [1–3]. Such "resting-state" BOLD correlation structure reflects learning [7], conscious states [8], brain maturity [9], cognitive control, and intelligence [10], as well as neuropsychiatric diseases [2, 11–13]. However, in contrast to the local BOLD signal [14–17], the relation between BOLD correlation structure and neuronal correlation structure remains largely elusive.

Recent methodological advances [5, 18] facilitate the direct investigation of neuronal interactions based on electrophysiological measures of frequency-specific neuronal population activity. Magnetoencephalography (MEG) in resting human subjects revealed brain-wide correlation of electrophysiological signals that is spatially highly structured [4–6] and varies with the frequency of neuronal activity [5]. It has been suggested that such frequency-specific electrophysiological correlation structures bear some resemblance to hemodynamic correlation structure [4–6]. However, a direct and spatially co-registered comparison, which is needed to assess whether and, if so, how the spatial structures of BOLD and neuronal correlation are related, has not been performed. Here, we demonstrate and characterize this relation.

Spatially Co-registered Electrophysiological and Hemodynamic Correlations

We performed MEG and fMRI in 20 healthy human subjects at rest with eyes closed. We source reconstructed the MEG data and spatially co-registered it with the fMRI data at 457 locations that homogeneously covered the cerebral cortex about 7 mm below the skull (Figure S1 and Supplemental Experimental Procedures). For each modality (MEG and fMRI), we derived the correlation between signals from all these locations (~100,000 values quantifying the global correlation structure; Figure 1A). For MEG data, we performed a frequency-specific analysis of amplitude correlations for band-limited neuronal activity at 25 frequencies logarithmically spaced in the range of 2 to 128 Hz. Importantly, we employed a method that discounts any spurious correlation caused by the limited spatial resolution of MEG and thus derives unequivocal measures of neuronal interactions [5, 18].

Relation between Global Electrophysiological and Hemodynamic Correlation Structures

We set out to investigate whether global, i.e., brain-wide, electrophysiological and hemodynamic correlation structures are related. To this end, we first compared the frequency-unspecific electrophysiological correlation structure to the hemodynamic correlation structure by averaging the electrophysiological correlation structures of band-limited activity across all frequencies. Across subjects, we found a significant positive correlation

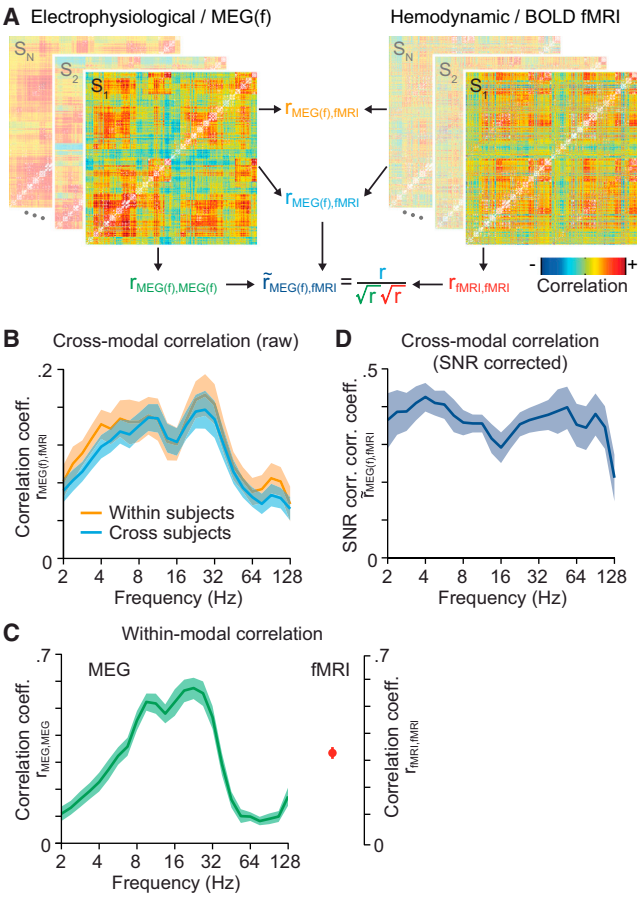

Figure 1. Relation between Global Electrophysiological and Hemodynamic Correlation Structures

(A) Illustration of the analysis workflow. Electrophysiological and hemodynamic all-to-all correlation matrices were correlated either within subjects (orange) or between subjects (cyan) to derive the cross-modal (i.e., MEG–fMRI) correlation between electrophysiological and hemodynamic correlation structures (see Figure S1 for details on the analyzed source space). The signal-to-noise ratio (SNR) within each modality was derived as the correlation (i.e., consistency) of electrophysiological (green) and hemodynamic (red) correlation matrices between subjects. SNR-corrected cross-modal correlation was derived by normalizing the cross-modal correlation by the within-modality SNR (blue).

(B) Correlation between frequency-specific electrophysiological and hemodynamic correlation structures. Bands indicate SEM.

(C) Correlation (i.e., consistency) of within-modality correlation structure across subjects.

(D) SNR-corrected correlation between electrophysiological and hemodynamic correlation structures.

($r_{MEG,fMRI}$ = 0.120 ± 0.0518; mean ± SD across subjects; one-tailed t test for r > 0, p = 1.31 × 10^{-9}).

However, the question of whether this cross-modal similarity is simply coincidental arises. Any two random, unrelated patterns are positively correlated with 50% probability. If each of these patterns were highly consistent across subjects, such a coincidental positive correlation would also be consistent, and thus statistically significant, across subjects. Thus, the critical statistic is not to test for a positive correlation that is consistent across subjects, but to test whether the measured magnitude of correlation between patterns could be observed by chance for random patterns with the dimensionality (i.e., spatial smoothness) of the measured patterns. To compute this statistic, we employed a randomization approach that included estimating the effective dimensionality of the data (see Supplemental Experimental Procedures). We found that the observed correlation was indeed significantly non-coincidental, i.e., reflecting a true relation between electrophysiological and hemodynamic correlation structure ($p < 10^{-16}$). This finding establishes a direct link between electrophysiological and hemodynamic correlation structures.

Frequency-Resolved Relation between Global Correlation Structures

The correlation between global electrophysiological and hemodynamic correlation structures may differ for neuronal activity in different frequency ranges. Thus, we next quantified the relation between global electrophysiological and hemodynamic correlation structures for individual electrophysiological frequencies. For all investigated frequencies, we found a non-coincidental positive cross-modal correlation ($p < 0.01$). The strength of correlation varied with frequency (Figure 1B; ANOVA with the factor frequency, Greenhouse-Geisser correction, $F_{24,456}$ = 5.52, ε = 0.13, p = 0.002) and prominently peaked in the alpha to beta frequency range (8–32 Hz), indicating a frequency-specific cross-modal relation.

However, the alpha to beta frequency range is exactly the frequency range with the strongest extracranial electrophysiological signals [19] and with the strongest and most consistent power correlations [4, 5]. This raised the question of whether the peak correlation in the alpha to beta frequency range reflects a genuinely stronger link to the BOLD correlation structure or merely a high "signal-to-noise ratio" (SNR) in this frequency range.

To address this question, we first quantified the SNR of correlation structures for both modalities by measuring the consistency of correlation structures across subjects. Indeed, for MEG, the consistency of correlation structures peaked in the alpha to beta frequency range (Figure 1C). In other words, correlation matrices were much more consistent across subjects in the alpha frequency range than, e.g., in the theta or gamma frequency range. Second, to account for these differences in SNR across frequencies with respect to the cross-modal correlation, we employed Spearman's correction of attenuated correlation coefficients (Figure 1A; Supplemental Experimental Procedures). We normalized the cross-modal correlation (Figure 1B) by both modalities' consistency of correlation structures to derive SNR-corrected correlation values (Figure 1D). This SNR correction had a strong effect. First, the magnitude of the correlation between modalities increased to r = 0.38 ± 0.121 (mean ± SD across frequencies). Second, the cross-modal correlation no longer showed a peak in the alpha to beta frequency range. Instead, there were high correlations across a broad frequency range that only dropped for very high frequencies (>100 Hz). Indeed, after SNR correction, there was no longer a significant modulation of the cross-modal correlation across frequencies (ANOVA with the factor frequency, Greenhouse-Geisser correction, $F_{24,456}$ = 1.10, ε = 0.13, p = 0.36; uncorrected: p = 0.33). In sum, the SNR-corrected correlation between hemodynamic

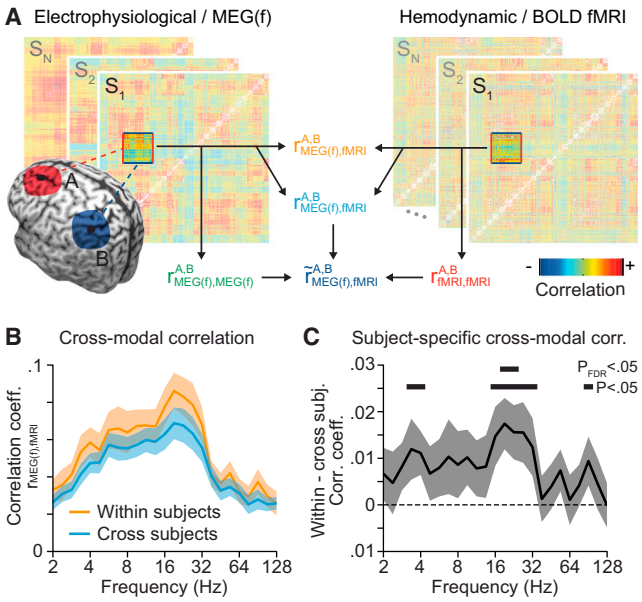

Figure 2. Relation between "Connection-Resolved" Electrophysiological and Hemodynamic Correlation Structures

(A) Illustration of the analysis workflow.

(B) Correlation between connection-resolved electrophysiological and hemodynamic correlation structures averaged across all connections. Bands indicate SEM. See Figure S2 for additional analyses.

(C) Subject-specific cross-modal relation, i.e., the difference between within-subject and cross-subject cross-modal correlations. Gray band indicates SEM; black bars indicate uncorrected and FDR-corrected significance.

and electrophysiological correlation structures was highly significant and strong ($r \sim 0.4$), and it extended across a broad frequency range, suggesting that the apparent peak of uncorrected global correlations in the alpha to beta frequency range reflects differences in signal-to-noise ratios across frequencies.

Connection-Resolved Cross-Modal Correlation

The above analyses were all based on the global correlation structure, i.e., correlations between all pairs of investigated cortical locations. However, as oscillatory processes vary across the brain, the relation between electrophysiological and hemodynamic correlation structures may also vary across the brain. This spatial variability would not be captured in the analysis of the global correlation structure. Furthermore, the global correlation analysis may mostly reflect coarse correlation structure or even monotonic gradients of correlation across the brain. Thus, the global analysis may miss local relations between modalities that are potentially subject specific. To explore these possibilities, we next resolved the cross-modal relation in (connection) space. To this end, we derived for any "connection," i.e., for any pair of cortical locations, the cross-modal correlation from local neighborhoods (~2.5 cm radius) around the two locations (Figure 2A; Supplemental Experimental Procedures). In other words, for each connection, we derived the cross-modal correlation as the similarity of correlation patterns in the cortical neighborhood of each connection. This resulted in a matrix of "connection-resolved cross-modal correlations" (Figure S2).

The average connection-resolved cross-modal correlation across all connections was positive, highly consistent across subjects, and non-coincidental (Figure 2B; $r_{MEG,fMRI} = 0.054 \pm 0.0188$; for all frequencies: one-tailed t test for $r_{MEG,fMRI} > 0$: $p < 4.35 \times 10^{-4}$; test for non-coincidental correlation: $p < 10^{-16}$; see Figures S3A and S3B for additional analyses). The average correlation strength was about half the strength of that found in the global analysis (see above). This suggests that the global correlation between electrophysiology and BOLD fMRI largely reflected smooth spatial changes of correlation across the brain that are common to both modalities. Furthermore, finding significant connection-resolved cross-modal correlations showed that this analysis indeed provided access to local cross-modal correlation structures on the centimeter scale.

We next tested whether the connection-resolved cross-modal correlation reflected subject-specific variability of the anatomical structure and activated brain networks. Indeed, we found that cross-modal correlations within subjects (MEG and fMRI from the same subject) were significantly stronger than between subjects (Figure 2C; $p < 0.05$, FDR corrected; no such effect was found for the corresponding global analysis $p > 0.05$). In other words, beyond the population average, the BOLD correlation structure of individual subjects was predicted by the corresponding subject-specific electrophysiological correlation structure. This provides additional strong evidence for the neurophysiological origin of BOLD fMRI correlations.

Spectral Specificity

The SNR-corrected global analysis revealed a rather frequency-unspecific correlation between electrophysiological and hemodynamic correlation structures across a broad frequency range (Figure 1D). This may be different for locally resolved cross-modal correlations. Thus, in analogy to the global analysis, we next tested whether, on the connection-resolved spatial scale, the cross-modal correlation was characterized by spectral specificity. We first employed Spearman's correction of attenuated correlation coefficients to the connection-resolved cross-modal correlation to allow for comparing across frequencies with different SNRs (Figures 2A and S3C–S3H; Supplemental Experimental Procedures). Then, for all connections with non-coincidental correlation (82.5% of all connections had non-coincidental correlation for at least one frequency), we performed an ANOVA with the factor frequency. We found that 21% of connections had a significant frequency-specific relation between local electrophysiological and hemodynamic correlation structures (ANOVA threshold $p < 0.05$). This is a highly significant fraction of connections (binominal test, $p < 10^{-10}$). We next investigated the strength of this frequency specificity. The average cross-modal correlation at the peak frequency of significantly modulated connections was $r \approx 0.5$, which was substantially higher than the average correlation across all frequencies with non-coincidental correlation ($r \approx 0.2$). Thus, about six times as much BOLD correlation variance ($r^2 \approx 0.25$ versus $r^2 \approx 0.04$) was explained by correlation of electrophysiological activity at the best frequency as compared to the average across frequencies. Although this should be considered an upper bound due to a positive selection bias, we can conclude that there is a strong difference in how local electrophysiological correlation

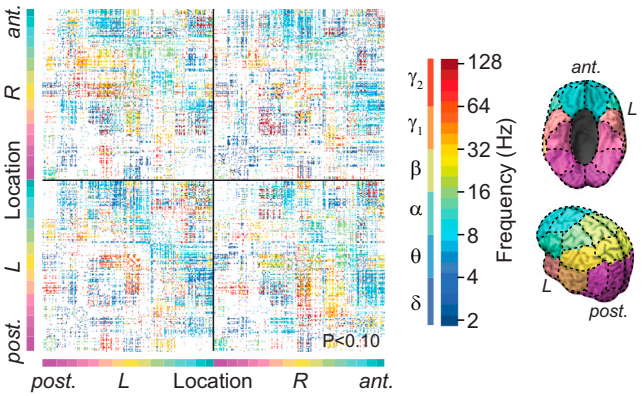

Figure 3. Peak Frequencies of the Correlation between Electrophysiological and Hemodynamic Correlation Structures

The matrix displays the color-coded peak frequencies for all significantly frequency-specific connections (i.e., ANOVA across frequency with $p < 0.1$). The matrix is sorted according to brain locations that are color coded with a different color scale indicated on the brains to the right of the matrix. See Figure S3 for further analyses.

structure at different frequencies relates to local hemodynamic correlation structure.

Spatial Variation of Frequency-Specific Relations

This frequency specificity may correspond to two different scenarios. First, there may be the same frequency specificity throughout the brain; i.e., there may be a generic cross-modal relation, where, throughout the brain, correlation structure in the same frequency band has the tightest link to hemodynamic correlation structure. Alternatively, the frequency with the strongest link to BOLD correlation may differ for different cortico-cortical connections. We found evidence for the latter scenario. Across all connections, the frequencies with strongest cross-modal correlation were broadly distributed across the entire spectrum (Figures 3, S3I, and S3J). For statistical analysis, we split the frequency range into six frequency bands (2–4 Hz, 4–8 Hz, 8–16 Hz, 16–32 Hz, 32–64 Hz, 64–128 Hz). Each of these six frequency bands showed strongest correlation with BOLD correlations for a significant number of connections (random permutation test, $p < 0.025$ for all frequency bands; Supplemental Experimental Procedures; see Figure S4 for control analyses based on a different analysis approach and for a different selection of frequency bands, both showing highly similar results). This suggests that, throughout the brain, BOLD correlation structure reflects correlations of different electrophysiological processes.

Spatial Structure of Frequency-Specific Relations

We next investigated, for each frequency range, which cortico-cortical BOLD correlations were best predicted by electrophysiological correlation in that frequency range. We visualized these connections and the corresponding connected cortical regions (Figures 4 and S4). For all frequency bands, we found well-structured cortical patterns that were significantly mirror symmetric across the midline (random permutation test, $p < 10^{-4}$; Supplemental Experimental Procedures). There were marked differences between frequency bands. While hemodynamic correlation between medial prefrontal and temporoparietal cortex mostly reflected correlation of theta-band activity (4–8 Hz), inter-hemispheric BOLD correlation between homologous somato-motor areas indexed correlation of beta-band activity (16–32 Hz). These patterns accord well with the prominent role of local theta rhythms in medial prefrontal and medial temporal areas as well as of local beta rhythms in somato-motor areas [19]. On the contrary, the relation between alpha correlation and hemodynamic correlation was particularly pronounced between frontal and temporal areas, which does not match the prominent role of local alpha rhythms in parietal and occipital areas [19].

DISCUSSION

Here, we provide, to the best of our knowledge, the first direct evidence for a non-coincidental relationship between electrophysiological and hemodynamic correlation structures. We show that the relation is frequency and subject specific, presumably reflecting different neuronal processes and individual anatomical or functional variability, respectively. Our work provides insight into the neuronal origin of the widely studied hemodynamic correlation and underlines its importance as a window into large-scale neuronal interactions.

Relation of BOLD fMRI Correlation to Correlation of Frequency-Specific Neuronal Activity

We found that the relation between electrophysiological and hemodynamic correlation structures is strongest in the alpha to beta frequency range. This accords well with studies that found strongest brain-wide correlation of electrophysiological activity in the alpha to beta frequency range [4–6], with studies that found a tight link between local BOLD and electrophysiological signals [20, 21], and with studies investigating the relation between BOLD correlation and electroencephalogram (EEG) sensor signals [22, 23]. Our results show that the apparent dominance of the alpha to beta frequency range reflects differences in the SNR between electrophysiological frequencies. In fact, the SNR-corrected correlation revealed strong correlation between electrophysiological and hemodynamic correlation structures across a broad range of electrophysiological frequencies (2–128 Hz).

Importantly, the dominant frequency, i.e., the electrophysiological frequency with highest SNR-corrected correlation with BOLD correlation, varied across cortico-cortical connections. As the specific frequencies of neuronal oscillations reflect the biophysical properties of underlying network interactions [24–26], our results suggest that, for different pairs of brain regions, BOLD correlations index correlations between different neuronal network processes.

One possibility is that the variability of the dominant cross-modal frequency across the brain reflects different strengths of neuronal oscillations. E.g., theta-, alpha-, and beta-band activity is particularly strong in frontal, partial, and somato-motor cortex, respectively. For the theta and beta bands, the dominant cross-modal connections indeed spatially coincided with strong local signal power. In contrast, the strength of local alpha power was a poor predictor for cross-modal connections dominated by the alpha frequency range. Thus, our work suggests a regionally specific link between electrophysiological and hemodynamic

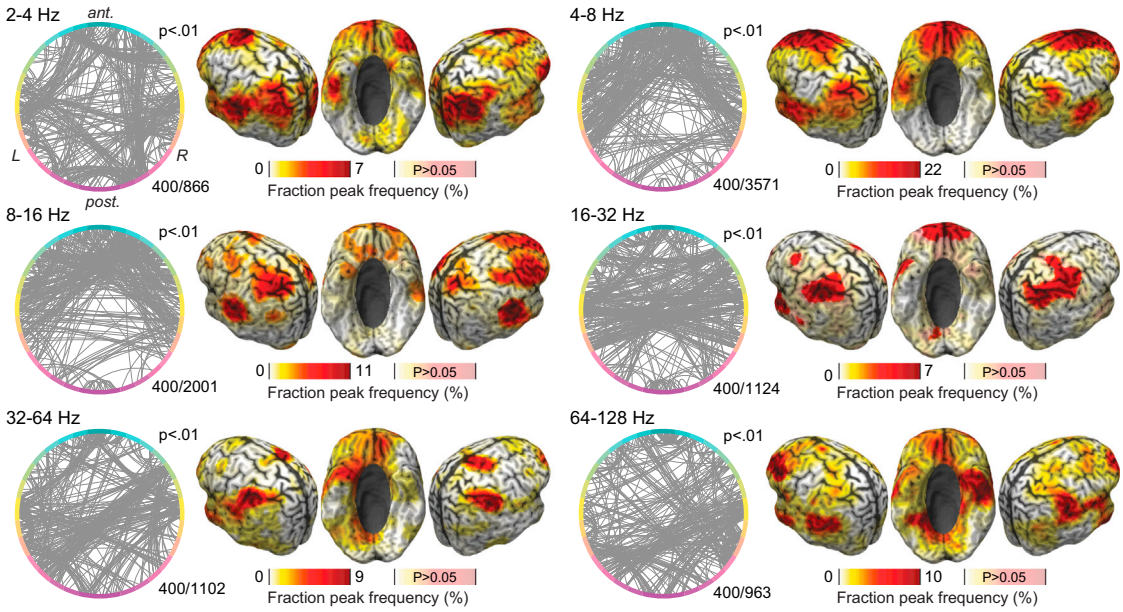

Figure 4. Brain-wide Distribution of Frequency-Specific Correlation between Electrophysiological and Hemodynamic Correlation Structures
Left: Connection plot showing a randomly selected subset of connections (n = 400) that had the strongest relation for the respective frequency band ($p < 0.01$). The mapping of brain regions on the circle is color coded (see Figure S1C for color mapping). Right: Brain-wide distribution of the fraction of connections that exhibited the strongest correlation for the respective frequency band ($p < 0.01$). The fraction is statistically masked ($p < 0.05$, random permutation test; see Supplemental Experimental Procedures). See Figure S4 for a control analysis testing for above-average correlations.

correlation structures that does not simply reflect the dominance of specific local rhythms.

The present study focuses on frequency-specific, rhythmic neuronal population activity. However, similar to the univariate BOLD signal [14, 17], and in addition to the link to frequency-specific activity shown here, BOLD correlations may also be linked to correlations of broad-band and spiking activity. In fact, electrophysiological population signals such as the MEG or local field potential (LFP) reflect not only band-limited oscillatory neuronal activity but also non-rhythmic broad-band activity that is thought to reflect average spiking activity [27]. Indeed, we also found a substantial fraction of cortico-cortial connections with non-coincidental cross-modal correlation that had no significant frequency specificity. This finding is well compatible with a link of hemodynamic correlation also to correlation of non-rhythmic, broad-band population activity, and neuronal spiking. Further, and in particular invasive, studies are required to investigate this potential link.

Relation to fMRI Resting State Networks

The analysis of BOLD fMRI correlation structure in resting humans revealed sets of mutually correlated areas, so-called "resting state networks" [3]. It has been suggested that specific resting state networks are linked to specific electrophysiological frequencies [23]. Although we did not explicitly address this question, and did not investigate deep sources typically part of resting state networks, our results cast doubt on this notion. For the somato-motor network [1], we found indeed a good correspondence with the cross-modal relation that is dominated by the beta frequency range. However, other more complex resting state networks, such as, e.g., the "default mode network" or the "control network" seem to lack simple frequency-specific correspondents in the cross-modal relation. Thus, our results suggest that, in general, BOLD resting state networks reflect a mixture of neuronal activity in different frequency bands rather than being linked to individual specific frequencies.

Spatial Scales, Sources of Neuronal Variance, and Other Factors

Our findings shed new light on an apparent conflict between invasive and non-invasive studies. While many invasive studies found a particularly strong relation between gamma-band activity and BOLD on the univariate [15, 16, 28, 29] and bivariate [30, 31] level, non-invasive studies—including our results presented here—find strong correlations mostly between alpha to beta-band activity and BOLD [20–23]. This apparent conflict may be related to the different spatial scales at which the signals are sampled. While extracranial, non-invasive measures may be particularly sensitive to signals with a large spatial extent such as alpha oscillations, invasive intracranial recordings may be more sensitive to high-frequency processes with less spatial extent, such as gamma oscillations. In accordance with this hypothesis, we found that SNR correction turns the cross-modal relation into a broad-band relation that includes the gamma range. Thus, SNR correction may effectively counteract the reduced extracranial sensitivity to local rhythms, such as gamma oscillations.

Beyond the spatial scale, other factors such as the investigated cortical location and species as well as the source of neuronal variance (i.e., the cognitive task, sensory drive, or motor output at hand) may underlie different results between experiments. For example, in the presence of a strong visual stimulus,

the BOLD signal also co-varies with visual gamma-band activity in the human EEG [32]. It remains to be determined how far our findings in resting humans generalize to other species and to other sources of neuronal variance, such as, e.g., specific cognitive tasks.

Electrophysiological Correlation Carries Complementary Information

Our work shows that there is no generic, brain-wide transfer function from hemodynamic correlation to the correlation of frequency-specific neuronal population activity but that this transfer function depends on the specific cortico-cortical connection at hand. This insight is of great importance for the neurophysiological interpretation of BOLD fMRI correlation. Furthermore, this finding indicates that frequency-specific electrophysiological correlations provide a unique window into large-scale neuronal interactions. Recent methodological advances provide unequivocal measures of neuronal interactions based on frequency-specific correlations from EEG and MEG [5, 18, 33]. Furthermore, measures of neuronal interaction dissociate from measures of local signal power [5, 34]. Thus, frequency-specific electrophysiological measures provide information on neuronal interactions in the healthy and diseased human brain that can be accessed neither with univariate electrophysiological measures nor with BOLD fMRI correlation.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures and four figures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2015.03.049.

AUTHOR CONTRIBUTIONS

J.F.H. and M.S. designed the research and wrote the manuscript. J.F.H. recorded the data and performed the data analysis.

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