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Concurrent EEG- and fMRI-derived functional connectomes exhibit linked dynamics

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## Abbreviations

| Abbreviation                                      | Full Form                  |
|--------------------------------------------------|----------------------------|
| Dynamic Functional Connectivity                  | dFC                        |
| Default Mode Network                             | DMN                        |
| Functional Connectivity                          | FC                         |
| Imaginary part of the Coherency                  | iCoh                       |
| Intrinsic Connectivity Networks                  | ICN                        |
| Mutual Information                               | MI                         |
Abstract

Long-range connectivity has become the most studied feature of human functional Magnetic Resonance Imaging (fMRI), yet the spatial and temporal relationship between its whole-brain dynamics and electrophysiological connectivity remains largely unknown. fMRI-derived functional connectivity exhibits spatial reconfigurations or time-varying dynamics at infraslow (<0.1Hz) speeds. Conversely, electrophysiological connectivity is based on cross-region coupling of fast oscillations (~1-100Hz). It is unclear whether such fast oscillation-based coupling varies at infraslow speeds, temporally coinciding with infraslow dynamics across the fMRI-based connectome. If so, does the association of fMRI-derived and electrophysiological dynamics spatially vary over the connectome across the functionally distinct electrophysiological oscillation bands? In two concurrent electroencephalography (EEG)-fMRI resting-state datasets, oscillation-based coherence in all canonical bands (delta through gamma) indeed reconfigured at infraslow speeds in tandem with fMRI-derived connectivity changes in corresponding region-pairs. Interestingly, irrespective of EEG frequency-band the cross-modal tie of connectivity dynamics comprised a large proportion of connections distributed across the entire connectome. However, there were frequency-specific differences in the relative strength of the cross-modal association. This association was strongest in visual to somatomotor connections for slower EEG-bands, and in connections involving the Default Mode Network for faster EEG-bands. Methodologically, the findings imply that neural connectivity dynamics can be reliably measured by fMRI despite heavy susceptibility to noise, and by EEG despite shortcomings of source reconstruction. Biologically, the findings provide evidence that contrast with known territories of oscillation power, oscillation coupling in all bands slowly reconfigures in a highly distributed manner across the whole-brain connectome.

1 Introduction

To date, our knowledge about the topography of functional connectivity in the human brain is largely derived from fMRI, an indirect measure of neural activity. Using fMRI, the brain has been characterized in terms of different large-scale intrinsic connectivity networks (ICNs) (Damoiseaux et al., 2006; Fox et al., 2005; Yeo et al., 2011). Collectively, the connectivity within and between ICNs can be represented as a whole-brain connectivity graph, or connectome (Sporns et al., 2005). Extensive efforts have been undertaken towards establishing the neural origin of this functional connectivity (FC) organization (Brookes et al., 2011; Deligianni et al., 2014; He et al., 2008; Hipp and Siegel, 2015; Kucyi et al., 2018; Logothetis et al., 2001; Wirsich et al., 2017). This line of research has traditionally focused on static properties of FC by averaging brain activity across the entire recording period. To date, a comparable spatial organization of static whole-brain FC has been observed across EEG and fMRI (Deligianni et al., 2014; Wirsich et al., 2017), MEG and fMRI (Brookes et al., 2011; Hipp and Siegel, 2015) and intracranial EEG and fMRI (He et al., 2008; Kucyi et al., 2018).

Because cognitive processes are inherently dynamic, time-varying reconfigurations across the fMRI-derived functional connectome occurring at infraslow speeds (typically defined as < 0.1Hz (Hiltunen et al., 2014; Leistner et al., 2010)) are receiving increasing attention (Chang and Glover, 2010; Zalesky et al., 2014). Such reconfigurations or dynamics of functional connectivity (dFC) are suggested to represent flexible changes across distinct cognitive architectures that support different cognitive processes (Deco et al., 2013). This intriguing possibility derived from fMRI could explain the role of intrinsic connectivity in cognition (Sadaghiani et al., 2015; Sadaghiani and Kleinschmidt, 2013). However, the relationship between fMRI-derived dFC and electrophysiological mechanisms of information exchange, specifically oscillatory synchrony (Singer, 2013; Varela et al., 2001), has not yet been substantiated in direct measures of neural connectivity across the connectome.
Such direct neural measures are essential because investigations of time-varying fMRI connectivity have been plagued by concerns about physiological noise, head motion, and sampling variability (Laumann et al., 2017; Leonardi and Van De Ville, 2015), as well as uncertainty regarding how to adequately model and account for such spurious ‘dynamics’ (Hindriks et al., 2016; Zalesky et al., 2014). In particular, three questions remain unanswered in direct neurophysiological recordings. Does neurophysiological connectivity (specifically phase coupling) typically derived from fast neural oscillations (~1-100 Hz) fluctuate in strength at infraslow speeds (< 0.1Hz) across regions of the connectome? If so, do such infraslow changes in neurophysiological connectivity co-occur with fMRI-derived connectivity changes across corresponding connectome regions? And to what extent is the putative cross-modal link frequency-dependent? More specifically, changes in fMRI-derived connectivity between a given set of brain regions could be accompanied by infraslow connectivity changes in all canonical oscillation frequencies. Alternatively, fMRI connectivity dynamics could be accompanied by fluctuations of different frequency bands across different sets of brain regions. In the following sections, we discuss the status quo and knowledge gap regarding these questions. Since studying the temporal relationship of dFC between fMRI and neurophysiological signals necessitates concurrently recorded data, the following overview focuses largely on multimodal research.

The dynamic modulation in phase coupling of neurophysiological oscillations as measured by EEG and MEG is a well-established mechanism for long-range neural connectivity (Singer, 2013; Varela et al., 2001). However, it is unknown whether these neurophysiological connectivity dynamics extend to infraslow time scales comparable to those driving dFC in fMRI. Indications that this may be the case come from concurrent EEG-fMRI studies assessing neurophysiological phase coupling at sensor level and building a coarse global connectivity average across all EEG electrode pairs (Jann et al., 2009; Sadaghiani et al., 2012). Such spatially averaged neurophysiological connectivity timecourses indeed exhibit fluctuations at infraslow timescales. However, connectivity across electrodes does not adequately reflect neurophysiological connectivity across brain regions (Lai et al., 2018), and global averaging further removes any spatial information. Additionally, these studies relate neurophysiological connectivity to fMRI amplitude but not fMRI connectivity.

Conversely, other concurrent EEG-fMRI studies have compared neurophysiological signal amplitude to fMRI-derived connectivity dynamics. EEG band-limited global field power (average across all electrodes) has been linked to fMRI-derived dFC both in specific ICNs (Chang et al., 2013) and the whole brain (Lamoš et al., 2018; Tagliazucchi et al., 2012). Similarly, Allen et al. (2017) demonstrated that the reoccurring states of fMRI-based dFC co-occur with changes in the EEG power spectrum of certain electrodes. Again, no information about neurophysiological connectivity across brain regions can be obtained from these studies since they use sensor-level EEG amplitude. Thus, it remains unknown whether neurophysiological dFC across regions of the connectome changes in unison with the distributed dynamics observed in concurrent fMRI.

Another set of studies made the crucial advance to comparing fMRI connectivity with spatially localized neurophysiological connectivity obtained from invasive recordings. Neurophysiological oscillations recorded invasively in the rat show interhemispheric connectivity across homologous somatosensory areas that co-fluctuate with concurrent fMRI-derived dFC across the same regions (Pan et al., 2011; Thompson et al., 2013). Concurrent intracranial-EEG and fMRI in presurgical patients has revealed that region pairs showing high levels of connectivity dynamics in fMRI do so in invasive neurophysiological recordings as well (Ridley et al., 2017). Unfortunately, the spatial coverage of such invasive electrophysiology studies is inherently limited. Consequently, they don’t inform about the correspondence of dynamic changes in the connectome’s whole-brain FC topography across neurophysiology and fMRI.
Closing this gap requires the study of neurophysiological connectivity dynamics across all regions of the whole-brain connectome concurrently with fMRI. Neurophysiological recordings over the scalp, i.e. EEG and MEG, are subject to limited spatial localizability. However, recent methodological advances have made it possible to measure whole-brain connectivity patterns and their dynamics from source-reconstructed signals, at least for coarse whole-brain parcellations (Hassan and Wendling, 2018; O’Neill et al., 2018). The reliability of MEG- and EEG-derived source-localized connectomes is confirmed by significant spatial correspondence of their static connectivity patterns to both structural and fMRI-derived static connectomes (Deligianni et al., 2016, 2014; Finger et al., 2016; Wirsich et al., 2017). However, no studies have investigated this whole-brain cross-modal correspondence in a dynamic framework, leaving the question of the relation between neurophysiological and fMRI-derived dFC across the connectome unanswered.

An interesting observation of the above-mentioned static cross-modal studies is that a stable connectome architecture comparable to that of fMRI exists for all canonical oscillation frequencies in EEG, albeit to varying degrees. Only two sets of studies have compared fMRI-derived and concurrently recorded neurophysiological whole-brain connectomes (source-localized EEG). Specifically, Deligianni et al. (2016, 2014) found significant spatial similarity across whole-brain fMRI-derived FC and EEG-based band-limited amplitude-coupling, and this similarity was stronger for slower EEG frequencies than for β and γ bands. Investigating EEG phase-coupling rather than amplitude-coupling (Wirsich et al., 2017), we likewise observed significant spatial similarity between concurrent static EEG and fMRI connectomes for all oscillation bands, albeit weakening in the γ band ($r > 0.3$ for δ through β bands, $r = 0.16$ for γ). While the EEG frequency band with strongest static connectivity differed across connections (also cf. (Hipp and Siegel, 2015) for offline MEG), the connectivity pattern for a given band was not restricted to specific ICNs. Here, we seek to answer whether the putative time-varying co-evolution of fMRI and EEG dFC is likewise spatially extensive in all oscillatory frequency bands.

We hypothesize that dFC derived from source-space EEG shows infraslow changes that covary over time with fMRI dFC on a connection-wise basis across the whole brain. Further, we aim to characterize the whole-brain topographical organization of this cross-modal relationship for each canonical EEG frequency band.
2 Methods

In short, we addressed the neurophysiological basis of fMRI dFC, its spatial topography, and its frequency-specificity in a main concurrent EEG-fMRI dataset during task-free resting state (n=26, 3x10min), and assessed generalization in a second dataset (n=16, 10min). The generalization dataset is openly available at https://osf.io/94c5t/ and described in detail in Deligianni et al. (2016, 2014). While eyes were closed in the first dataset, the second dataset was recorded with eyes open, allowing us to further assess generalization or differences across these conditions. After conservatively eliminating head motion based on both data modalities, preprocessed fMRI signal was averaged to the 68 cortical regions of the Desikan atlas (Desikan et al., 2006; Fischl et al., 2004). Preprocessed EEG signals were source-reconstructed (Baillet et al., 2001; Kybic et al., 2005; Tadel et al., 2011) to the same atlas (Fig. 1a).

2.1 Main Dataset

2.1.1 Subjects

We recruited 26 healthy subjects (8 females, mean age 24.39, age range 18-31) with no history of neurological or psychiatric illness. Ethical approval has been obtained from the local Research Ethics Committee (CPP Ile de France III) and informed consent has been obtained from all subjects.

2.1.2 Data Acquisition

We acquired three runs of 10 minutes eyes-closed resting-state in one concurrent EEG-fMRI session (Tim-Trio 3T, Siemens). FMRI parameters comprised 40 slices, TR=2.0s, 3.0x3.0x3.0mm, TE = 50ms, field of view 192, FA=78°. EEG was acquired using an MR-compatible amplifier (BrainAmp MR, sampling rate 5kHz), 62 electrodes (Easycap), referenced to FCz, 1 ECG electrode, and 1 EOG electrode. Scanner clock was time-locked with the amplifier clock (Mandelkow et al., 2006). Additionally, an anatomical T1-weighted MPRAGE sequence was acquired (176 slices, 1.0x1.0x1.0 mm, field of view 256, TR=7min).

The acquisition was part of a study with two additional naturalistic film stimulus of 10 minutes not analyzed in the current study, and acquired after runs 1 and 2 of the resting state as described in Morillon et al. (2010). The three runs resulted in a total length of 30 minutes of resting-state fMRI per subject. Subjects wore earplugs to attenuate scanner noise and were asked to stay awake, avoid movement and close their eyes during resting-state recordings. In three subjects, one of three rest sessions each was excluded due to insufficient EEG quality.

2.1.3 Data processing

Atlas

T1-weighted images were used to delineate 68 cortical regions of the Desikan atlas (Desikan et al., 2006; Fischl et al., 2004) and to extract a gray matter mask (recon-all, Freesurfer suite v6.0.0, http://surfer.nmr.mgh.harvard.edu/).

fMRI

The BOLD timeseries were corrected for slice timing and spatially realigned using the SPM12 toolbox (revision 6906, http://www.fil.ion.ucl.ac.uk/spm/software/spm12). Mean white matter and cerebrospinal fluid timecourses were extracted from a manually defined spherical 5mm ROIs using MarsBar (v0.44, http://marsbar.sourceforge.net/). Using the FSL toolbox (v5.0, https://fsl.fmrib.ox.ac.uk/fsl/) the skull-stripped T1 image (fsl-bet), Desikan atlas, and grey matter delineation were linearly coregistered into the subject space of the T2* images (fsl-flirt v6.0). The fMRI timeseries were averaged for each of the 68 atlas regions, and the six movement parameters (from realignment), signal of CSF and white matter ROIs and grey matter global signal were regressed
out of the region-wise timeseries. The resulting timeseries were bandpass-filtered at 0.009-0.08 Hz (Power et al., 2014).

**EEG**

EEG was corrected for the gradient artefact induced by the scanner using the template subtraction and adaptive noise cancelation followed by lowpass filtering at 75Hz, downsampling to 250Hz (Allen et al., 2000) and cardioballistic artefact template subtraction (Allen et al., 1998) using EEGLab v.7 (http://sccn.ucsd.edu/eeegl) and the FMRIIB plug-in (https://fsl.fmrib.ox.ac.uk/eeeglab/fmribplugin/). Data was then analyzed with Brainstorm software (Tadel et al., 2011), which is documented and freely available under the GNU general public license (http://neuroimage.usc.edu/brainstorm, version 10th August 2017). Bandpass-filtering was carried out at 0.3-70 Hz (no correction for line-noise was carried out, see SI Results). Data was segmented according to TR of the fMRI acquisition (2s epochs). Epochs containing head motion artefacts in EEG were visually identified after semi-automatically preselecting epochs where signal in any channel exceeded the mean channel timecourse by 4 std. These segments were excluded from the analysis. Electrode positions and T1 were coregistered by manually moving the electrode positions onto the electrode artefacts visible in the T1 image. Using the OpenMEEG BEM model, a forward model of the skull was calculated based on the individual T1 image of each subject (Gramfort et al., 2010; Kybic et al., 2005).

The EEG signal was re-referenced to the global average and was projected into source space using the Tikhonov-regularized minimum norm (Baillet et al., 2001) with the Tikhonov parameter set to 10% (Brainstorm 2016 implementation, assumed SNR ratio 3.0, using current density maps, constrained sources normal to cortex, depth weighting 0.5/max amount 10). Source activity was averaged to the regions of the Desikan atlas. For each epoch (length 2s) imaginary coherence of the source activity was calculated between each region pair (Nolte et al., 2004) at 2Hz frequency resolution. The 2Hz bins were averaged for 5 canonical frequency bands: δ (0.5-4Hz), θ (4-8Hz), α (8-12Hz), β (12-30Hz), γ (30-60Hz).

**Joint motion scrubbing**

For all analyses, both fMRI volumes and EEG epochs were excluded for time periods where motion was identified in either modality. Time periods with motion were defined as volumes exceeding the framewise displacement threshold FD=0.5 in fMRI (Power et al., 2012), and by visual inspection in EEG as described above. Additionally, for sliding window connectivity (see section Sliding window connectivity below), windows with more than 10% of their datapoints (>3 fMRI volumes or >3 EEG epochs) removed by this motion scrubbing procedure were excluded from dynamic connectivity analysis. The joint motion scrubbing approach resulted in a mean of 544 out of 870 sliding windows (range 262-813) for the main dataset and 216 out of 272 sliding windows (range 112-259) for the generalization dataset.

2.1.4 Connectivity

**Static connectivity**

Static connectivity was estimated for fMRI data by calculating Pearson’s correlation of the BOLD timecourse between each region pair over the duration of each run and averaged across the 3 runs. For EEG, the connectivity (imaginary coherence) calculated for each 2s epoch was averaged across all runs (Fig. 1a).

**Sliding window connectivity**

dFC matrices were calculated using a rectangular sliding window of 1 min. We averaged imaginary coherence of all 2s epochs over the 60s window for EEG (average over 30 datapoints per window),
and used Pearson’s correlation over the 60s timecourse for fMRI (correlation over 30 datapoints at a TR of 2s per window). The step size of the sliding window was set to 1 TR (2s). The window length was chosen to capture infraslow dynamics characteristic of fMRI dFC within limits of the following methodological considerations. The window size represents a tradeoff between maximizing the number of datapoints without discarding relevant dynamic BOLD frequencies (Power et al., 2014; Shine et al., 2016; Shirer et al., 2012) while also taking into account the theoretical limitations of shorter window lengths to reliably detect dFC (Leonardi and Van De Ville, 2015; Zalesky and Breakspear, 2015).

Leonardi and van de Ville (Leonardi and Van De Ville, 2015) propose a rule of thumb choosing a window length exceeding the longest wavelength of the BOLD signal around 100s. This rule of thumb has been confirmed by Zalesky and Breakspear (2015), but the authors also noted that a dynamic signal can still be detected (with lower power) for shorter window lengths (40s such as used in Shirer et al. (2012)). Shine et al. (2016) showed that those theoretical limits can be undersampled down to 10s (14 data points in their data). Chang et al. (2013) find a significant relationship between fMRI dFC and global α power dynamics peaking at 30s to 55s, and θ power dynamics peaking at window sizes between 65s and 70s. Given these results from prior studies we consider the 60s window (30 data points) a good tradeoff between being able to detect dynamics and having high detection power. Most importantly, we show that our results reliably replicated across two independent datasets with the chosen parameter set.

Normalized mutual information defined by $Y(M; N) = \frac{H(M) + H(N)}{H(M, N)}$ with H(M), H(N) being the entropies of observations N and M and H(M,N) the joint entropy (Studholme et al., 1998, 1997) was calculated for the resulting EEG and fMRI dFC matrices, building a new connectivity matrix of joint EEG-fMRI, based on mutual information strength between the modalities (for each EEG frequency band). In contrast to linear measures such as correlation, mutual information is an information theoretic measure which is able to also capture cross-modal relationships in connectivity dynamics without assuming linearity or Gaussian constraints (Shannon, 1948). Mutual information has previously been shown to be helpful when combining EEG and fMRI (Ostwald et al., 2010).
Fig. 1: a) Construction of EEG and fMRI connectomes. EEG was source reconstructed and fMRI signal was averaged for the 68 cortical regions of the Desikan atlas (Desikan et al., 2006). Pearson’s correlation of fMRI timecourses and imaginary coherence of band-limited EEG source signal for each region pair were used to build connectomes. b) In each data modality, dynamic FC was derived from a 1min window sliding at 2s (= repetition time of fMRI). For fMRI Pearson’s correlation at each connection was calculated over all samples of the 1-min window. For EEG, imaginary coherence was calculated at each connection in 2s segments (corresponding to the repetition time of fMRI), then averaged over the 1min window. To quantify the similarity of the connectivity dynamics across the data modalities, mutual information between the fMRI connectivity timecourse and the EEG connectivity timecourse was calculated at each connection. The ensuing mutual information at each connection was statistically compared to a null model. The null model consisted of the mutual information between the EEG connectivity timecourse and temporally phase scrambled fMRI connectivity timecourse (Prichard and Theiler, 1994; Theiler et al., 1992).

Null model

For each connection, mutual information was then compared to a null model of EEG-fMRI mutual information (Fig. 1b) using temporally phase-randomized fMRI dFC timecourses of each connection (Prichard and Theiler, 1994; Theiler et al., 1992). Specifically, we applied the approach of phase-randomization proposed by Theiler et al. (1994) to whole-brain connectomes by Fourier transforming the fMRI dFC timecourse at each connection. Then the phases of this transformation were randomly shifted. The result of the phase-shift was then back-transformed using the inverse Fourier transform. Importantly, this operation will create surrogate data with Fourier spectra and autocorrelation equal to that of the original timecourse. Note that unlike unimodal studies of fMRI dFC that are interested in the relationship between two fMRI signal timecourses and thus phase randomize the signal timecourse (e.g. (Hindriks et al., 2016)), we are interested in the relationship across EEG and fMRI connectivity timecourses, hence randomizing the connectivity timecourse for one modality.

The randomization process was carried out 50 times for the fMRI dFC timecourse for each subject and connection, and mutual information between the phase-randomized fMRI dFC timecourse and the unaltered EEG dFC timecourse was calculated for each iteration. For group-level statistical comparison of this null model to the original EEG-fMRI mutual information, we calculated an average null mutual information matrix from the 50 iterations for each subject. We subjected the original mutual information matrix to connection-wise paired t-tests against the null model over subjects. The ensuing p-values were Bonferroni corrected for the number of connections. This procedure was repeated for each EEG frequency band.
Intrinsic network analysis

To further interpret outcomes in the context of neurocognitive networks, we mapped the extracted 200 connections to 7 canonical ICNs (Visual, Somato-Motor, Default Mode, Fronto-Parietal, Dorsal Attention, Limbic, and Ventral Attention [largely corresponding to Cingulo-Opercular (Dosenbach et al., 2006)]) as described in Yeo et al. (2011). We restricted the analysis to the top 200 connections to have the same number of connections for all frequency bands (limited by 293 connections with significant γEEG-fMRI co-dynamics in the generalization dataset, see results). See Table S9 for the exact mappings between each brain region and ICN. The number of connections falling into each network pair were counted (e.g. DMN to Visual). To assure that the observed connectivity pattern did not arise from random sampling into the different networks, we also created 100,000 random networks of 200 connections to derive the probability that a connection randomly falls into one of the ICN pairs.

Frequency-specific analysis

To test for frequency-specificity, we included frequency-specific Fisher z-transformed mutual information matrices of all bands (δEEG-fMRI, θEEG-fMRI, etc.) and for all subjects in an ANOVA (frequency band as one factor with 5 levels). Note that this analysis compares EEG-fMRI mutual information matrices from different bands to each other, and as such does not require the above-described null model generated for the first statistical analysis. An F-Test was carried out at each connection to determine if the EEG-bands contributed differentially to the mutual information with fMRI-derived dFC. We used Network Based Statistics (NBS) to correct for multiple comparisons (Zalesky et al., 2010) (https://sites.google.com/site/bctnet/comparison/nbs, Version 1.2). NBS controls the family-wise error rate of the mass-univariate testing at every connection. This method is a non-parametric cluster-based approach to finding connected sets of nodes that significantly differ across thresholded connectivity matrices. Posthoc t-tests between one band vs. mean of all the other bands were carried out at each connection followed by NBS to explore if any EEG band expressed a network of stronger mutual information than observed in the other bands.

2.2 Generalization dataset

2.2.1 Subjects

This dataset comprises 17 healthy adults. Ethical approval has been obtained from the UCL Research Ethics Committee (project ID:4290/001) and informed consent has been obtained from all subjects. One subject was excluded as T1 data quality was not sufficient to run the Freesurfer recon-all command, resulting in a final group of 16 subjects (6 females, mean age: 32.41, range 22-53).

2.2.2 Data Acquisition

We used one session of 10 minutes 48 seconds eyes-open resting-state (Avanto 1.5T, Siemens, 30 slices, TR=2.16s, slice thickness 3mm + 1mm gap, effective voxels size 3.3x3.3x4.0mm, TE = 30ms, field of view 210, flip angle 75 degrees) concurrent EEG-fMRI (63 scalp electrodes BrainCap MR, referenced to FCz, 1 ECG electrode). Scanner clock was timelocked with the MR-compatible amplifier (BrainAmp MR, sampling rate 1kHz) clock. A T1-weighted structural image was also obtained (176 slices, 1.0x1.0x1.0 mm, field of view 256, TR=11min). During the resting-state run, the subjects had their eyes open and were asked to remain awake and fixate on a white cross presented on a black background. To minimize movement artefacts in the scanner the subject’s head was immobilized using a vacuum cushion during scanning (Bénar et al., 2003).

2.2.3 Data processing

The fMRI data was processed as described for the main dataset with the exception that no slice-time correction was carried out (in accordance with the original processing in Deligianni (2014)). EEG was
corrected for the gradient artefact using the template subtraction and adaptive noise cancelation followed by a downsampling to 250Hz and cardiobalistic artefact template subtraction using the Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany) followed by ICA-based denoising (for removal of potential eye-blinks and muscle artifacts). Due to apparent low frequency drift artefacts in several subjects, EEG data was high pass filtered at 0.05Hz instead of the 0.03Hz used in the main dataset. Because of the differing TR the sliding window for 1 minute was now consisting of 28 volumes (28*2.16s = 60.48s). EEG data processing was equivalent to the main dataset, with the epochs being 2.16s instead of 2s to match the fMRI TR. The sliding window step size was adopted accordingly to 1 TR (2.16s).

All following analysis steps were identical to the main dataset.
3 Results

Static connectivity relationship across EEG and fMRI

First, we sought to confirm that the previously reported static relation between fMRI-derived and EEG-derived connection-wise connectivity strength (Deligianni et al., 2014; Wirsich et al., 2017) holds true for the two datasets of this study. To this end, we assessed connectivity averaged across the total duration of EEG and fMRI data. Connectivity in source-projected EEG was quantified as band-limited (canonical frequency bands: δ, θ, α, β, γ) phase coupling using imaginary coherence (Engel et al., 2013; Nolte et al., 2004), and connectivity in fMRI was quantified as Pearson’s r for the same whole-brain parcellation atlas. In line with our prior work (Wirsich et al., 2017), static FC of all EEG bands were spatially correlated to FC of fMRI (main dataset fMRI vs. δ/θ/α/β/γ: \( r=0.34/0.34/0.33/0.36/0.29 \); generalization dataset fMRI vs. δ/θ/α/β/γ: \( r=0.34/0.33/0.36/0.41/0.39 \), taking the average FC for each connection across all subjects. See SI Fig. 1). This observation reaffirms the link between the spatial organization of connectivity across modalities and confirms sufficient quality of EEG source localization to the whole-brain parcellation.

Dynamic connectivity relationship across EEG and fMRI

Next, we used a sliding window approach to assess whether time-varying changes in the whole-brain connectivity pattern derived from fMRI are linked to dynamics in band-limited phase coupling across modalities (Fig. 1b). We applied a 1min-wide window sliding at the resolution of the fMRI recordings in order to focus on infraslow dynamics characteristic of fMRI dFC (within the limits of methodologically reliable temporal resolution, as detailed in Methods). We used the information-theoretic measure of mutual information, which assesses the relationship between the modalities without assuming linearity. We tested these co-dynamics against a null model that randomizes the temporal phase of the fMRI connectivity timecourse for all connections (Prichard and Theiler, 1994; Theiler et al., 1992). SI Fig. 2/SI Fig. 3 show the distribution of mutual information of one randomly selected subject/all subjects per dataset. Dynamic FC in δ, θ, α, β and γ EEG showed high mutual information with fMRI connectome dynamics, significantly outperforming the null model in virtually all region-pairs: in 99.21% of connections for δEEG-fMRI, 98.82% in θEEG-fMRI, 98.2% in αEEG-fMRI, 96.88% in βEEG-fMRI and 98.24% in γEEG-fMRI (paired t-test, \( p<0.05 \), Bonferroni corrected for 2248 connections). This strong cross-modal relationship was confirmed in the generalization dataset, although it was significant in a smaller number of connections, especially for βEEG-fMRI and γEEG-fMRI: \( δEEG-fMRI=39.07\% \), \( θEEG-fMRI=30.64\% \), \( αEEG-fMRI=27.22\% \), \( βEEG-fMRI=15.63\% \), \( γEEG-fMRI=13.04\% \) (paired t-test, \( p<0.05 \), Bonferroni corrected for 2248 connections). The relative reduction of significant connections and different magnitude of MI in the replication dataset is in line with the smaller sample size and shorter recording duration (see SI Results). Fig. 2 shows the statistical outcome against the null model at a connection-wise resolution.
Fig. 2: Distribution of t-values of the paired t-test mutual information across all connections between fMRI and EEG dFC time courses using real vs. phase-scrambled fMRI connectivity timecourses (null model) for each EEG band. Minimum t-values is defined by the Bonferroni corrected threshold \( t_{25}=5.21 \) (main data set) and \( t_{15}=6.06 \) (generalization data set). Almost all connections passed this threshold in the main dataset (>96.9% for all EEG bands). In the less extensive generalization dataset, a large proportion of connections passed the significance threshold, but the proportion progressively decreasing with increasing EEG frequency (39% to 13% from \( \delta \) to \( \gamma \)). Connections are arranged according to canonical intrinsic networks (Visual (VIS), Somatomotor (SM), Dorsal Attention (DA), Ventral Attention (VA), Limbic (L), Fronto-Parietal (FP), and Default Mode Network (DMN)).

Additionally, we tested for generalizability at a connection-wise level. The connection-wise strength of EEG-fMRI mutual information averaged across all subjects was strongly correlated between main and replication datasets for fMRI compared to \( \delta/\theta/\alpha \)EEG (r=0.49/0.47/0.33), although very modest to no correlation was observed for fMRI vs. \( \beta/\gamma \)EEG (r=0.06/-0.01, Fig. 3). A split-half approach indicated that the lack of connection-wise generalization for \( \beta \) and \( \gamma \) bands is due to the lower signal-to-noise ratio compared to slower frequencies especially in the less extensive generalization dataset (SI Results and Table S1).

We further observed that mutual information between fMRI and \( \delta/\theta/\alpha \)EEG dFC was correlated with the Euclidian Distance of each brain region. The correlation of mutual information (fMRI vs. \( \delta/\theta/\alpha \)EEG) across datasets remains significant when controlling for Euclidian Distance (SI Results). Another factor affecting fMRI to EEG mutual information was the sign of (static) fMRI FC in the respective connection. For fMRI vs. \( \delta/\theta/\alpha \)EEG mutual information was higher in regions that have anticorrelated fMRI static connectivity (SI results).

Fig. 3: Connection-wise comparison of the EEG-fMRI relationship across the two datasets. Each data point reflects the mutual information between EEG dFC and fMRI dFC for a given connection averaged across all subjects of the respective datasets. Scatter plots are provided for the relation of fMRI dFC to a) \( \delta \)EEG, b) \( \theta \)EEG, c) \( \alpha \)EEG, d) \( \beta \)EEG, and e) \( \gamma \)EEG-dFC. The whole-brain distribution of mutual information correlated across the two datasets for \( \delta \), \( \theta \), and \( \alpha \)EEG.

In summary, fMRI signal correlations were linked to slow modulations of oscillatory phase-coupling across vast proportions of the connectome’s region-pairs. This was true for all canonical EEG frequency bands in both datasets. The strength of the EEG-fMRI relationship was correlated on a connection-wise basis between main and generalization datasets in the \( \delta \), \( \theta \), and \( \alpha \) bands.

Spatial topography of the dynamic relationship
Next, we sought to characterize the spatial topography of co-dynamics beyond the above-described all-encompassing relation between EEG and fMRI dFC. Specifically, we assessed how the connections for which fMRI dFC was most strongly linked to EEG dFC were distributed over canonical ICNs (Yeo et al., 2011) for each EEG frequency band. To this end, we selected the 200 connections with the strongest similarity of EEG and fMRI dFC over time, i.e. highest cross-modal mutual information (compared to the null data as assessed by the above-described $t$-statistic).

Fig. 4 visualizes the networks of the top-200 connections linked between fMRI dFC and EEG dFC for each canonical oscillation band. To understand the distribution of the top-200 connections with respect to ICNs, we mapped the connections to an atlas of seven canonical networks (Visual, Somatomotor, Dorsal Attention, Ventral Attention, Limbic, Fronto-Parietal, and Default Mode (DMN) networks (Yeo et al., 2011), Fig 4a). The number of connections between any given pair of canonical ICNs is visualized in Fig 4b. This distribution of pairwise ICN connection density was strongly correlated across main and generalization datasets for all bands ($\delta/\theta/\alpha/\beta/\gamma$: $r=0.72/0.84/0.80/0.87/0.71$). We established that this distribution of the top-200 connections was not driven by the number of ICN nodes or other potential biases. For each ICN pair (e.g. DMN-Visual), we tested whether the number of connections was significantly higher than chance by randomly selecting ($n=100,000$) 200 connections to derive a statistic of the number of connections randomly mapping to each ICN-pair (Tables S3-S7). Interestingly, the dynamic reconfigurations of the top-200 connections with strongest tie across EEG and fMRI were situated between rather than within ICNs (off-diagonal compared to diagonal of matrices in 4b). A notable exception to this observation was the within-DMN connectivity, most notably in the $\beta$ band. A high number (significantly above permutation chance) of connections with strongest cross-modal relationship connected DMN regions among themselves and to other ICNs, especially in $\alpha$, $\beta$ and $\gamma$ frequencies. Further, the $\delta$, $\theta$ and $\alpha$ frequencies showed strongest cross-modal link of FC dynamics between the Visual and Somatomotor networks. Additionally, a significantly high number of strong connections was observed beyond the above-described DMN-dependent connectivity and Visual-Somatomotor connectivity, most notably for Visual to Ventral Attention in $\delta$, and Somatomotor to Dorsal Attention in $\theta$ and $\gamma$ bands (Fig. 4b, Tables S3-S8).

When repeating the above-described permutation test in the generalization dataset (comparison of top-200 to 200 randomly selected connections), we replicated the large number of connections for Visual-Somatomotor in $\delta$ and $\theta$ bands, and for DMN-DMN in the $\beta$ band (Tables S3-S7, green cells). The Somatomotor-Visual dominance did not replicate for the $\alpha$ band, presumably because of the unique sensitivity of this band to eyes closed vs. open conditions (main vs. generalization dataset, respectively). We performed an additional analysis to further ascertain that the topographic similarity of the top-200 connections across datasets was not due to chance. This permutation analysis (detailed in supplementary materials) found that the connection counts in the two datasets were drawn from the same distribution in all ICN pairs. Overall, these results support generalization of the spatial topography of co-dynamics between fMRI and EEG dFC at the coarser ICN-wise resolution.
Fig. 4: Spatial characterization of temporally linked EEG-fMRI connectivity dynamics. a) Topographical distribution of the 200 connections with the strongest EEG-fMRI dFC relationship for each EEG frequency band. Connections are color-coded according to the seven major canonical intrinsic networks (Yeo et al., 2011). Individual region labels are listed in table S9. For a matrix notation of this graph see SI Fig. 4. b) Mapping of those 200 connections to the intrinsic networks. The color scale depicts the count of connections falling between a given pair of canonical intrinsic networks (Visual (VIS), Somatomotor (SM), Dorsal Attention (DA), Ventral Attention (VA), Limbic (L), Frontoparietal (FP), and Default Mode Network (DMN)). The top-200 connections are dominated by within- and between-network connections of the DMN, especially for α, β and γ frequencies. Additionally, a large number of the top-200 connections fall between VIS and SM networks in the δ, θ and α frequencies. Results are visualized for the main dataset. According to Tables S3-S8, highlighted squares show significant networks when comparing the number of top-200 most significant EEG-fMRI connections for a given EEG band falling within an ICN-ICN pair as compared to randomly sampling 200 connections of the brain (100,000 iterations). Orange cells show connections significant at p<0.0018 (p<0.05, Bonferroni corrected for 28 comparisons) in the main dataset. The green cells replicated at p<0.05 uncorrected in the generalization dataset.

In summary, while our first analysis showed a significant relationship between fMRI and EEG for a large proportion of connections and irrespective of oscillation frequency, the strength of this relationship varied over space depending on the EEG frequency. The connections with the strongest cross-modal relationship (top 200) for each EEG frequency band were positioned between a different set of ICNs. In particular, we observed a dominant role of the DMN -- especially in the faster frequency bands (β and γ) -- as well as a dominance of connections between the Visual and Somatomotor networks in slower frequency bands (δ and θ). The α band exhibited characteristics of both the faster and slower frequencies.

Frequency-specificity of the dynamic relationship

Finally, we sought to directly and statistically corroborate the frequency-specificity of the cross-modal relationship on a connection-wise basis. To this end, we combined the EEG-fMRI mutual information matrices for all EEG bands into an ANOVA (5 levels for 5 frequency bands). First, we tested if the band-specific mutual information strength is driven by global shifts in the EEG connectivity due to head movement. To this end, we assessed the correlation of the fMRI-derived framewise displacement with the global EEG connectivity (average across connections) of each band in each run. We found no notable relationship between movement and EEG connectivity (all R<0.05; see SI: table S2). To further exclude global shifts that may be induced by parameters that are difficult to control (e.g. impact of the cardiobalistic artefact on the EEG connectome, and impact of the residual gradient artefact) and that may differentially affect each EEG band, we z-transformed each band’s mutual information matrix. As such, the connection-wise ANOVA assessed whether the connections with strongest mutual information in individual EEG bands overlap across bands, or instead are unique to specific bands. Statistical testing indicated a main effect of EEG band (main dataset: auxiliary uncorrected threshold F_{4,125}>2.29; p<0.05, and p<0.05 NBS-corrected, with the
significant cluster comprising 21.8% of connections; Generalization dataset: auxiliary uncorrected threshold $F_{4,75}>2.34$; $p<0.05$, and $p<0.05$ NBS-corrected, comprising 14.9% of connections).

Exploratory post-hoc $t$-tests revealed that $\delta$, $\beta$ and $\gamma$ band dFC are each organized in a frequency specific network with higher correspondence to fMRI dFC relative to all other EEG bands. Table 1 shows connection-wise $t$-thresholds resulting in a connected set of 100 region pairs at corrected statistical level ($p<0.05$, NBS-corrected). Fig. 5a visualizes this frequency-specific network for $\delta$, $\beta$ and $\gamma$ bands in physical brain space, and Fig. 5b maps the connections according to canonical ICNs. Confirming the observations described above (Fig. 4b), networks of frequency-specific cross-modal dynamics consisted predominantly of DMN connections to itself and the rest of the brain. Additionally, the $\delta$-specific set of connections comprised a high number of Somatomotor-Visual and Somatomotor-Frontoparietal connections, whereas the $\beta$-specific set showed a dominance of DMN-Limbic connections. Finally, the $\gamma$-specific set comprised a high number of DMN-Somatomotor and DMN-Limbic connections (Fig. 5c). Exploratory post-hoc analysis in the generalization dataset replicated a set of connections with significantly higher mutual information for $\delta$EEG-fMRI, $\beta$EEG-fMRI, and $\gamma$EEG-fMRI (Table 1). We do not further discuss connections showing stronger cross-modal relationship in $\theta$ compared to other bands, since this result did not replicate in the generalization dataset. SI Fig. 5 demonstrates that the top-100 connection with strongest tie between fMRI dFC and $\delta$-, $\beta$- and $\gamma$-band dFC are largely non-overlapping in both main and generalization datasets (A full breakdown of all possible posthoc tests is documented in SI Fig. 6 and SI table 9). To conclude, when contrasted directly across frequency bands, frequency-specificity of the EEG-fMRI relationship was confirmed with a DMN (especially to Limbic) and Somatomotor-Visual dominance.

Table 1: NBS (5000 iterations) shows a network of significantly increased mutual information for $\delta$EEG-fMRI and $\gamma$EEG-fMRI (connection-wise $T$-threshold is chosen to limit the network size to 100 connections, one sided $t$-test one band to all the others). The ensuing top 100 connections are visualized in Fig. 5.

| Main dataset       | $T$   | P (NBS-corrected) |
|--------------------|-------|-------------------|
| $\delta$EEG-fMRI > All other bands | 2.41  | <0.0002           |
| $\theta$EEG-fMRI > All other bands  | 2.025 | <0.0002           |
| $\beta$EEG-fMRI > All other bands   | 2.61  | <0.0002           |
| $\gamma$EEG-fMRI > All other bands  | 2.53  | <0.0002           |
| Generalization dataset |      |                   |
| $\delta$EEG-fMRI > All other bands | 1.889 | 0.019             |
| $\beta$EEG-fMRI > All other bands  | 1.93  | 0.0008            |
| $\gamma$EEG-fMRI > All other bands | 2.765 | <0.0002           |
Fig. 5: Frequency-specificity of temporally linked EEG-fMRI connectivity dynamics. a+b) Topographical distribution of the top-100 connections in which connectivity dynamics were more strongly linked between fMRI and δEEG than other EEG bands (left), between fMRI and δEEG than other EEG bands (center), and between fMRI and γEEG compared to other bands (right) (determined by NBS, 5000 iterations, cf. table 1). Color code and region labels correspond to Fig. 4. a) Location (center of gravity) of brain regions comprised in the respective top-100 connections. Sphere size depicts the number of the region’s connections among the top-100 cluster. c) The count of connections among the top-100 falling between a given pair of canonical intrinsic networks. The δ-dominated set most dominantly comprises connections of the Visual network to Somatomotor and Frontoparietal networks, as well as connections of the DMN especially to itself and Somatomotor areas. The β-dominated set of connections has a largely ventral distribution, most prominently comprising connections between the DMN to the Limbic network. The γ-dominated set predominantly contains connections between the DMN to the Somatomotor and Limbic networks. Results are visualized for the main dataset, while frequency-specificity for δ, β and γ bands was likewise observed in the generalization dataset (table 1, SI Figure 3).
4 Discussion

Temporal dynamics of neural connectivity are necessary for human behavior, since behavior is inherently flexible. While connectivity dynamics are most commonly studied using fMRI, the relationship between fMRI-derived whole-brain connectome reconfigurations and the dynamics of fast neurophysiological connectivity is still unclear. In this simultaneous EEG-fMRI study, we compared fMRI- and EEG-derived dynamic functional connectivity (dFC) concurrently across all cortical region pairs of the connectome. We demonstrated that the timecourse of fMRI-derived dFC shares mutual information with the timecourse of EEG-derived dFC across a vast proportion of cortical region pairs. Interestingly, the cross-modal relationship of dFC was not dominated by any particular EEG frequency band, although the relationship progressively weakened with increasing EEG frequency when data points were limited (generalization dataset). In spite of the extensive spatial distribution of the cross-modal relationship in all frequencies, the region-pairs with the strongest tie between EEG- and fMRI-based connectivity dynamics varied across oscillation-bands (frequency-specificity in 21.8% of region pairs of the main dataset and 14.9% of the generalization dataset). These results provide strong evidence that fMRI-derived dFC patterns are directly linked to neurophysiological dFC between corresponding region pairs distributed across the whole-brain connectome.

Static connectivity

In line with our prior work, the spatial pattern of static EEG and fMRI connectomes were significantly correlated (SI Fig. 1). Only three prior studies have investigated whole-brain connectomes in concurrent EEG and fMRI (Deligianni et al., 2016, 2014; Wirsich et al., 2017), and the current study confirms this important observation. Interestingly, as in the prior studies, the spatial correspondence of the static connectivity architecture across fMRI and EEG was not restricted to any single oscillation frequency; rather, it was spatially extensive in all EEG frequency bands. However, the three prior studies were limited to static relationships, while the core advantage of concurrent EEG-fMRI recordings lies in its potential to reveal dynamics co-fluctuating across modalities.

Connectivity dynamics of neural origin in both EEG and fMRI

Dynamic FC has been shown to exist both on slow hemodynamic (Chang and Glover, 2010) and fast electrophysiological timescales (de Pasquale et al., 2010; Vidaurre et al., 2018). Regarding the relationship between EEG and fMRI, Chang et al. (2013), Allen et al. (2017) and Lamoš et al. (2018) showed that BOLD FC dynamics are linked to band-limited EEG power in all or subsets of electrodes. The current study advances beyond EEG power to source-localized EEG connectivity, permitting edge-wise cross-modal comparison of connectivity dynamics over the whole connectome. This approach revealed that oscillatory coherence between brain regions in canonical EEG frequencies, i.e. fast electrophysiological connectivity, exhibits time-varying changes in the temporal range of infraslow BOLD connectivity dynamics. Our core finding is that the slow changes in EEG-derived FC temporally co-occur with changes in fMRI-derived FC across vast proportions of region pairs. The strength of this cross-modal correspondence varied over connections by EEG frequency (see section on frequency-specificity below).

This finding has implications for the interpretation of fMRI-derived dFC. Since physiological and non-physiological noise contribute to fMRI-derived dFC (Hutchison et al., 2013), the degree to which such dynamics reflect changes in neural connectivity is difficult to assess. Further, choosing an appropriate null model can be challenging (Hindriks et al., 2016; Zalesky et al., 2014). Instead of comparing fMRI dFC to a null model, we chose to compare fMRI dynamics to a direct measure of neural dynamics, i.e. EEG. Our approach of concurrently assessing dFC in EEG provides evidence that veridic dynamics can indeed be derived from fMRI, as they are directly related to slow changes in the underlying


electrophysiological connectivity. Another important advantage of our approach is the independence of outcomes from both EEG- and fMRI-related artefacts (e.g. eye movements in EEG or magnetic field inhomogeneities in fMRI), since spurious dynamics due to random noise in each modality will cancel each other out in the joint model we utilized. As an example, eye movements disturb the EEG signal of frontal regions and are thus expected to broadly affect EEG-based connectivity involving those regions. Contrarily, fMRI connectivity dynamics is unlikely to be affected by eye movements as the impact of the latter on the magnetic field is minimal, and potential fMRI connectivity changes due to eye movement-related neural activity would likely involve a spatially specific pattern deviating from the broad frontal EEG topography (Ramot et al., 2011). Comparing a spatially unspecific EEG parameter such as band-limited sensor-level power to local fMRI connections (Allen et al., 2017; Chang et al., 2013; Lamoš et al., 2018) is an approach prone to spurious cross-modal links stemming from a connection-unspecific global shift (e.g. breathing (Power et al., 2017)). In contrast, our approach comparing both modalities on a connection-wise level is unlikely to be impacted by averaged global patterns.

Our results also have important implications for neurophysiological connectivity dynamics with respect to methodological reliability and observed timescales. Due to concerns regarding the ill-posed nature of EEG source localization, connectivity approaches in whole-brain parcellation space are underused (O’Neill et al., 2018). The close connection-wise relationship to fMRI-derived dFC provides strong support for the relevance of source-localized EEG to the study of the whole-brain functional connectome. With respect to timescales, prior MEG-based whole-brain investigations have established fast dynamics in interregional connectivity at ~50-100ms (de Pasquale et al., 2010; Vidaurre et al., 2018). Connectivity dynamics at these fast timescales in EEG have been shown to correlate with the slow changes observed in fMRI, albeit in EEG sensor space rather than reconstructed brain parcellations (Britz et al., 2010; Hunyadi et al., 2018). Concurrent EEG-fMRI studies investigating neurophysiological dynamics at infraslow speeds have been either limited to a coarse global field average of connectivity across EEG electrode pairs (Jann et al., 2009; Sadaghiani et al., 2012), or have focused solely on amplitude fluctuations (Hiltunen et al., 2014). Extending beyond these important studies, we show that connectivity derived from fast oscillation phase coupling in EEG exhibits meaningful fluctuations in the infraslow range.

Spatial distribution of the cross-modal dynamics

Interestingly, connections with the strongest interrelation between EEG and fMRI connectivity predominantly spanned across thecanonical intrinsic networks. While we found that the vast majority of connections were dynamically linked between EEG and fMRI, the cross-modal relation was weaker within as compared to across networks with the exception of DMN-DMN connectivity. In line with this result, we found that MI between EEG and fMRI dFC is positively correlated to Euclidian Distance, such that MI is stronger in inter-ICN connectivity which tends to be longer-range. The stronger cross-ICN co-dynamics may seem counterintuitive since the investigation of EEG amplitude fluctuations (as opposed to connectivity) shows a strong link between EEG and fMRI within ICNs (Laufs et al., 2003; Sadaghiani et al., 2010). However, while amplitude fluctuations may be suggestive of strong static within-network connectivity, they don’t inform about connectivity dynamics. Studying dynamics of amplitude correlations in MEG, De Pasquale et al. (2012) observed strong connectivity dynamics both within and between networks for α- and β-bands. One likely explanation for our results is that within-network connections are less dynamic than connections between different intrinsic networks.

Indeed, this interpretation is in line with the observation that DMN regions are among the most dynamic, as measured by fMRI-derived dFC (Zalesky et al., 2014). We found the strongest relationship between EEG and fMRI dynamics in cortico-DMN as well as Somatomotor-Visual...
In light of the DMN’s tendency to anticorrelate with task-positive areas (Chang and Glover, 2010; Fox et al., 2005), the here-observed dominance of DMN interactions with other ICNs is in line with our finding of increased MI in regions that are anticorrelated in static fMRI functional connectivity (see SI results). This DMN dominance has been previously demonstrated for dynamic connectivity derived from MEG (de Pasquale et al., 2012). Similarly, Vidaurre et al. (2018) observed increased MEG coherence in a higher-order network comprising both DMN and Somatomotor-Visual connections. More generally, the DMN has been proposed to form a central hub that integrates multisensory input from different brain regions (Margulies et al., 2016). This functional interpretation aligns with our observation that connections between DMN and the Visual and Somatomotor systems showed some of the strongest relations between EEG and fMRI dFC.

Frequency-specificity of the cross-modal dynamics

We found both convergence and divergence between the different EEG frequencies; we observed a spatially widespread significant link to fMRI dFC for all EEG bands (Fig. 2), but also a considerable difference in the strength of this cross-modal relationship between bands across connectome space. Specifically, when directly contrasting frequency bands, we observed that the link between EEG and fMRI dFC was particularly strong for the δ band compared to all other bands in Somatomotor-Visual connections, and for β and γ bands in DMN-Limbic connections (Fig. 5). In the following, we discuss how the similarity of our findings across frequencies as well as the frequency-specific differences fit with prior literature.

The relationship between static MEG/EEG and fMRI connectivity mirrors our observations in the dynamic framework, namely that the cross-modal relationship is at the same time spatially widespread in all frequencies and exhibits variations across connections depending on neurophysiological frequency (Hipp and Siegel, 2015). Brookes et al. (2011) showed that static intra-network connectivity of ICNs (no whole-brain approach) best correlates between MEG and fMRI for α and β bands (but no frequency showed a link between fMRI and MEG for the Visual network). In accordance with this study, we observed that EEG-fMRI co-dynamics within the DMN (the only ICN with strong cross-modal link for intra-network connections) are most prominent in the β band (Figure 4). However, contrasting Brookes et al. (2011), Hipp and Siegel (2015) stress that after taking into account the different SNR levels of the different frequency bands, the static whole-brain connectome is linked across MEG and fMRI over a broad frequency range from 2-128 Hz. A significant correlation between static connectivity in fMRI and all EEG bands is also backed by the results of Deligianni et al. (2014) and our prior study (Wirsich et al., 2017) showing spatially distributed correlation of static connectivity across fMRI and all canonical EEG bands (replicated in the current study in both datasets; SI Fig. 1). Importantly, in spite of the widespread cross-modal correspondence of static connectivity in all frequencies, Hipp and Siegel (2015) report that the strength of this correspondence varies over frequencies for 21% of all connections. This ratio is very close to the 21.8% connections for which we report significant frequency-specificity in the dynamic framework.

On the dynamic timescale, less work compares frequency-specific patterns of the cross-modal relationship. At first glance, previous findings mapping band-limited EEG power (not connectivity) to fMRI dFC seem to promote a spatially localized and frequency-confined cross-modal relationship, but a closer look paints a picture of a spatially widespread relationship comprising all EEG frequencies. fMRI dFC correlates of α power, the most extensively studied band in this context, is widespread over several ICNs. Scheeringa et al. (2012) showed that dynamic posterior α power co-fluctuates with fMRI-derived dFC within the Visual system, but also spreads to frontal and temporo-parietal regions mostly comprising the DMN. Chang et al. (2013) showed that the link between EEG α power dynamics to fMRI-derived dFC extends beyond the Visual system to the DMN and Dorsal Attention ICNs. Tagliazucchi et al. (2012) observed anticorrelation of central α to fMRI dFC of central regions.
Extending this existing work to EEG connectivity dynamics, we demonstrate (in two independent datasets) that the link between fMRI-derived and α dFC spreads to the whole brain albeit with strongest effect size in Visual-Somatomotor connections. Chang et al. (2013) extended investigations of EEG power beyond the α band to the θ frequency and showed that the variance of θ power is linked to dFC in all the ICNs they investigated (DMN, Dorsal Attention and Somatomotor). Finally, investigating all frequency bands, Tagliazucchi et al. (2012) observed correlation of fMRI-derived dFC and fronto-central γ power dynamics, and correlation of fMRI-derived dFC with the centrally located dynamic α and β power. Though Allen et al. (2017) found strong cross-modal effects for α power (that also comprised high θ), they further observed an occipitally centered fMRI dFC state correlated to central δ/θ EEG power, which interestingly was also the most commonly occurring state. Lamoš et al. (2018) observed that θ power is linked to fMRI-derived dFC in the Visual ICN, whereas α and β power were linked to Somatomotor and attentional ICNs. Exploring intracranial EEG-fMRI dynamics, Ridley et al. (2017) observed correlated variance of dFC in all frequency bands especially at higher frequencies such as γ. Tight coupling between high gamma (~60-200Hz) power amplitude/FC and static BOLD FC has been consistently observed in intracranial EEG recordings combined with separately recorded fMRI (Foster et al., 2015; Hacker et al., 2017; Keller et al., 2013; Kucyi et al., 2018; Nir et al., 2008). We were unable to assess the dynamics of this cross-modal relationship due to the limits imposed by scalp EEG recordings that led to a lowpass cutoff at 60Hz.

Taken together, although studies of EEG power cannot be directly compared to our study of EEG connectivity dynamics, the wide frequency range of the reviewed findings in that literature is in line with our observations regarding co-dynamics of fMRI and EEG connectivity. Further, this conclusion is backed by animal recordings finding electrophysiological correlates of dFC across all frequencies (albeit with very limited spatial coverage (Pan et al., 2011; Thompson et al., 2013)). The wide frequency range becomes most apparent in a comprehensive review of the respective literature (Keilholz, 2014). In conclusion our study not only confirms findings of previous studies with respect to the wide range of frequencies, but also extends them to the whole-brain scale, and most importantly to a connection-wise comparison of fMRI dFC to EEG connectivity dynamics. This study demonstrates for the first time that fMRI dynamics co-fluctuate with electrophysiological connectivity dynamics across all frequencies, and that those connectivity co-fluctuations are not driven by the dominant power of the α band. Indeed, we find more stable effects in terms of generalizability between the two datasets in lower frequencies (δ and θ, cf. Fig. 3) in line with previous work (Allen et al., 2017; Chang et al., 2013).

Methodological considerations and limitations

When choosing a single brain parcellation for both EEG and fMRI we faced several competing considerations. fMRI FC would strongly benefit from a high spatial resolution parcellation (i.e. with large number of regions, such as Glasser et al. (2016) or Schaefer et al. (2018)). However, having no more than 64 EEG electrodes that limit EEG to around 70 regions (Farahibozorg et al., 2018) required us to use a relatively low-resolution atlas. A future approach could be extending the MR-compatible EEG setup to 128 or 256 electrodes (Iannotti et al., 2015) to gain data quality comparable to MEG recordings (Hedrich et al., 2017). Among low-resolution parcellations, we could either adopt one that permits optimal estimation of fMRI connectivity, impose one that prioritizes EEG connectivity, or choose an anatomical atlas that is more neutral with respect to both functional modalities. Specifically, while it has been shown that a parcellation adapted to the actual EEG montage improves the quality of the source reconstruction (Farahibozorg et al., 2018), it is unclear if the fMRI signal would suffer from a parcellation scheme imposed by the EEG montage. On the other hand, choosing a low-resolution parcellation defined from fMRI FC (e.g. (Yeo et al., 2011)) improves fMRI FC estimates and permits more direct conclusions about fMRI-based ICNs. However, this approach may
bias against EEG since EEG and fMRI ICNs have been shown to be similar but not exactly overlapping (Brookes et al., 2011). Further, from a dynamic point of view it has been shown that fMRI dFC states are similar but not equal to ICNs (Vidaurre et al., 2017). The here taken approach to map EEG and fMRI to an anatomical atlas (Desikan et al., 2006) does not impose the constraints of fMRI- or EEG-based atlases and fulfills the requirement of having around 70 regions. However, the anatomical atlas does not reflect the complexity of multimodal ICN networks. As such, our approach to map the ‘canonical’ ICN-networks from (Yeo et al., 2011) to the Desikan atlas should be interpreted very carefully. Future work should investigate how multimodal atlases can be used to better reflect EEG and fMRI ICN dynamics.

Another methodological choice pertains to the measures used to estimate FC. While fMRI connectivity is most commonly derived using correlation there is less consensus about the connectivity measure in the EEG community. Our previous work investigating the EEG-fMRI relationship of static connectivity used imaginary part of the coherency (Wirsich et al., 2020, 2017), while e.g. Deligianni et al. (2014) and Brookes et al. (2011) use amplitude correlations to compare static M/EEG and fMRI connectivity. From a static connectivity point of view, Colclough et al. (2016) showed that most EEG connectivity measures are highly correlated (r>0.7, including amplitude correlations vs. imaginary part of the coherency). Siems and Siegel (2020) confirmed this overlap but also stress the complimentary contributions of both measures. From a dynamic point of view, Vidaurre et al. (2018) demonstrated that dynamic connectivity can be derived from MEG using amplitude correlations. For a more detailed discussion we refer to our recent review discussing the similarities and differences between phase- and amplitude-coupling in the context of the M/EEG-fMRI relationship (Sadaghiani and Wirsich, 2020). This background literature suggests to us that EEG amplitude coupling would show similar co-dynamic with fMRI dFC, but this suggestion should be validated in future studies.

Acquisition differences across datasets can support generalizability but may also lead to differences in results. While subjects of our main dataset had their eyes closed, the generalization dataset was recorded in eyes-open condition. We did not observe any systematic differences in static EEG-fMRI connectivity between the two datasets, in line with our previous results (Wirsich et al., 2017). In support of this observation, static FC under eyes-open and eyes-closed conditions have been studied previously in MEG without indication of substantial differences (Tewarie et al., 2016). Regarding our dynamic analysis, we found largely overlapping results across datasets. Of note, this generalization in dFC extended to the alpha band whose power differs particularly strongly between eyes-open vs. closed conditions. However, we could not replicate the strong relationship between somatomotor and visual ICN in the generalization dataset. This difference across datasets might be linked to eyes-open vs. eyes-closed conditions (Agcaoglu et al., 2019), but as we do not have eyes the two conditions in the same subjects / scanner setup this question should be addressed in future studies.

Regarding temporal resolution, the sliding window approach has been previously criticized for assuming slowly changing dynamics as opposed to instantaneous switches (see (Preti et al., 2017) for review). While the timescale of observable dynamics depends on the choice of window length, our 1-min window was chosen based on careful consideration of published recommendations (Leonardi and Van De Ville, 2015; Zalesky and Breakspear, 2015) to strike a balance between maximizing the number of datapoints (reliability of FC) in each window, and keeping the window short enough to detect FC dynamics at relevant timescales (see Methods). Future multi-modal studies with accelerated fMRI sequences (particularly simultaneous multislice acquisitions) will allow for a comparative analysis of different windowing parameters. Importantly, we show that results from the chosen parameter set generalize across two independent datasets, speaking to the robustness of the findings with the current window size.
Finally, due to the more limited sample size and recording duration of the generalization dataset, β- and γ-connectivity seem to be particularly influenced by the low signal-to-noise ratio of that dataset; 84% and 87% of βEEG- and γEEG-derived connections lacked significant co-dynamics with fMRI (albeit showing the same range of MI values as δ/θ/α), as opposed to virtually no insignificant connections in the main dataset. Indeed, limiting the main dataset to 16 subjects and 200 datapoints likewise resulted in 84% and 86% of βEEG- and γEEG-derived connections lacking significant co-dynamics with fMRI (SI results). Beyond the signal-to-noise limitations in human concurrent EEG-fMRI, there is evidence that lower statistical power of dynamic γ- and β-band connectivity may be linked to lower mutual dynamics shared with fMRI and stronger expression of dynamics complementary to fMRI-derived connectivity. Specifically, a weaker relation to fMRI connectivity has been reported for β and low-γ than for other bands in intracranial electrophysiological recordings in humans (Hacker et al., 2017; Ridley et al., 2017) and animals (Lu et al., 2007; Pan et al., 2011). The weaker relationship for β- and low γ-bands likely reflects a general property of the electrophysiology-fMRI relationship. This interpretation is also in line with our previous finding that γ-connectivity shows a unique relationship to structural connectivity not shared by fMRI-derived connectivity (Wirsich et al., 2017). Importantly, at the coarser ICN-wise (Fig. 4) as opposed to connection-wise resolution (Fig. 3), the results generalized across all bands including β and γ. The generalization of effects in this study is especially supportive of the robustness of the EEG-fMRI dFC relationship in light of substantial differences across the two datasets (3T vs. 1.5T MRI field strength, eyes-closed vs. eyes-open resting-state and differences in fMRI sequences and subject demographics).

Conclusion

We observed a link between electrophysiological and fMRI-derived dFC across a large proportion of the connectome’s region pairs. This observation demonstrates that fMRI-derived connectivity captures infraslow dynamics of fast electrophysiological phase coupling. While the cross-modal link of dFC exists across all canonical electrophysiological frequency bands in a spatially distributed fashion, the strength of the cross-modal relationship varies over connections in a frequency-specific manner. The cross-modal tie was strongest in Visual to Somatomotor connections for the slower EEG-bands, and in connections involving the DMN (especially to the Limbic network) for faster EEG-bands. In conclusion, this study provides strong multimodal evidence for the existence of infraslow time-varying intrinsic connectivity dynamics across the connectome. This finding motivates taking such whole-brain connectivity reconfigurations into account when studying the foundations of cognition or clinical symptoms, be it with fMRI or neurophysiological methods such as EEG and MEG.
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6 Data availability
Main data will be made available by request to ALG. The generalization dataset is publicly available at https://osf.io/94c5t/. Custom analysis code is publicly available at https://github.com/jwirsich/dFC-EEG-fMRI.

7 Author contributions
JW and SS designed the study, developed the methods and wrote the manuscript. ALG collected data.

8 Competing Interests
The authors declare no competing interests.

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Concurrent EEG- and fMRI-derived functional connectomes exhibit linked dynamics

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Supplementary Information

1 SI: Results

1.1 Static connectivity

SI Fig. 1: Correlation of EEG-fMRI static connectivities (averaged over each session and all subjects)

1.2 Mutual information strength

SI Fig. 2: Distribution of mutual information across all connections between fMRI and EEG dFC time courses using real vs. phase-scrambled fMRI connectivity timecourses (null model) for each EEG band. Data are shown for a randomly selected subject of a) the main dataset and b) the generalization dataset. Comparison to the null distribution revealed that EEG and fMRI dynamics are significantly linked over time irrespective of EEG oscillation band for virtually all connections of the main dataset. A similar effect is observed for a large proportion of connections in the generalization dataset (see main manuscript Fig. 2).
SI Fig. 3: Distribution of mutual information across all connections between fMRI and EEG dFC time courses using real vs. phase-scrambled fMRI connectivity timecourses (null model) for each EEG band. Data are stacked for the connections of all subjects of a) the main dataset and b) the generalization dataset. Comparison to the null distribution revealed that EEG and fMRI dynamics are significantly linked over time irrespective of EEG oscillation band for virtually all connections of the main dataset. A similar effect is observed for a large proportion of connections in the generalization dataset (see main manuscript Fig. 2).

When assessing generalization at a connection-wise resolution, we observed correlation of connection-wise EEG-fMRI mutual information for δ, θ, and α bands but not for β and γ EEG (Fig. 3). To assess whether this discrepancy was due to lower signal to noise ratio in the higher frequencies, we investigated whether replication within each dataset would show a similar pattern. We divided the main dataset (respectively the generalization dataset) into two groups of 8 subjects each (taking only the first 16 subjects of the main dataset). Indeed, we observed a within dataset correlation of fMRI vs. δ/θ/α connection-wise mutual information, whereas no correlation between fMRI vs. β/γ was observed (Table S1). This outcome confirms that β and γ bands had lower SNR, which likely contributed to the lack of correlation of connection-wise mutual information across the main and generalization datasets.

|          | δEEG-fMRI | θEEG-fMRI | αEEG-fMRI | βEEG-fMRI | γEEG-fMRI |
|----------|------------|------------|------------|------------|------------|
| Main dataset | 0.51       | 0.36       | 0.19       | 0.04       | 0.03       |
| Generalization Data | 0.26       | 0.30       | 0.22       | 0.04       | 0.002      |

1.3 Impact of Movement

We took the precaution to remove movement confounds affecting fMRI and EEG by excluding all EEG-segments and fMRI volumes that either had above threshold framewise displacement (Power et al., 2012) or showed motion artefacts on the EEG timecourse. The imaginary coherence used to measure EEG connectivity provides additional cleaning as it discards spurious zero-lag connectivity from global artifacts, which could be caused by residuals of movement, cardiobalistic and gradient artefacts. Nevertheless, as oscillations recorded in scalp EEG might be particularly impacted by head movement (Jansen et al., 2012), we tested how much the framewise displacement value, a measure of head motion derived from raw fMRI volumes (see Methods), is correlated over time to the global connectivity of each EEG band (imaginary coherence timecourse over the 2s segments, averaged across all connections). Only segments included in the main analyses, i.e. those with low movement, were considered. We found no consistent evidence for a (linear) relationship between the framewise displacement and global EEG connectivity. Specifically, correlations were significant only for a small subset of sessions (table S2),
but importantly at negligible effect sizes; Mean correlation (average across sessions) between the two measures was consistently low (peaking at $R=0.04669$ for gamma of the main data set).

Table S2: Correlation between EEG imaginary coherence timecourse (averaged across all connections) and framewise displacement (Power et al., 2012) of fMRI volumes as a measure of head motion.

|                       | Mean R (SD)       | Number of sessions reaching p<0.05 (Bonferroni corrected by total no. of sessions) |
|-----------------------|-------------------|----------------------------------------------------------------------------------|
| **Main data set**     |                   |                                                                                  |
| δEEG                  | 0.0019 (0.07447)  | 0/75                                                                              |
| θEEG                  | -0.0040 (0.07669)| 1/75                                                                              |
| αEEG                  | -0.02038 (0.06652)| 1/75                                                                              |
| βEEG                  | 0.03100 (0.09112)| 3/75                                                                              |
| γEEG                  | 0.04669 (0.1178)  | 11/75                                                                             |
| **Replication data set** |                 |                                                                                  |
| δEEG                  | 0.02769 (0.08942)| 2/16                                                                              |
| θEEG                  | 0.02125 (0.06674)| 0/16                                                                              |
| αEEG                  | 0.02652 (0.06836)| 0/16                                                                              |
| βEEG                  | 0.03418 (0.06376)| 0/16                                                                              |
| γEEG                  | 0.02217 (0.07287)| 0/16                                                                              |

1.4 Non-random nature of mutual information distribution across canonical ICNs

We established that the distribution of the top-200 connections and the ensuing DM, VIS and SM network dominance (Fig. 4, SI Fig. 4) were not driven by the number of ICN nodes or other potential biases. For each network pair (e.g. DMN-VIS) we tested whether the number of connections was significantly higher than chance by randomly selecting (n=100,000 iterations) 200 connections from the main dataset (Table S3-S7 for five EEG frequencies). Additionally, table S8 represents an equivalent analysis for a global measure of each ICN’s connectivity to the entirety of the connectome by averaging all connections of the respective ICN irrespective of where they connect to.

1.5 Spatial correspondence of ICN-mapping across datasets

We observed that the topographic distribution of the top-200 connections (connections with strongest mutual information between EEG dFC and fMRI dFC) over intrinsic connectivity networks (ICNs, Fig. 4) was similar across datasets. We performed an additional permutation analysis (n=100,000 iterations) to ascertain that this similarity was not due to chance. Specifically, starting with the top-200 connections of
both main and generalization datasets, we randomly reassigned which dataset each of these connections belonged to. Next, we calculated the number of connections across each ICN pair for the permuted data (equivalent to Fig. 4b). We then calculated the difference between ICN-ICN connection counts in the permuted versions of main and generalization datasets. Finally, for each ICN pair we compared this difference of counts to the difference calculated from the actual main and generalization datasets. The difference (dissimilarity) of connection counts was not statistically distinguishable between the original data and the permutation null distribution in any ICN pair for any band (p>0.0018 for all EEG frequency bands, Bonferroni corrected for multiple comparisons in 28 network pairs). This outcome indicates that the connection counts in the main and generalization datasets were drawn from the same distribution in all ICN pairs, showing that the strongest connections have comparable topographic distribution over ICNs in the two datasets.

Caption for Tables S3-S7: p-values of comparing the number of top-200 most significant EEG-fMRI connections for a given EEG band falling within an ICN-ICN pair as compared to randomly sampling 200 connections of the brain (100,000 iterations). Orange cells show connections significant at p<0.0018 (p<0.05, Bonferroni corrected for 28 comparisons) in the main dataset. The green cells additionally replicated at p<0.05 uncorrected in the generalization dataset.

Table S3: p-values (as described in the above caption) for δEEG-fMRI.

|     | VIS | SM | DA | VA | L | FP | DMN |
|-----|-----|----|----|----|---|----|-----|
| VIS | 0.8992 | 0 | 0.0151 | 0.0005 | 0.6765 | 0.0044 | 0.7043 |
| SM  | 0.4827 | 0.0247 | 0.1860 | 0.7815 | 0.5019 | 0.4624 |
| DA  | 0.0095 | 0.1976 | 0.3664 | 0.0076 | 0.0291 |
| VA  | 0.8407 | 0.8402 | 0.6865 | 0.2662 |
| L   | 0.9787 | 0.9848 | 0.9999 |
| FP  |      | 0.4067 | 0.0127 |
| DMN |      |       | 0.9635 |

Table S4: p-values (as described in the above caption) for θEEG-fMRI.

|     | VIS | SM | DA | VA | L | FP | DMN |
|-----|-----|----|----|----|---|----|-----|
| VIS | 0.9804 | 0 | 0.2328 | 0.0269 | 0.5434 | 0.2324 | 0.2944 |
| SM  | 0.3024 | 0.0002 | 0.0093 | 0.9694 | 0.4980 | 0.8289 |
| DA  | 0.0815 | 0.6904 | 0.7721 | 0.1429 | 0.0125 |
| VA  | 0.8387 | 0.7109 | 0.1973 | 0.0365 |
| L   | 0.9785 | 0.9179 | 0.9970 |
| FP  | 0.4073 | 0.0626 |
| DMN |       | 0.9302 |

Table S5: p-values (as described in the above caption) for αEEG-fMRI.

|     | VIS | SM | DA | VA | L | FP | DMN |
|-----|-----|----|----|----|---|----|-----|
| VIS | 0.8995 | 0 | 0.0434 | 0.3590 | 0.9764 | 0.4255 | 0.1457 |
| SM  | 0.6846 | 0.0666 | 0.0095 | 0.6682 | 0.7213 | 0.4604 |
| DA  | 0.4057 | 0.1977 | 0.2031 | 0.0383 | 0.5018 |
| VA  | 0.8389 | 0.9993 | 0.0757 | 0.6262 |
| L   | 0.9214 | 0.7742 | 0.5291 |
Table S6: p-values (as described in the above caption) for $\delta$EEG-fMRI.

|       | VIS   | SM   | DA   | VA   | L    | FP    | DMN    |
|-------|-------|------|------|------|------|-------|--------|
| VIS   | 0.8990| 0.1957 | 0.9698| 0.3589| 0.6776| 0.9695| 0.8639 |
| SM    | 0.6820| 0.5009 | 0.9987| 0.2004| 0.4996| 0.3615|        |
| DA    | 0.4060| 0.4104 | 0.7750| 0.7507| 0.8040|        |        |
| VA    | 0.2516| 0.5525 | 0.4132| 0.7398|        |        |        |
| L     |       | 0.1753| 0.0018| 0.0008|        |        |        |
| FP    |       | 0.0830| 0.0128|        |        |        |        |
| DMN   |       |        | 0.0000|        |        |        |        |

Table S7: p-values (as described in the above caption) for $\theta$EEG-fMRI.

|       | VIS   | SM   | DA   | VA   | L    | FP    | DMN    |
|-------|-------|------|------|------|------|-------|--------|
| VIS   | 0.8974| 0.0036| 0.4256| 0.1216| 0.8847| 0.8560| 0.0951 |
| SM    | 0.4841| 0.0002| 0.0495| 0.4136| 0.8923| 0.0001|        |
| DA    | 0.4052| 0.1989| 0.9193| 0.3886| 0.2127|        |        |
| VA    | 0.8398| 0.7127| 0.4131| 0.0372|        |        |        |
| L     |       | 0.8114| 0.3653| 0.7970|        |        |        |
| FP    |       | 0.4075| 0.9676|        |        |        |        |
| DMN   |       |        | 0.9306|        |        |        |        |

Table S8: p-values of comparing the number of top-200 most significant EEG-fMRI connections linked to a specific ICN as compared to randomly sampling 200 connections of the brain (100,000 iterations). In contrast to tables S3-S7, for each frequency all connections of a given ICN are aggregated irrespective of what other ICN they connect to. This provides a global measure of an ICN’s connectivity to the entirety of the connectome. Significant connections are highlighted in green and orange p<0.0071 (p<0.05, Bonferroni corrected for 7 comparisons). Green cells replicated at uncorrected threshold p<0.05 in generalization dataset.

|       | VIS   | SM   | DA   | VA   | L    | FP    | DMN    |
|-------|-------|------|------|------|------|-------|--------|
| $\delta$EEG-fMRI | 0    | 0.0003| 0.0001| 0.1152| 1    | 0.0569| 0.9601 |
| $\theta$EEG-fMRI | 0    | 0    | 0.0040| 0.0177| 1    | 0.3252| 0.7609 |
| $\alpha$EEG-fMRI | 0.0262| 0.0030| 0.0360| 0.6145| 0.9994| 0.4187| 0.0671 |
| $\beta$EEG-fMRI | 0.9895| 0.7436| 0.9952| 0.9696| 0.0020| 0.0571| 0.0001 |
| $\gamma$EEG-fMRI | 0.1685| 0    | 0.0873| 0.0598| 0.9917| 0.9947| 0.0254 |
1.6 Frequency-specific networks and their mutual information strength

**a) Main Data Set**

**b) Generalization Data Set**

_Si Fig. 5: The outcome of post hoc t-tests of frequency-specificity (NBS-network limited to 100 connections, see Table 1). Plot a) depicts the connections shown in Fig. 5 but projected into one matrix for a direct spatial comparison. Plot b) shows equivalent data for the generalization dataset. Purple dots signify connections that were both significant for the ‘β>all other bands’ and ‘γ>all other bands’ contrasts. No overlap was observed for δ with the other bands. Overall, the distribution for the δ, β, and γ bands encompass largely different sets of connections._

To test if the mutual information values in the frequency-specific subnetworks (Fig. 5) are generally the highest values of the band-specific mutual information distribution, we determined whether for a given band mean mutual information was generally higher compared to the rest of the brain network. This is the case for all band-specific subnetworks (delta>other bands: \( p = 7.7 \times 10^{-41} \), beta>other bands: \( p=8.0 \times 10^{-19} \), gamma>other bands: \( p=2.8 \times 10^{-9} \)). This relationship also holds when masking the generalization dataset by the band-specific subnetworks of the main dataset (delta>bands: \( p=1.2 \times 10^{-5} \), beta>bands: \( p = 2.0 \times 10^{-6} \), gamma>bands: \( p=0.0051 \)), thus demonstrating the generalizability of the subnetworks selected as frequency-specific.

Further, when counting the number of the top-100 significant connections in each band-specific subnetwork over the seven canonical ICNs (cf. Fig. 5b), the distribution of the count (visualized in Fig. 5c) was correlated across datasets for delta, beta and gamma subnetworks: δEEG-fMRI/βEEG-fMRI/γEEG-fMRI: \( r=0.68/0.82/0.96 \), \( p=0.00062/4.7 \times 10^{-6}/6.2 \times 10^{-12} \). This outcome additionally supports spatial correspondence across datasets with respect to canonical neurocognitive networks for the three bands.
Table S9: NBS (5000 iterations) shows a network of significantly increased mutual information (connection-wise T-threshold is chosen to limit the network size to 100 connections, one-sided t-test of one band to each of the others). The ensuing top 100 connections are visualized in SI Fig. 9.

|                  | Main dataset |                     | Generalization |                     |
|------------------|--------------|---------------------|----------------|---------------------|
|                  | T | P (NBS-corrected) | T | P (NBS-corrected) |
| δEEG-fMRI > αEEG-fMRI | 2.06 | <0.0002 | n/a | >0.05 |
| δEEG-fMRI > βEEG-fMRI | 2.735 | <0.0002 | 2.045 | <0.0002 |
| δEEG-fMRI > γEEG-fMRI | 2.547 | <0.0002 | 2.2385 | <0.0002 |
| θEEG-fMRI > αEEG-fMRI | 1.83 | 0.0254 | n/a | >0.05 |
| θEEG-fMRI > βEEG-fMRI | 2.435 | <0.0002 | 2.125 | <0.0002 |
| θEEG-fMRI > γEEG-fMRI | 2.28 | <0.0002 | 2.32 | <0.0002 |
| αEEG-fMRI > δEEG-fMRI | 2.215 | <0.0002 | n/a | >0.05 |
| αEEG-fMRI > θEEG-fMRI | 1.9088 | 0.002 | n/a | >0.05 |
| αEEG-fMRI > βEEG-fMRI | 2.028 | <0.0002 | 1.96 | <0.0002 |
| αEEG-fMRI > γEEG-fMRI | 2.075 | <0.0002 | 2.17 | <0.0002 |
| βEEG-fMRI > δEEG-fMRI | 3.2231 | <0.0002 | 2.0697 | <0.0002 |
| βEEG-fMRI > θEEG-fMRI | 2.76 | <0.0002 | 2.1 | <0.0002 |
| βEEG-fMRI > αEEG-fMRI | 2.103 | <0.0002 | 1.9 | 0.0014 |
| βEEG-fMRI > γEEG-fMRI | n/a | >0.05 | 1.93 | 0.0044 |
| γEEG-fMRI > δEEG-fMRI | 3.170 | <0.0002 | 2.6 | <0.0002 |
| γEEG-fMRI > θEEG-fMRI | 2.6365 | <0.0002 | 2.7 | <0.0002 |
| γEEG-fMRI > αEEG-fMRI | 2.195 | <0.0002 | 2.43 | <0.0002 |
| γEEG-fMRI > βEEG-fMRI | 1.845 | 0.0356 | 1.9694 | <0.0002 |
| δEEG-fMRI | θEEG-fMRI | αEEG-fMRI | βEEG-fMRI | γEEG-fMRI |
|-----------|-----------|-----------|-----------|-----------|
| ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) | ![Image](image5.png) |
| ![Image](image6.png) | ![Image](image7.png) | ![Image](image8.png) | ![Image](image9.png) | ![Image](image10.png) |
| ![Image](image11.png) | ![Image](image12.png) | ![Image](image13.png) | ![Image](image14.png) | ![Image](image15.png) |
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| ![Image](image31.png) | ![Image](image32.png) | ![Image](image33.png) | ![Image](image34.png) | ![Image](image35.png) |

# of connections
1.7 Effect of electrical line noise

In order to test if γ connectivity is influenced by a lack of correcting for line noise (50Hz), we recalculated γEEG connectivity while excluding the two 2Hz bins from 48Hz-52Hz. When comparing the whole-brain connectivity of γEEG upon including or excluding 48Hz-52Hz, γEEG did not change in the main dataset: the static γEEG connectivity matrix correlated at $r=0.9983$ (average across sessions/subjects, with minimum $r=0.97579$ and maximum $r=0.99781$). This was equally true for the generalization dataset (average across subjects $r=0.9987$, with minimum: $r=0.98287$, and maximum: $r=0.99903$). Removing the 48Hz-52Hz bins resulted in a minimal decrease of static γEEG-fMRI correlation from $r=0.292$ to $r=0.285$ for the main dataset ($r=0.390$ $r=0.384$ for the generalization dataset). Therefore, as cutting out the two bins resulted in marginally lower EEG-fMRI correlation and renders unlikely that spurious 50Hz connectivity degrades the cross-modal relationship, we report all results without removing the bins.

1.8 Effects of Euclidian distance

As discussed in (Wirsich et al. 2017) Euclidian distance (ED) is anticorrelated with static FC of EEG and of fMRI (for this study: main dataset: ED vs. fMRI/ δ/Θ/α/β/γEEG $r=-0.42/-0.54/-0.54/-0.50/-0.56/-0.56$; generalization dataset: ED vs. fMRI/ δ/Θ/α/β/γEEG $r=-0.41/-0.50/-0.51/-0.60/-0.69/-0.67$). As such, we analyzed the effects of ED on both the cross-modal correlation of static FC and on the MI of EEG-fMRI dynamic connectivity.

When taking the partial correlation of static EEG-fMRI FC accounting for ED we observed a reduced correlation between EEG-fMRI FC (main dataset: δEEG-fMRI $r=0.15$; ΘEEG-fMRI $r=0.14$; αEEG-fMRI $r=0.16$; βEEG-fMRI $r=0.17$; γEEG-fMRI $r=0.08$; generalization dataset: δEEG-fMRI $r=0.17$; ΘEEG-fMRI $r=0.16$; αEEG-fMRI $r=0.15$; βEEG-fMRI $r=0.20$; γEEG-fMRI $r=0.17$). This reduction in effect size indicates that common impact of ED on unimodal FC partially contributes to the cross-modal static FC association.

Next, we addressed the role of ED in the context of cross-modal FC co-dynamics. Note that the null model shares and therefore would account for any potential spurious contributions to MI due to common ED impact on fMRI FC. Beyond such spurious impact however, MI of EEG-fMRI dFC can vary as a function of ED. Indeed, we observed that MI was correlated with ED in the lower frequencies. Specifically, the farther the regions from each other, the more strongly their dynamic FC fluctuations are linked to each other for fMRI-δ/Θ/αEEG (main data $r=0.51/0.46/0.39$; generalization data $r=0.39/0.42/0.36$), while results for β/γEEG-fMRI were inconclusive across both datasets (main dataset $r=0.05/0.06$, generalization dataset $r=0.16/-0.18$). To follow up, we asked if the correlation of connection-wise MI strength between the two datasets (cf. Fig. 3) is primarily driven by common ED. This was not the case; when partialling out ED we still find the previously observed correlation of MI between datasets for fMRI compared to δ/Θ/αEEG ($r=0.37/0.34/0.21$), while MI of fMRI compared to β/γEEG continues to lack strong correlation ($r=0.05/-0.001$).
1.9 Dynamics of anticorrelated connections
Chang et al. (2013) observed that time-varying α and θ power increases predict stronger anticorrelation of $F_{\text{FC}}$, in connections typically anticorrelated in the static fMRI connectome. As apparent in Figure S1, negative fMRI timecourse correlation is associated with low EEG imaginary part of the coherence. In order to test how the results of Chang et al. (2013) relate to our study and to MI of the EEG-fMRI dFC, we selected from the static fMRI connectome (averaged across subjects) of each dataset the correlated and anticorrelated connections that had $F_{\text{FC}}>0.1$ and $F_{\text{FC}}<-0.1$, respectively. We then compared the average MI of anticorrelated and correlated connections across subject (paired t-test). When correcting for multiple comparisons ($p=0.05/5=0.01$), we observed that MI of $\delta/\theta/\alpha$ EEG-fMRI dFC was higher in anticorrelated connections (main dataset: $p=4.5*10^{-16}/8.1*10^{-12}/8.5*10^{-12}$, generalization dataset $p=1.6*10^{-7}/7.2*10^{-9}/2.0*10^{-7}$). MI of $\beta$ EEG-fMRI dFC was not different between anticorrelated and correlated connections (main dataset $p=0.170$, generalization dataset $p=0.025$), whereas dFC MI in $\gamma$ EEG-fMRI was larger only in anticorrelated connections of the main but not generalization dataset (main dataset $p=0.0065$, generalization dataset $p=0.973$). As such, we show that in line with and extending the results of Chang et al. (2013) higher MI of $(\delta/\theta)$ EEG-fMRI dynamics is linked to anticorrelation in the static fMRI connectivity matrix. Additionally, we show that this link also exists in the $\delta$-band.

1.10 Effect of number of datapoints on magnitude of MI
The magnitude of MI was found to be different between the main dataset and the generalization dataset (two-sided t-test between main dataset and generalization dataset for mean MI between fMRI and $\delta/\theta/\alpha/\beta/\gamma$ EEG: $p=1.2*10^{-10}/1.3*10^{-10}/7.5*10^{-11}/1.8*10^{-10}/2.3*10^{-7}$). However, when calculating MI for only the first 200 timepoints of each subject we observed no difference between main and generalization datasets (two-sided t-test between main dataset and generalization dataset for mean MI between fMRI and $\delta/\theta/\alpha/\beta/\gamma$ EEG: $p=0.76/0.56/0.76/0.43/0.26$). As expected from the definition of MI (Studholme et al., 1998, 1997), this measure is correlated with the number of datapoints used for each subject ($p$(Bonferroni-corrected)$<0.05$ for average MI of EEG-fMRI dFC of all frequency bands), so it is indirectly linked to the number of scrubbed volumes. We accounted for this relationship in the main analysis by constructing an individual null-model for each subject. When taking only the first 200 datapoints of each subject, mean MI of EEG-fMRI dFC is no longer significantly correlated with movement (average FD, $p$(Bonferroni-corrected)$>0.05$, all frequency bands). The latter observation further supports the notion that the MI difference across dataset is largely due to the difference in the size of the datasets.

1.11 Effect of number of datapoints and number of subjects on significance of MI
As shown in Fig 2, there are much fewer significant connections in the shorter generalization dataset when compared to the main dataset. To test if this observation is directly linked to the number of sliding windows, we cut down each subject’s data to the first 200 sliding windows (note that for 2 subjects in the generalization dataset which had 115 and 114 samples after scrubbing the datasets were not further cut down). For the main dataset we also limited this analysis to the first 16 subjects to make the group size equal to the generalization dataset. Like in the main analysis we then compared each subject’s MI to a null model (equally cut down to the first 200 windows). Upon reduction of the main dataset sparsity of significant connections was indeed comparable across the two datasets (main dataset $\delta/\theta/\alpha/\beta/\gamma$ EEG-fMRI 36.5%/32.7%/23.7%/15.4%/13.9% vs. generalization dataset 30.0%/22.9%/19.7%/11.0%/9.0%).
This outcome confirms that the number of significant dynamically linked connection depends on the number of subjects and the length of the data recording.

1.12 Atlas and ICN labels

| Region name                  | Short name | ICN       |
|------------------------------|------------|-----------|
| 1 left cuneus                | lCUN       | Visual    |
| 2 left fusiform              | lFUS       | Visual    |
| 3 left lateraloccipital      | LOG        | Visual    |
| 4 left lingual               | LING       | Visual    |
| 5 left pericalcarine         | lperiCAL   | Visual    |
| 6 right cuneus               | rCUN       | Visual    |
| 7 right fusiform             | rFUS       | Visual    |
| 8 right lateraloccipital     | rLOG       | Visual    |
| 9 right lingual              | rLING      | Visual    |
| 10 right pericalcarine       | rperiCAL   | Visual    |
| 11 left paracentral          | lparaC     | Somato Motor |
| 12 left postcentral          | lpostC     | Somato Motor |
| 13 left precentral           | lpreC      | Somato Motor |
| 14 left superiortemporal     | lSTG       | Somato Motor |
| 15 left transversetemporal   | lTT        | Somato Motor |
| 16 right paracentral         | rparaC     | Somato Motor |
| 17 right postcentral         | rpostC     | Somato Motor |
| 18 right posteriorcingulate  | rPCC       | Somato Motor |
| 19 right precentral          | rpreC      | Somato Motor |
| 20 right superiortemporal    | rSTG       | Somato Motor |
| 21 right transversetemporal  | rTT        | Somato Motor |
| 22 left caudalmiddlefrontal  | lcMFG      | Dorsal Attention |
| 23 left superiorparietal     | ISPL       | Dorsal Attention |
| 24 right caudalmiddlefrontal | rcMFG      | Dorsal Attention |
| 25 right superiorparietal    | rSPL       | Dorsal Attention |
| 26 left caudalanteriorcingulate | lcACC | Ventral Attention |
| 27 left parsopercularis      | lpOPER     | Ventral Attention |
| 28 left supramarginal        | lSMAR      | Ventral Attention |
| 29 left insula               | lINS       | Ventral Attention |
| 30 right caudalanteriorcingulate | rcACC | Ventral Attention |
| 31 right supramarginal       | rSMAR      | Ventral Attention |
| 32 right insula              | rINS       | Ventral Attention |
| 33 left entorhinal           | lENT       | Limbic    |
| 34 left inferiortemporal     | lITG       | Limbic    |
| 35 left lateralorbitofrontal | ILOF       | Limbic    |
| 36 left medialorbitofrontal  | lMOF       | Limbic    |
|   | Region                          | Abbreviation | Network   |
|---|---------------------------------|--------------|-----------|
| 37 | left frontal pole               | IFP          | Limbic    |
| 38 | left temporal pole              | ITP          | Limbic    |
| 39 | right entorhinal                | rENT         | Limbic    |
| 40 | right inferior temporal         | rITG         | Limbic    |
| 41 | right lateral orbitofrontal     | rLOF         | Limbic    |
| 42 | right medial orbitofrontal      | rMOF         | Limbic    |
| 43 | right frontal pole              | rFP          | Limbic    |
| 44 | right temporal pole             | rTP          | Limbic    |
| 45 | left rostral middle frontal     | lrMFG        | Fronto Parietal |
| 46 | right parsopercularis           | rpOPER       | Fronto Parietal |
| 47 | right parstriangularis          | rpTRI        | Fronto Parietal |
| 48 | right rostral middle frontal    | rrMFG        | Fronto Parietal |
| 49 | left bankssts                   | IBSTS        | Default Mode |
| 50 | left inferior parietal          | I IPL        | Default Mode |
| 51 | left isthmus cingulate          | lICC         | Default Mode |
| 52 | left middle temporal            | lMTG         | Default Mode |
| 53 | left pars orbitalis             | lpORB        | Default Mode |
| 54 | left parstriangularis           | lpTRI        | Default Mode |
| 55 | left posterior cingulate        | lpCC         | Default Mode |
| 56 | left precuneus                  | IPCUN        | Default Mode |
| 57 | left rostral anterior cingulate | lrACC        | Default Mode |
| 58 | left superior frontal           | ISFG         | Default Mode |
| 59 | right bankssts                  | rBSTS        | Default Mode |
| 60 | right inferior parietal         | r IPL        | Default Mode |
| 61 | right isthmus cingulate         | rICC         | Default Mode |
| 62 | right middle temporal           | rMTG         | Default Mode |
| 63 | right pars orbitalis            | rpORB        | Default Mode |
| 64 | right precuneus                 | rPCUN        | Default Mode |
| 65 | right rostral anterior cingulate| rrACC        | Default Mode |
| 66 | right superior frontal          | rSFG         | Default Mode |
| 67 | left parahippocampal            | lPARH        | Default Mode |
| 68 | right parahippocampal           | rPARH        | Default Mode |
1 SI: References

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