Graph properties of synchronized cortical networks during visual working memory maintenance

Satu Palva a,⁎, Simo Monto a,⁎ J. Matias Palva a,c,⁎

a Neuroscience Center, University of Helsinki, Finland
b BioMag laboratory, HUSLAB, Helsinki University Central Hospital, Finland
c Department of Radiology, Helsinki University Central Hospital, Finland

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A B S T R A C T

Oscillatory synchronization facilitates communication in neuronal networks and is intimately associated with human cognition. Neuronal activity in the human brain can be non-invasively imaged with magneto- (MEG) and electroencephalography (EEG), but the large-scale structure of synchronized cortical networks supporting cognitive processing has remained uncharacterized. We combined simultaneous MEG and EEG (MEEG) recordings with minimum-norm-estimate-based inverse modeling to investigate the structure of oscillatory phase synchronized networks that were active during visual working memory (VWM) maintenance. Inter-area phase-synchrony was quantified as a function of time and frequency by single-trial phase-difference estimates of cortical patches covering the entire cortical surfaces. The resulting networks were characterized with a number of network metrics that were then compared between delta/theta- (3–6 Hz), alpha- (7–13 Hz), beta- (16–25 Hz), and gamma- (30–80 Hz) frequency bands. We found several salient differences between frequency bands. Alpha- and beta-band networks were more clustered and small-world like but had smaller global efficiency than the networks in the delta/theta and gamma bands. Alpha- and beta-band networks also had truncated-power-law degree distributions and high k-core numbers. The data converge on showing that during the VWM-retention period, human cortical alpha- and beta-band networks have a memory-load dependent, scale-free small-world structure with densely connected core-like structures. These data further show that synchronized dynamic networks underlying a specific cognitive state can exhibit distinct frequency-dependent network structures that could support distinct functional roles.

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Introduction

Anatomical and functional neuronal networks share properties with network descriptions of many other complex systems and can be characterized with graph theoretical tools (Bullmore and Sporns 2009). In graph representation of brain networks, the brain areas are the graph’s vertices and the inter-areal connections are the edges. Structural connectivity networks in the human brain have been investigated by diffusion-weighted magnetic resonance imaging (Gong et al., 2009; Hagmann et al., 2003; He et al., 2009; Iturria-Medina et al., 2008; Sporns, Tononi, Kötter 2005) and recently also by diffusion-spectrum imaging (Hagmann et al., 2007; Hagmann et al., 2008; Honey et al., 2009). These anatomical networks have a modular structure with dense intra-modular connectivity and a smaller amount of inter-modular connections (Gong et al., 2009; Hagmann et al., 2007; Hagmann et al., 2008). Anatomical networks also have high clustering and short average path lengths (Gong et al., 2009; He et al., 2009; Iturria-Medina et al., 2008; Sporns, Tononi, Kötter 2005), which, together with the modularity, are hallmarks of small-world organization. Small-world networks can be seen as lattice structures (networks with only local connections) with rare long-range connections. Because of the dense local connectivity, small-world networks have greater local clustering than random networks. Yet, because of the long-range “short-cut” connections, their characteristic path length, i.e., the mean of shortest paths from each node to other nodes, are close to those of random networks (Watts and Strogatz 1998). Small-world structures are interesting from the point-of-view of neuronal network communication because small-world networks are associated with high local and global efficiency in information transmission as well as facilitated parallel processing within hierarchically organized modules (Bassett and Bullmore 2006; Bullmore and Sporns 2009). In addition to small-world properties, the distribution of vertex degrees is an important graph measure of complex networks. Degree is the number of edges that connect a vertex with other vertices. Many real-life networks have heavy-tailed degree distributions that are indicative of scale-free, small-world architecture when they are well fit by a power
law or by a product of a power law and an exponential (truncated power law) (Barabasi and Albert 1999; Barabasi 2009).

In functional magnetic resonance imaging (fMRI), the blood-oxygenation-level-dependent (BOLD) signal fluctuates in time-scales of seconds (~0.01–0.1 Hz). Temporal correlations among brain regions of these spontaneous fluctuations have revealed a “default mode” resting-state (Achard et al., 2006; De Luca et al., 2006; Gusnard and Raichle 2001) as well as task-specific (Greicius et al., 2003; Lowe et al., 2000) networks. The default mode network, in particular, has characteristics of small-world architecture (Achard et al., 2006; van den Heuvel et al., 2008; van den Heuvel et al., 2009). However, whereas some fMRI studies report that the dynamics (Kitzbichler et al., 2009) and vertex degrees in anatomical (Iturria-Medina et al., 2008) and functional (van den Heuvel et al., 2008) brain networks are power-law distributed, others suggest that the functional networks have a truncated power-law degree distribution (Achard et al., 2006).

Much of the ongoing electrical brain activity takes place in time-scales much shorter than those reflected in BOLD signal fluctuations. Human cognition operates in time-scales around 10^{-1} s and is based on anatomically distributed neuronal activity that is temporally correlated in time-scales from milliseconds to hundreds of milliseconds. Oscillatory synchronization integrates anatomically distributed processing (Singer, 1999; Singer, 2009) and facilitates communication between distinct oscillatory brain networks (Stam 2004; Fries 2009), and thus has a central mechanistic role in human cognition (Fries 2009; Singer, 2009; Varela et al., 2001). In humans, oscillatory synchronization can be investigated with MEG and EEG recordings, which have a sufficient temporal resolution. Several earlier studies have investigated network properties of inter-areal synchrony using EEG (Micheloyannis et al., 2009; Smit et al., 2008; Stam et al., 2007) or MEG (Stam 2004; Stam et al., 2009). Sensor-level MEG and EEG analyses are in line with the fMRI data and suggest that also oscillatory synchronization gives rise to networks with small-world characteristics (Bassett et al., 2006; Bassett and Bullmore 2009; Deuker et al., 2009; Smit et al., 2008; Stam 2004; Stam et al., 2009).

However, the sensor-based approaches can be confounded by the mixing of signals from multiple sources in a single sensor as well as by artificial sensor-to-sensor interactions that arise from two sensors picking up a signal from a single source, although the effects of volume conduction can be minimized by using an interaction measure that is insensitive to zero-phase lag phase correlations, such as the phase-lag index or the imaginary coherence (Stam, Nolte, Daffertshofer 2007). Artificial synchrony can be considerable especially when using axial gradiometers, magnetometers, or EEG electrodes because of their widespread lead fields. Only the MEG planar gradiometers are sensitive exclusively to current dipoles directly below the sensor (Hämäläinen et al., 1993). Problems in sensor space analyses can be tackled by using an interaction measure that is insensitive to zero-phase lag phase correlations, such as the phase-lag index or the imaginary coherence (Stam, Nolte, Daffertshofer 2007). Artificial synchrony can be considerable especially when using axial gradiometers, magnetometers, or EEG electrodes because of their widespread lead fields. Only the MEG planar gradiometers are sensitive exclusively to current dipoles directly below the sensor (Hämäläinen et al., 1993). Problems in sensor space analyses can be tackled by using an interaction measure that is insensitive to zero-phase lag phase correlations, such as the phase-lag index or the imaginary coherence (Stam, Nolte, Daffertshofer 2007).

In this study, we analyzed the data separately in all six memory-load conditions using those artifact-free trials where the subject had responded correctly. The analyses are focused on those inter-areal synchronies that were significantly stronger during the VWM-retention period (four 300 ms time windows with centers from 480 to 945 ms after the onset of the Sample stimulus) than during the baseline (averaged across three 300 ms time windows with centers from $-450$ to $-140$ ms before the onset of the Sample stimulus).

Subjects and recordings

13 healthy right-handed volunteers participated in this study ($age \pm SD$, 28±3, mean±SD, 4 females). Subjects had a normal or corrected to normal vision. 366-channel MEG with 204 planar gradiometers, 102 magnetometers, and 60 EEG electrodes (Elekta Neuromag Ltd., Finland) was recorded at 600 Hz throughout the experiment (Fig. 1A). The thumb-twitch responses were detected with electromyography of abductor/flexor pollicis brevis, and the electrooculogram was used to detect ocular artifacts. Trials with electrooculogram signal exceeding 50 μV were excluded from further analysis. MaxFilter (Elekta Neuromag Oy., Finland) was used to suppress extra-cranial noise and to co-localize the recordings in signal space. T1-weighted anatomical data for cortical surface models was obtained at a $\leq 1\times 1\times 1$-mm resolution with a 1.5 T MRI scanner (Siemens, Germany) (Fig. 1B). This study was approved by the ethical committee of Helsinki University Central Hospital and was performed according to the Declaration of Helsinki. Written informed consent was obtained from each subject prior to the experiment.

Filtering

Each channel, $y(t)$, of single-trial MEG time-series data, $Y(t)$, with $n$ channels $1 = \ldots n$, was filtered into 36 frequency bands, $f = 3...90$ Hz, with a bank of Morlet wavelets $h(t,f)$, so that the complex filtered signal $y(t,f)$ is given by $y(t,f) = Y(t) \ast h(t,f)$, where $\ast$
denotes convolution and \( h(t, f) = A \exp\left(-t^2 / 2\sigma_t^2\right) \exp(2\pi ft) \) (Fig. 1C). The time-domain standard deviation of the wavelet is given by \( \sigma_t = m / 2nf \), where the parameter \( m, m = 5 \), defines the compromise between time and frequency resolution, and \( f \) is the center frequency of the wavelet.

**Forward and inverse modelling**

FreeSurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/), was used for automatic volumetric segmentation of the MRI data, reconstruction, flattening, and automatic labeling and parcellation of cortical surfaces (Dale, Fischl, Sereno 1999; Desikan et al., 2006; Fischl, Sereno, Dale 1999; Fischl, Liu, Dale 2001; Fischl et al., 2002; Fischl et al., 2004; Segonne et al., 2004) (Fig. 1D). The MNE-Suite software (http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/sofMNE.php) was used for creating three-layer boundary element conductivity models and cortically constrained source models, for MEG-MRI co-localization and for the preparation of the forward and inverse operators (Hämäläinen and Sarvas 1989; Hämäläinen and Ilmoniemi...
MINIMUM-NORM ESTIMATOR (HÄMÄLÄINEN AND SARVAS 1989; NENONEN, MANUSCRIPT IN PREPARATION). WAS OBTAINED FROM THE INVERSE ESTIMATES OF THE REAL, \( Y \), AND IMAGINARY, \( X \), FROM FILTERED SINGLE-TRIAL PRE-STIMULUS BASELINE WINDOWS OF ALL TRIALS (FIG. 1G). THE FREQUENCY-SPECIFIC COMPLEX INVERSE SOLUTION, \( X_0 = [x_0, \ldots, x_n]^T \), WAS OBTAINED FROM THE INVERSE ESTIMATES OF THE REAL, \( Y_{RE} \), AND IMAGINARY, \( Y_{FI} \), PARTS OF THE FILTERED DATA \( Y_F \) SO THAT \( X_0 = M_F Y_{RE}(t) + l_M Y_{FI}(t) \), WHERE \( i \) IS THE IMAGINARY UNIT (FIG. 1H).

SURFACE PARCELLATION

WE OBTAINED TWO PARCELLATIONS OF THE SOURCE MODEL VERTICES FOR THE QUANTIFICATION OF INTER-AREAL INTERACTIONS. A PARCELLATION MEANS THE GROUPING OF VERTICES INTO A NUMBER OF PATCHES. THE FIRST ONE, CLUSTER PARCELLATION \( P_{CL} \), WAS OBTAINED WITH A MEAN LINKAGE CLUSTERING ALGORITHM THAT YIELDED 365 MAXIMALLY INDEPENDENT CORTICAL PATCHES IN INDIVIDUAL ANATOMY, AND WAS USED TO COMPUTE THE WITHIN-SUBJECT PHASE SYNCHRONY ESTIMATES. THE SECOND ONE, ANATOMICAL PARCELLATION \( P_{AN} \), WAS BASED ON AUTOMATIC COR-TICAL LABELING (FISCHL ET AL., 2002) AND WAS USED FOR GROUP STATISTICS AND VISUALIZATION.

CLUSTERING PARCELLATION

SOURCE–SPACE INTERACTION MAPPING WOULD BE POSSIBLE DIRECTLY WITH A COMPUTATION OF VERTEX-BY-VERTEX (~7000 × 7000) PHASE SYNCHRONY MATRICES, BUT THESE WOULD BE HIGHLY REDUNDANT AND COMPUTATIONALLY CUMBERSOME. HENCE, AFTER THE INVERSE MODELING AND BEFORE PHASE SYNCHRONY ESTIMATION, WE COLLAPSED THE TIME SERIES OF THE ~7000 SOURCE VERTICES INTO TIME SERIES OF THE CORTEX PATCHES (FIG. 1I). THE COLLAPSED INVERSE SOLUTION, \( X_{FP} = [x_{FP,1}, \ldots, x_{FP,I}]^T \), IS GIVEN BY \( X_{FP} = \Pi(X_F, P) \), \( \Pi \) IS A COLLAPSE OPERATOR, \( P \) IS THE PARCELLATION, \( P = [p_1, \ldots, p_D] \), AND \( n_I \) IS THE NUMBER OF PATCHES, \( P = [p_1, \ldots, p_D] \), AND \( n_I \) IS THE NUMBER OF PATCHES, \( P = [p_1, \ldots, p_D] \), AND \( n_I \) IS THE NUMBER OF PATCHES, \( P = [p_1, \ldots, p_D] \), AND \( n_I \) IS THE NUMBER OF PATCHES, \( p_1, \ldots, p_D \). WE DEFINED \( \Pi \) SO THAT THE FREQUENCY-SPECIFIC PATCH-WISE SOURCE-LEVEL TIME SERIES IS \( X_{FP} = \Pi(X_F, P) \).

ESTIMATION OF INTER-AREAL INTERACTIONS

WE USED THE COLLAPSED INVERSE VECTORS, \( X_{FP}(t) \), OF SINGLE TRIALS \( r = 1, \ldots, n_R \), FOR THE MAPPING OF CORTICAL-WISE INTER-AREAL INTERACTIONS SO THAT \( I = S(X_{FP}(t)) \), WHERE \( S \) IS THE MATRIX OF INTERACTION STRENGTHS, \( S \) IS THE INTERACTION OPERATOR, AND \( n_I \) IS THE TOTAL NUMBER OF TRIALS IN THE EXPERIMENTAL CONDITION (FIG. 1M). IN THIS STUDY, NEURONAL INTERACTIONS WERE INVESTIGATED BY QUANTIFYING THE PAIR-WISE PHASE SYNCHRONY OF EACH COR-TICAL PATCH WITH EVERY OTHER PATCH. TWO SIGNALS ARE SAID TO BE PHASE SYNCHRONIZED IF THEIR PHASE DIFFERENCE DISTRIBUTION IS NON-RANDOM. PHASE SYNCHRONY BETWEEN A GIVEN PAIR OF PATCHES \( p_a \) AND \( p_b \) WAS QUANTIFIED ACROSS TRIALS BY USING A PHASE-LOCKING VALUE, \( PLV(t_f) \), GIVEN BY \( PLV = 1/(n_I - 1)|\Sigma_c[X_{FP}(t_f) \times conjugate(X_{FP}(t_f))]| \), WHERE \( x^\ast \) IS THE Complex Conjugate OF \( x \). THE MATRIX \( I \), FOR A GIVEN PARCELLATION, \( P \), IS THEN OBTAINED BY COMPUTING \( PLV \) FOR EACH PAIR \( (a, b) \), \( a = 1, \ldots, n_P \), \( b = 1, \ldots, n_P \), WHICH IS ALSO DIRECTLY GIVEN BY THE OUTER PRODUCT \( I = (n_I - 1)|\Sigma_c[X_{FP}(t_f) \times conjugate(X_{FP}(t_f))]| \). AN ESTIMATE OF PHASE SYNCHRONY, \( I \), CAUSED BY SIGNAL COMPONENTS THAT WERE PHASE LOCKED TO THE SAMPLE STIMULUS WAS ESTIMATED AS \( I \) BUT BY USING A TRIAL-SHIFTED \( PLV \) THAT WAS GIVEN BY \( PLV_c = 1/(n_I - 1)|\Sigma_c[X_{FP}(t_f) \times conjugate(X_{FP}(t_f))]| \). I AND \( I_C \) WERE OBTAINED FOR EACH SUBJECT, CONDITION, TIME WINDOW (WIDTH 300 MS, OVERLAP 145 MS), AND FREQUENCY BAND (35 BANDS FROM 3 TO 90 Hz). ONE WAVELET FREQUENCY AT AROUND 50 Hz WAS EXCLUDED BECAUSE OF PUTATIVE MAINS INTERFERENCE.

THE SIGNAL SPACE ANALYSIS OF INTER-SENSOR INTERACTIONS WAS COMPUTED AS ABOVE, BUT BY USING PLANAR GRADIEMETER DATA. THE SIGNALS FROM THE 102 PAIRS OF ORTHOGONAL PLANAR GRADIEMETERS WERE COMPILED BEFORE THE INTER-SENSOR SYNCHRONY ANALYSIS INTO 102 COMPOSITE TIME SERIES BY SUMMING THE PAIRS OF COMPLEX SIGNALS AFTER FILTERING (FIG. 1C).

GROUP STATISTICS

BEFORE THE STATISTICAL GROUP ANALYSIS (FIG. 10), THE INDIVIDUAL SUBJECT’S INTERACTION STRENGTH MATRICES, \( I(t_f) \), WERE FIRST BASELINE-CORRECTED TO OBTAIN \( I_{BL_CORR}(t_f) \) AND THEN MORPHED TO THE ANATOMICAL PARCELLATION THAT WAS COMMON TO ALL SUBJECTS. THE BASELINE CORRECTION WAS GIVEN BY \( I_{BL_CORR}(t_f) = I(t_f) - \max[I_{BL}(t_f), I(t_f)] \), WHERE \( I_{BL}(t_f) \) IS THE MEAN OF \( I(t_f) \) ACROSS THE BASELINE PERIOD (BL, −600…0 MS) AND THE MAX-OPERATION IS THE MAXIMUM OF \( I_{BL}(t_f) \) OR \( I(t_f) \) SEPARATELY FOR EACH \( PLV(t_f) \). THE \( I_{BL_CORR}(t_f) \) WERE BIASED NEITHER BY BASELINE NOR BY STIMULUS-LOCKED ACTIVITY. THE BASELINE CORRECTION ALSO INTRINSICALLY REMOVES RESIDUAL PAIR-WISE SYNCHRONY BRING ABOUT BY THE MEEG RECORDING OR INVERSE MODELING. INDIVIDUAL SUBJECTS’ INTERACTION MATRICES, \( I_{BL_CORR}(t_f) \), THAT WERE OBTAINED IN \( P_{AN} \), WERE MORPHED BY PATCH-AREA-WEIGHTED AVERAGING INTO THOSE INDIVIDUALS’ ANATOMICAL PARCELLATIONS, \( I_{AN,BL_CORR}(t_f) \).
The statistical interaction matrix, $I_{d}(t_f)$, contains the significance ($p$-value) of each pair-wise interaction for one condition and it was obtained from the $I_{AN,BLcorr}(t_f)$ of each subject by applying a statistical test separately for each pair-wise PLV, for each $r$ and $f$, and for each VWM load. $I_{AN,BLcorr}(t_f)$ were tested against a null hypothesis of $PLV=0$ and an alternative hypothesis of $PLV>0$ by using the Wilcoxon-signed-rank test (One-tailed alpha level, $A=0.025$, and false discovery rate, FDR $<0.01$). A rejection of the null hypothesis thus indicates that the inter-areal phase synchrony was significantly stronger during retention than at the baseline.

Graph characterization

We used network metrics from graph theory to characterize the interaction data (Bullmore and Sporns 2009; Rubinov and Sporns 2009) (Fig. 1P). In our graphs, vertices are the brain areas of $P_{AN}$, and the connecting edges are the statistically significant inter-areal interactions of $I_d$. Binary and undirected graphs, $G$, were obtained from adjacency matrices $A, A=T[I_{d}(t_f)]$, where $T$ denotes a threshold operator. The thresholding was carried out by first nulling elements of $I_{d}(t_f)$ for which $p>A$, where $A$ is the alpha level. From the remaining non-zero $I_{d}(t_f)$, we removed in decreasing order 99% of the number of interactions that was predicted by the estimated false discovery rate (FDR) and corroborated by an inspection of the baseline period. Hence, in all of the graphs analyzed in this study, the final FDR is less than 0.01.

Network metrics

Statistical phase synchrony matrices for both source and MEG gradiometer data and for each time-window, frequency band, and memory-load condition were taken as adjacency matrices of undirected binary graphs where cortical areas $i$ ($i=1 \ldots n_v$) are the vertices and significant inter-areal interactions of $I_d$. Binary and undirected graphs, $G$, were obtained from adjacency matrices $A, A=T[I_{d}(t_f)]$, where $T$ denotes a threshold operator. The thresholding was carried out by first nulling elements of $I_{d}(t_f)$ for which $p>A$, where $A$ is the alpha level. From the remaining non-zero $I_{d}(t_f)$, we removed in decreasing order 99% of the number of interactions that was predicted by the estimated false discovery rate (FDR) and corroborated by an inspection of the baseline period. Hence, in all of the graphs analyzed in this study, the final FDR is less than 0.01.

Comparison of network metrics across frequency bands

The network metrics in this study were computed for graphs for each six memory-load conditions during the VWM retention period comprising four 300 ms time-windows with centers from 480 to 945 ms. We divided the spectrum of 35 wavelet center frequencies to four frequency bands with eight wavelets in each (see Fig. 2). Inter-frequency-band differences in the clustering coefficient, characteristic path length, small-worldness, global efficiency, cost-efficiency, and maximum k-core number were thus estimated with a collection of 192 graphs in each of the four frequency bands. As a schematic reference value for each metric, we measured these graph properties for random and lattice graphs that had an equal number of vertices ($n_v=240$ in the source space and $n_v=102$ in the signal space) and spanned connection densities from 0.001 to 0.8. To prevent frequency-band specific connection density distributions from biasing the inter-frequency statistics, we evaluated inter-frequency differences by normalizing band-specific metric values with corresponding random graph values and resampled the graph values into constant 10-step interpolations. For the source space data, the captured degree values starting from 1 and the 20th bin the degree values ending at $d_{max}$, where $d_{max}$ is the graph’s greatest degree. Band-pooled degree distributions (see Fig. 7A) were obtained as a sum of the individual graph’s histograms.
interpolations were obtained in the range \(0.008 \leq K \leq 0.06\), where the lower end corresponds to the onset of the small-world regime at \(K = 2(n_v - 1)^{-1}\) and the upper end to the connection density after which not all frequency bands were well represented (see Fig. 3A). The statistics of source space data were robust against changes in this range in the number of interpolations. For the signal space data, we used \(0.01 \leq K \leq 0.06\), where the lower end corresponds to \(K = (n_v - 1)^{-1}\). We used a lower value here to sample also the weakly connected gamma-band graphs. Using \(K = 0.02 = 2(n_v - 1)^{-1}\) as the lower end abolishes both statistical trends in Fig. 4B and F. The inter-frequency-band differences in the mean values of the interpolated network metrics were estimated by pair-wise permutation testing of the interpolations, where we obtained the difference of the means of all possible mixings of the 10 interpolations and then evaluated the percentile of the original statistics of source space data were robust against changes in this range in the number of interpolations. For the signal space data, we used \(0.01 \leq K \leq 0.06\), where the lower end corresponds to \(K = (n_v - 1)^{-1}\). We used a lower value here to sample also the weakly connected gamma-band graphs. Using \(K = 0.02 = 2(n_v - 1)^{-1}\) as the lower end abolishes both statistical trends in Fig. 4B and F. The inter-frequency-band differences in the mean values of the interpolated network metrics were estimated by pair-wise permutation testing of the interpolations, where we obtained the difference of the means of all possible mixings of the 10 interpolations and then evaluated the percentile of the original
difference of means in this distribution. The resulting $p$ values were Bonferroni-corrected with the number of independent pair-wise tests (6 in Figs. 3–6).

To evaluate the effect of object load, we denote graphs corresponding to VWM memory loads between one to three as the low-load condition and those corresponding to VWM memory loads between four to six as the high-load condition. We then compared network metrics as above between graphs for these two low- and high object loads. To ensure comparable connection density distributions, we used the interval $0.01 \leq K \leq 0.03$ for the interpolations. The resulting $p$ values were Bonferroni-corrected with the number of pair-wise tests (4, see Fig. 8).

Results

366-channel MEEG data were recorded from 13 subjects performing a VWM task. We investigated here the graph properties of inter-areal phase synchrony that was quantified both with source modelling and, for comparison, directly with MEG planar gradiometer data. The workflow for the source-space analysis of inter-areal synchrony is summarized in Fig. 1. In short, we created cortical surface reconstructions with the anatomical MRI data of each subject and used a novel cortical parcellation algorithm to obtain 365 maximally separable cortical patches. Complex single-trial phase estimates for each cortical patch in the source space were obtained from cortically-constrained minimum-norm estimates of Morlet-wavelet filtered MEEG data. Complete inter-areal (inter-patch) phase synchrony matrices were then computed across trials for each subject, time window, frequency band and VWM load. In the signal space, inter-sensor phase synchrony matrices were obtained directly from the single-trial Morlet-wavelet filtered MEG planar gradiometer data. Pairs of brain regions or planar gradiometers among which phase synchrony was stronger during the VWM retention period than during the pre-stimulus baseline (one-tailed $p_{\text{B}} < 0.025$, FDR $p_{\text{F}} < 0.01$) were identified with Wilcoxon-signed-rank test across subjects and represented as graphs where cortical areas are the vertices and the significant interactions are the edges. In this study, we characterized these significantly-synchronized VWM-retention-period networks with a number of graph metrics.

We first plotted the connection density, $K$, of each graph as a function of frequency both for source modelled MEEG data (Fig. 2A) and for the MEG planar gradiometer data (Fig. 2B). Connection density is the proportion of edges present in the graph from all possible edges. Both source and signal space analyses showed that the VWM retention was associated with strengthened inter-areal phase synchrony in delta/theta- (3–6 Hz), alpha- (7–13 Hz), beta- (14–25 Hz), and gamma- (30–80 Hz) frequency-bands. The spectral patterns revealed by source and signal space analyses, on the other hand, were different especially in the delta- and alpha-frequency bands.
We then characterized several network metrics as a function of connection density, K, for graphs in each of the four frequency bands (192 graphs/band, see Methods). We first addressed the small-world properties of synchronized networks. In the source space, clustering coefficients, C, in all frequency bands fell in between those of random graphs (C_R) and lattices with corresponding connection densities (Fig. 3A). We then estimated the C_L for each graph with 0.008<K<0.06, computed the ratio C/C_R, and averaged the values within the delta/theta, alpha, beta and gamma bands (Fig. 3B). Permutation statistics of the C/C_R values indicated that the alpha- and beta-band networks had significantly (p<0.01, Bonferroni corrected with the number of tests, 6) stronger clustering than the delta/theta- networks (Fig. 3B). The clustering was also stronger in the alpha- and beta-band networks than in the gamma-band networks, although the difference between alpha- and beta-band clustering did not reach significance with multiple comparisons correction (p<0.01, uncorrected). We then analyzed characteristic path lengths, L, and found that they were close to those of random networks (L_R) (Fig. 3C). The permutation statistics of band-averaged (as above) L/L_R did not reveal significant differences between frequency bands (Fig. 3D, p>0.09, uncorrected). To estimate the small-worldness of these networks, we first plotted the ratio S=C/L as a function of connection density. The values of S were mostly greater than those of random graphs, S_R, (Fig. 3E). The small-worldness values σ, σ=S/S_R, indicated that the alpha- and beta-band networks had a much more pronounced small-world structure than the networks in the delta/theta and gamma bands (Fig. 3F, p<0.01 corrected). As for the clustering coefficients, the difference in σ between the alpha- and gamma-band networks did not exceed statistical significance after multiple comparison (p=0.02, uncorrected).

We next evaluated the small-world properties of synchronized networks in the signal space. The clustering coefficients (Fig. 4A), characteristic path lengths (Fig. 4C), and the small-worldness (Fig. 4E) revealed similar values for delta/theta- and gamma-band networks as observed in the source space, but did not show the strong clustering in the alpha and beta bands that was salient in the source space. Permutation statistics of the C/C_R (Fig. 4B), L/L_R (Fig. 4D), and σ (Fig. 4F) revealed that delta-band networks were slightly more clustered (Fig. 4B) and had larger small-worldness (Fig. 4D) values than alpha-
band networks, although these differences did not reach significance after correction with multiple comparisons ($p<0.02$, uncorrected).

We pursued the network analyses with source space data. To estimate the network capacity for parallel information processing (Achard et al., 2006), we evaluated global efficiency, $E_{glob}$. $E_{glob}$ is inversely related to the characteristic path length $L$, but weighs the most connected regions instead of the least connected regions as $L$ (Achard and Bullmore 2007). Global efficiency values for all frequency bands were in between those of random ($E_{glob,R}$) and lattice graphs (Fig. 5A). Statistics of $E_{glob}/E_{glob,R}$ showed that delta- and gamma-band networks had a higher global efficiency than the networks in the alpha band (Fig. 5B, $p=0.01$, corrected) or those in the beta band ($p=0.02$, uncorrected). We also evaluated the cost-efficiency values $\kappa$, $\kappa=E_{glob}-K$ (Bassett and Bullmore 2009) (Fig. 5C). The statistics of $\kappa/K_R$ indicated that, similarly with the global efficiency, the cost-efficiency of the delta/theta- and gamma-band networks was greater than that of alpha-band networks (Fig. 5D). The connection density reflects a cost in the sense that both physical wiring and transient synchronization consume resources. It is thus conceivably desirable to achieve maximal information transmission within the network with minimal cost. Cost-efficiency in neuronal networks has been associated with faster transmission times and lesser degradation (Bassett and Bullmore 2009).

Taken together, the network analyses in Figs. 3 and 5 showed that the structures of alpha- and beta-band networks were more core-like than the structures in other frequency bands. To further pursue this notion, we performed a $k$-core analysis on the present data. The graph’s maximum $k$-core number, $k$, indicates the largest size $k$ with which vertices remain in the graph when all vertices with degree $d<k$ have been recursively removed. Maximum $k$-core number hence indexes the presence of core structures with mutually interconnected high-degree vertices. The maximum $k$-core numbers of source-space networks were larger than those of random networks ($k_R$) in all frequency bands (Fig. 6A). Permutation statistics of $k/k_R$ showed that both alpha- and beta-band networks had larger maximum $k$-core numbers than the delta/theta- and gamma-band networks (Fig. 6B, $p<0.05$, corrected). This observation thus corroborates that the network structures in alpha and beta bands have a more pronounced small-world structuring and higher-degree cores than those in delta-/theta- and gamma-frequency bands. To address whether these networks differed in their community structure, we estimated the maximized modularity, $Q$ (Fig. 6C). A high modularity would indicate that vertices could be segregated into densely connected modules with sparse inter-module connections. The $Q$ values, however, were close to those of random graphs, $Q_R$, in all frequency bands showing that modularity was not a predominant feature of these networks. Moreover, the statistics of $Q/Q_R$ did not reveal significant differences between frequency bands (Fig. 6D), although the modularity data suggested a trend for increasing modularity with frequency: the $Q/Q_R$ were larger for the gamma- and beta-band networks than for the delta/theta-band networks ($p<0.01$ and $p=0.02$, uncorrected, respectively).

Finally, we estimated the degree distribution of each individual graph as well as the normalized, frequency-band-wise pooled degree distributions, and investigated whether they were best fit by a power law, an exponential, or by a Gaussian. In the pooled data, the delta/theta and gamma band degree distributions were best fit by a Gaussian and an exponential, respectively (Fig. 7A). The alpha- and beta-band distributions were best fit by a power law that predicted well the majority of the data (Fig. 7A). In alpha and beta bands, however, the high-degree, low-probability tail of the distribution decayed more rapidly than predicted by a power-law suggesting that alpha- and beta-networks have a truncated-power-law degree distribution. A similar trend was apparent in the coefficients of determination for functions that were fit to the individual graph’s degree distributions and averaged within frequency bands ($<R^2>$, Fig. 7B). Permutation statistics showed that the Goodness of fit value $R^2$ for the power-law fit was significantly larger for the alpha band than for the delta/theta and gamma bands ($p<0.05$, Bonferroni corrected with the number of tests: 18). The beta-band networks were close to those in the alpha band and were significantly better fit by a power-law than the networks in the gamma band. These data thus further support the conclusion that during VWM retention alpha- and beta-band networks have a stronger scale-free, small-world dynamic architecture than the networks in delta/theta- and gamma-frequency bands.

Finally, we evaluated the effect of VWM load on clustering, characteristic path lengths and small-worldliness properties of delta/theta-, alpha-, beta-, and gamma-band networks. We divided the graphs into low- and high-load conditions, the first of which corresponded to VWM memory loads from one to three objects and the second to memory loads from four to six. Permutation statistics showed that in the alpha- and beta-band networks, clustering ($C/K_R$) was significantly stronger in the high- than in the low-load condition (Fig. 8A, $p<0.01$, $p<0.05$, respectively, Bonferroni corrected with the number of tests: 4). We did not find significant differences in the characteristic path length ($L/L_R$, Fig. 8B). Moreover, because of variance in $L$, the small worldliness value ($\sigma$) was larger in the high- than in the low-load condition only in the alpha-band and without the multiple comparisons correction (Fig. 8C, $p<0.02$, uncorrected).

Discussion

In this study, we used MEEG and source localization to investigate the graph properties of cortical functional networks defined by transient inter-areal phase synchrony during VWM-retention period. Network synchrony in delta/theta-, alpha-, beta-, and gamma frequency bands was significantly stronger during the VWM-retention period than during the pre-stimulus baseline. Several network metrics used in this work provided converging evidence for two principal observations. First, cortical VWM-retention related alpha- and beta-frequency band networks had a small-world structure with high and memory-load dependent clustering, short characteristic path lengths, high $k$-coreness, and truncated-power-law degree distributions. Second, the structure of alpha- and beta-band networks was significantly different from that of theta/delta- and gamma-band networks in several respects despite comparable connection densities, which indicates that specific cognitive conditions may be associated with spectrally specific and highly dynamic network structures.

Methodological issues in the network analysis

Several prior studies have addressed the graph properties of inter-areal synchronization during task execution (Bassett et al., 2006; Bassett et al., 2006; Bassett and Bullmore 2009; Micheloyannis et al., 2009). Bassett and colleagues used MEG and an n-back working memory task to investigate global- and cost-efficiency of synchronized networks and found that these properties were positively correlated with task performance and were smaller in schizophrenic patients than in control subjects (Bassett and Bullmore 2009). The results also suggested that global- and cost efficiency values were higher in the gamma than in other frequency bands, which is in line with our data on global and cost efficiency (see Fig. 5). Network metrics of inter-areal synchronization have also been found to be comparable during finger tapping and rest (Bassett et al., 2006) but to be distinct between a mathematical task and rest in the alpha-frequency band (Micheloyannis et al., 2009). These studies thus agree with the present data in that the network structures of oscillatory synchrony can be dynamic and task-dependent.

Technical differences between our and prior studies, however, prevent a detailed comparison. Earlier studies were based on signal
space analyses and evaluated synchronization across time. The present study used source space synchrony mapping and dissociated temporally the VWM retention period from encoding, retrieval, and other task components. We also removed both the baseline synchrony and the synchronization that arises artefactually from the stimulus-evoked activity.

Another line of paradigmatic differences between our approach and that used in the previous studies is related to the thresholding of the interaction data. Most network metrics are dependent on graphs’ order (the number of vertices, which is a constant here) and connection density. Evaluation of the graph properties as a function of connection density is a feasible approach for data-driven characterization of graph properties without a need for subjective thresholding of the adjacency matrix (Achard and Bullmore 2007; Deuker et al., 2009). Connection density can be varied by systematically changing the threshold, or, as we did here, by pooling different graphs obtained with a constant statistical threshold. The first approach can be complicated by the fact that variation of the threshold changes the graph’s signal-to-noise ratio and can thus lead to undesirable variability in the graph property under investigation. In our approach, all edges are statistically significant and hence produce comparable graphs without an unknown number of spurious edges. Our approach, on the other hand, is confounded by the fact that temporally and spectrally distinct graphs are being compared. Our re-sampling procedure for the permutation statistics, however, ensured that the variability of the connection density distributions did not influence the comparisons. Hence, the frequency dependence of the graph properties reported here is attributable to distinct structuring of dynamic cortical networks.

Comparison of source and signal space analyses

The analyses in the source space with MEEG and in the signal space with MEG planar gradiometers yielded partially different results. Both approaches converged on finding of enhanced phase synchrony during VWM retention but revealed somewhat different spectral patterns (see Fig. 2). In the network analyses, both approaches showed that clustering was greater for cortical networks than for random graphs and that the characteristic path lengths were comparable with those of random graphs. The signal space analyses, however, did not show the differences in clustering between alpha-beta and delta/theta-gamma band networks that were conspicuous in source space data (cf. Fig. 3).

Several factors can underlie these differences. The MEG planar gradiometers are most sensitive to signals from superficial sulci whereas the MEEG has additional sensitivity for detecting signals from gyri and deeper structures, which is brought about by the combination of information from MEG planar gradiometers, MEG magnetometers, and EEG. Signal mixing and artefactual detection of synchrony are additional factors that confound the signal space analyses, even ones achieved with planar gradiometers.

Dynamic structural differences in networks supporting human VWM

Small-world properties have earlier been observed for functional brain networks in monkey field potential recordings (Yu et al., 2008), in fMRI (Iturria-Medina et al., 2008; van den Heuvel et al., 2008; van den Heuvel et al., 2009), and in sensor-level EEG (Stam, 2004) and MEG analyses (Bassett et al., 2009; Deuker et al., 2009; Stam et al., 2009). In our data, the small-worldness, \( \sigma \), was above one in both source and signal space analyses for all frequency bands (see Figs. 2 and 3), which is fully in line with the prior studies. However, the absolute values of \( \sigma \) in the present study cannot be taken as direct evidence for this conclusion, because the clustering and characteristic path length properties were compared against random graphs (Bassett et al., 2009) and not against degree-distribution- and "denied-edge"-matched surrogate data. While the degree distributions are known, there are, at present, no established means for taking “denied” or “artefactual” edges into account in network analyses. Artefactual edges arise from correlations in the primary data, such as those related to common sources in signal-space MEG/EEG analyses or to inverse modelling in source space analyses. When artefactual edges are removed, for instance by baseline correction, they turn into denied edges, i.e., edges that cannot take place in the graph. Both artefactual and denied edges bias the estimates of graph properties by enhancing and attenuating, respectively, the clustering and related metrics.

These considerations, however, do not influence the cross-frequency comparisons that are the main topic of the present study. In the source-space data, alpha- and beta-band networks had greater clustering and small-worldness values than the networks in the delta/theta and gamma bands. The alpha- and beta-band networks also had higher maximum \( k \)-core numbers and more power-law-like degree distributions than the delta/theta- and gamma-band networks. The truncated-power-law degree distributions of alpha- and beta-band networks are similar to those observed in recent structural and functional MRI data (Achard et al., 2006). Taken together, these data imply that alpha- and beta-band networks had, indeed, a small-world network structure that emerged dynamically during the VWM task execution and was dependent on VWM memory load.

Global- and cost-efficiency values were smaller for the alpha- and beta- than for the gamma-band networks. Together with the other results, this suggests that during the VWM retention period, the alpha-band networks are compact around densely connected core structures and hence locally more and globally less efficient than the networks in the other frequency bands. On the other hand, gamma-band networks were locally less clustered and globally more efficient. The graph properties of the beta-band networks were often in between those of the alpha- and gamma-bands networks. These graph theoretical “fingerprints” suggest that oscillations in distinct frequency bands have different functional roles in supporting the local and global neuronal communication in large-scale cortical networks during VWM maintenance. This is in line with the complementary functional roles earlier attributed to the neuronal interactions in these frequency bands (Palva and Palva 2007; Womelsdorf and Fries 2007).

Conclusion

Small-world networks combine both locally and globally efficient computation, which implies that dynamic small-world structures could be important for the emergence of coherent cognitive states in anatomically distributed neuronal networks (Bassett and Bullmore 2006; Sporns et al., 2004). Our data show that local clustering and global efficiency in the networks that support VWM retention are maximal in distinct frequency bands. Hence, optimally efficient joint local and global communication could involve cross-frequency interactions (Palva, Palva, Kaila 2005; Palva and Palva 2007; Schroeder and Lakatos 2009; Varela et al., 2001).

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References


