



Cognitive fitness of cost-efficient brain functional networks

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The human brain's capacity for cognitive function is thought to depend on coordinated activity in sparsely connected, complex networks organized over many scales of space and time. Recent work has demonstrated that human brain networks constructed from neuroimaging data have economical small-world properties that confer high efficiency of information processing at relatively low connection cost. However, it has been unclear how the architecture of complex brain networks functioning at different frequencies can be related to behavioral performance on cognitive tasks. Here, we show that impaired accuracy of working memory could be related to suboptimal cost efficiency of brain functional networks operating in the classical β frequency band, 15–30 Hz. We analyzed brain functional networks derived from magnetoencephalography data recorded during working-memory task performance in 29 healthy volunteers and 28 people with schizophrenia. Networks functioning at higher frequencies had greater global cost efficiency than low-frequency networks in both groups. Superior task performance was positively correlated with global cost efficiency of the β -band network and specifically with cost efficiency of nodes in left lateral parietal and frontal areas. These results are consistent with biophysical models highlighting the importance of β -band oscillations for long-distance functional connections in brain networks and with pathophysiological models of schizophrenia as a dysconnection syndrome. More generally, they echo the saying that “less is more”: The information processing performance of a network can be enhanced by a sparse or low-cost configuration with disproportionately high efficiency.

efficiency | graph theory | schizophrenia | working memory | magnetoencephalography

The brain is a complex system at many scales of space and time. At the largest spatial scale of whole-brain organization, primate brain anatomical and functional networks are sparsely connected (1), presumably to conserve axonal wiring costs of linking 2 remote cortical or subcortical regions. However, networks derived from brain imaging data are also topologically configured to deliver high global and local efficiency of parallel information transfer (2, 3); this can be equivalently described in terms of short path length and high clustering of brain networks compared with random graphs (4–7). Such “economical small-world” properties—combining high efficiency with low connection cost—have been described for other biological and infrastructural systems (8) and may represent the outcome of evolutionary selection for both low cost and high efficiency of connections between network nodes (9–11).

On the hypothesis that brain network organization has evolved by optimizing competitive selection criteria of cost and efficiency, we predicted that individual differences in cognitive performance should be related to variability in cost efficiency of human brain functional networks (12, 13). More specifically, based on several studies linking *N*-back working memory performance to high-frequency (β -band, 15–30 Hz, and γ -band,

30–60 Hz) brain dynamics (14, 15), especially in parietal (14, 16) and frontal cortex (17), we expected that cost efficiency of high-frequency networks should be particularly critical to accuracy of working-memory task performance.

We tested these predictions by measuring broad bandwidth (1–60 Hz) neurophysiological data from multiple (275) magnetoencephalographic (MEG) sensors in 29 healthy male volunteers and 28 males with schizophrenia performing a working-memory task. Frequency band-specific functional networks were derived from the MEG data by thresholding the mutual information—a statistical measure of linear and nonlinear association—between wavelet coefficients for each pair of sensors to construct undirected graphs or whole-brain functional networks at each wavelet scale (6, 7, 18). Maximal cost efficiency was estimated for each network (Fig. 1), and its relationship to accuracy was tested by using a general linear model; see *Methods* for details of the sample, experimental paradigm, and analysis methods.

Results

Task Performance. Healthy volunteers performed variably on the working-memory task, but accuracy, averaged over all 6 trials, was generally good: Mean percentage of correct trials was $88.2\% \pm 10.6$ (SD); mean reaction time was $0.49\text{ s} \pm 0.22$. As anticipated by extensive prior data on executive function deficits in schizophrenia (19, 20), the patients performed the working-memory task less accurately: Mean percentage of correct trials was $70.3\% \pm 18.4$ (SD); mean reaction time was $0.56\text{ s} \pm 0.24$. This represented a significant impairment compared with the accuracy of task performance by the healthy volunteer group: $t = 4.53$, $df = 55$, $P < 0.0001$. The reaction time was not significantly different between groups: $t = 0.97$, $df = 55$, $P = 0.33$.

Cost-Efficient Functional Networks. Economical small-world properties were generally most salient in conservatively thresholded MEG networks, which supported high efficiency *E* for disproportionately low cost *C*, i.e., they had positive cost efficiency, (*CE*) > 0 ; see Fig. 1. Maximum cost efficiency $\text{max}(CE)$ was typically observed for networks comprising 5–10% of the total number of possible functional connections (37,400) between all 275 sensors. For all subjects, the average mutual information between sensors was greatest in the lowest-frequency networks and decreased monotonically with increasing frequency; maxi-

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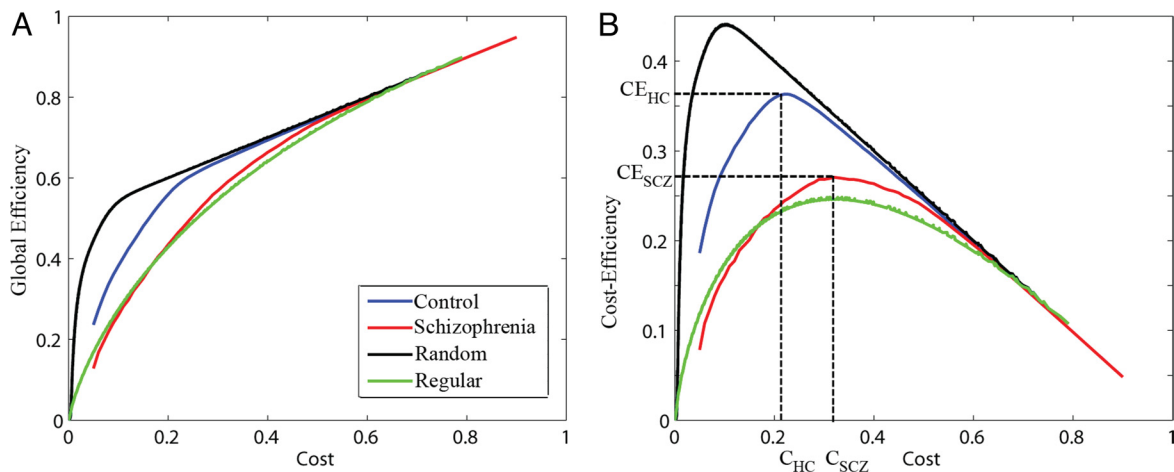


Fig. 1. Efficiency and cost efficiency as a function of network cost. (A) Plot of global efficiency in the γ -band network versus cost averaged over all 6 blocks of 2-back trials for 1 healthy control (blue), 1 person with schizophrenia (red), a random network (black), and a regular network (green). (B) Plot of cost efficiency in the γ -band versus cost averaged over all six 2-back trials for the same subjects, random, and regular networks. Broken lines indicate the maximum cost efficiency for the healthy control (CE_{HC}) and for the person with schizophrenia (CE_{SCZ}) and the costs at which these maximum differences occur: C_{HC} and C_{SCZ} , respectively.

imum cost efficiency showed the opposite trend and tended to increase as a function of frequency (Fig. 2; for details on the relationships between mutual information (MI), CE and related metrics, see supporting information (SI) Fig. S1). Although these frequency-related changes in strength of functional connectivity (MI) and network cost-efficiency were consistent across both groups, the patients with schizophrenia had greater average mutual information (21) and reduced $\max(CE)$, compared with healthy volunteers, especially in the midhigh-frequency [α (5- to 15-Hz) and β (15- to 30-Hz)] networks (Table S1).

Global Relationship Between Cost Efficiency and Accuracy. We used a linear model (analysis of covariance, ANCOVA) to investigate more formally the associations between each of the network metrics and both accuracy and diagnostic group. Considering first the network metrics averaged over the whole brain, we found that there were no significant effects of diagnostic group on global network organization when controlling for variation in task performance. However, there was a significant and specific association between working-memory performance and network cost efficiency on average over all frequency bands ($F = 5.6$, $df = 1,338$, $P = 0.017$); an equally strong association with cognitive performance was not found for mutual information or a number of other network metrics (Table S2). Modeling network metrics separately for each frequency band, we found the same pattern of association between cost efficiency and accuracy only for the β -band network ($F = 4.6$, $df = 1,53$, $P = 0.035$). The individual data for the β -band network indicate that the association between $\max(CE)$ and accuracy was quite consistent across groups (despite greater variability in the schizophrenic group), and that the individuals with greater cost efficiency tended to have superior cognitive performance; see Fig. S2.

Regional Relationships Between Cost Efficiency and Accuracy. To explore these global results in finer detail, we fitted the equivalent linear model to the maximum cost efficiency of each sensor's connections to the rest of the network and mapped the locations of significant association with accuracy or group on renderings of the scalp surface (Fig. 3). These maps confirm that cost-efficient configuration of individual nodes in the β -band network is strongly associated with task performance. Moreover, the spatial distribution of performance-critical nodes in the β -band map is concentrated over left temporal and parietal areas, and midline frontal areas, that have been implicated in

many previous electrophysiological studies of similar tasks (14, 16, 17). These foci of association between accuracy and $\max(CE)$ of nodes in the β -band network remained significant even after controlling for multiple tests with a false-discovery rate correction (FDR) of 5%.

The equivalent exploratory maps for α - and θ -band networks showed a comparable, although less significant, pattern of association between accuracy and cost efficiency of left temporoparietal nodes. Further focal associations existed between accuracy and cost efficiency of (predominantly left-sided) frontal nodes in the γ -band map and of posterior nodes in the δ -band maps; see Fig. 3. As anticipated by the results for whole-brain networks, the associations between diagnostic group and nodal cost efficiency were less salient but, in the β -band, there was evidence for reduced $\max(CE)$ of bilateral temporal and midline frontal nodes in the schizophrenic group, and in the γ -band there was reduced $\max(CE)$ in left prefrontal regions (Fig. 3).

β_1 and β_2 Rhythms. Given these results, strongly associating cost efficiency of β -band networks with accuracy of working-memory performance, we undertook a secondary, more refined analysis of networks operating in the β_1 (12- to 20-Hz) and β_2 (20- to 30-Hz) subintervals of the β -band. In both β_1 and β_2 networks, there was no significant effect of diagnostic group. However, there was a strong association between accuracy of task performance and cost efficiency of both β_1 ($F = 12.7$, $df = 1,53$, $P = 0.0007$) and β_2 ($F = 10.8$, $df = 1,53$, $P = 0.0018$) networks; see Fig. 4A. Head surface mapping of sensors where nodal cost efficiency was strongly associated with task performance highlighted left lateral frontal and parietal regions; see Fig. 4B Top.

These associations, over all subjects in the study, between task performance accuracy and global and nodal cost efficiency of β_1 and β_2 networks, were approximately replicated when each diagnostic group was considered separately. In healthy volunteers, global cost efficiency was positively correlated with accuracy in β_1 ($r = 0.33$, $P = 0.07$) and in β_2 ($r = 0.40$, $P = 0.02$) networks; and, likewise, in people with schizophrenia, accuracy was correlated with global cost efficiency of β_1 ($r = 0.47$, $P = 0.01$) and β_2 ($r = 0.41$, $P = 0.02$) networks. Nodal cost efficiency of sensors located over left lateral frontal or parietal regions was associated with task performance accuracy in both groups in both β_1 and β_2 networks; see Fig. 4B.

Discussion

Cost efficiency is an intuitively desirable property for any information-processing system. For example, greater efficiency,

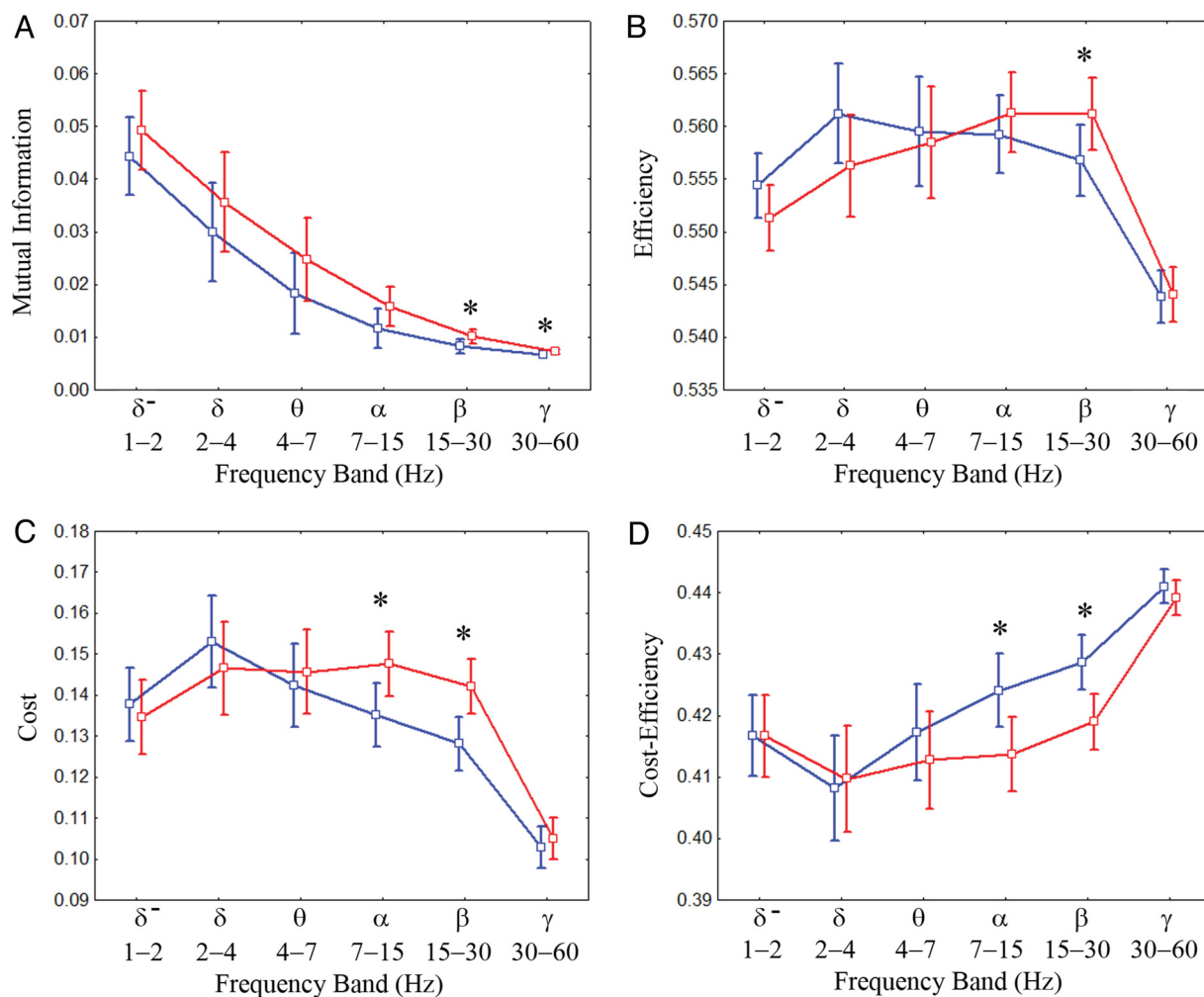


Fig. 2. Brain functional network properties as a function of frequency band for healthy volunteers (blue) and people with schizophrenia (red): average mutual information (A), efficiency (B), cost (C), and cost efficiency (D). Differences between groups significant at $P < 0.05$ uncorrected are identified by an asterisk. Error bars denote 95% confidence intervals. For specific t values and P values, see Table S1.

or shorter path length, of connections between elements of a nervous system will likely be associated with faster transmission times and less noise degradation. Extra efficiency can always be obtained by adding extra connections to a network; however, for a brain network, and many other physically embedded networks, each connection added represents an incremental cost in terms of wiring volume and operational, e.g., metabolic, resources. There is, thus, an inevitable tradeoff to be negotiated between efficiency and cost in the optimal configuration of brain networks.

In this context, we have shown that human brain functional networks show a disproportionate increase in efficiency as connection density—a simple marker of cost—is increased up to $\approx 15\%$. At this point of relatively sparse or low-cost configuration, the difference between network efficiency and cost is maximized, and addition of extra connections yields disproportionately smaller increases of efficiency in accordance with the law of diminishing returns. This “economical small-world” behavior was found in brain functional networks operating in all of the classical EEG frequency intervals in the range 1–60 Hz and in both groups. This conservation of topological properties across frequency scales is broadly compatible with other recent demonstrations of scale invariance in human brain functional networks (7, 22). However, it was also notable that there was a trend for global cost efficiency to increase with increasing

frequency, perhaps reflecting the relative premium on metabolic cost of higher-frequency oscillations demanding more episodes of energy-intensive membrane repolarization (23).

Working Memory and the β - and γ -Bands. Working memory, like many “higher-order” mental functions, is known to depend on the integrated function of a large-scale neurocognitive network comprising many spatially distributed regions of cortex including bilateral prefrontal and posterior parietal regions. Physiological activity at different cortical locations in these networks can be synchronized with respect to the phase of endogenous oscillations of neuronal populations. The β -band oscillation has recently attracted attention as a key coordinating frequency for large-scale networks because its periodicity, unlike that of the γ -oscillation, is long enough to coordinate neuronal activity in distant cortical sites that may be separated in time by an appreciable axonal conduction delay (24, 25). Our results, indicating that topological parameters of a β -band functional network were specifically related to the brain’s emergent cognitive performance, are compatible with a critical role for spatially coherent oscillations in this frequency interval as a dynamic mechanism for coordinating accurate cognitive processing in the frontoparietal memory network.

The β -band frequency itself may be generated by a variety of mechanisms, depending on its source location in the cortex (26,

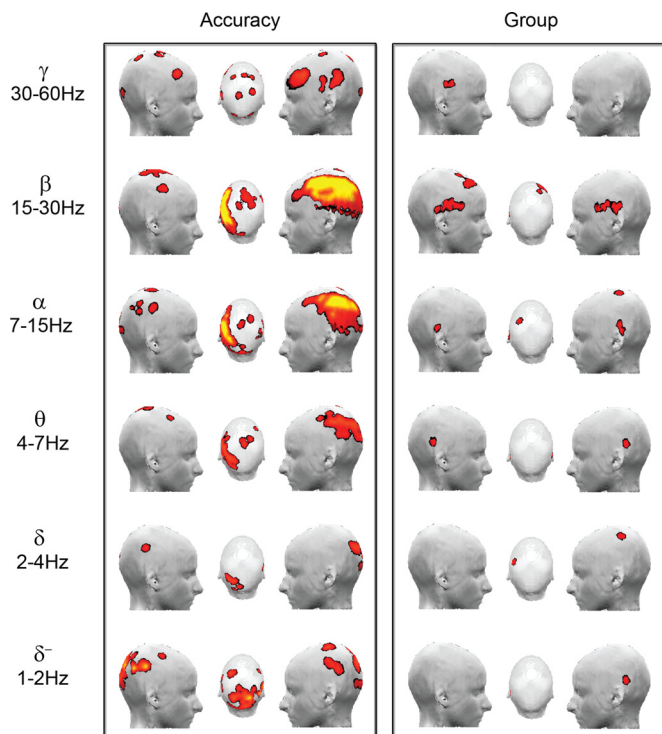


Fig. 3. Head surface mapping of associations between nodal cost efficiency and performance accuracy (*Left*) and diagnostic group (*Right*) for functional networks operating in all classical frequency bands from γ (top row) to δ (bottom row). Red indicates an association was significant at $P < 0.05$ uncorrected, orange indicates that the association passed false-positive correction (all $P < 0.0036$), and bright yellow indicates that the association passed FDR correction (minimum $P < 0.00018$). The strongest associations between nodal cost efficiency and task accuracy were found in left frontal and parietal nodes of the β -band network.

27). Although the activity of inhibitory interneurons may be particularly important in some contexts, there are also generative mechanisms that remain independent of intensive (metabolically costly) activation of chemical synapses. In this context, it was interesting to see that the pattern of association between cognitive performance and network cost efficiency was strengthened when we separately considered β_1 and β_2 subintervals of the classical β -band. Recent studies have suggested that β_1 and β_2 rhythms are mechanistically distinct and may serve complementary functions in the assembly of coherent neurophysiological systems (27, 28). This is compatible with our data indicating that maximizing cost efficiency of network connections in both β_1 and β_2 intervals was correlated with optimizing task performance.

In addition to the extensive and highly significant relationship between cost efficiency and accuracy in the β -network, we found a less salient association between cost efficiency and task performance in the γ -network, specifically in the left lateral and medial prefrontal regions. This is compatible with the interpretation that maximization of cost efficiency in the highest-frequency γ -network may be affiliated more strongly with attentional components and less directly with memory performance. Indeed, there is strong evidence to suggest that the γ -band is important as a physiological substrate for sensorimotor binding and may more specifically mediate attentional selection (29, 30).

Cost Efficiency in Schizophrenia. Our results show that differences in network configuration between healthy and schizophrenic groups, after controlling for differences in task performance, are not

strongly significant. However, we assume there are disease-related neural mechanisms that lead to both impairments in task accuracy and related abnormalities (reduced cost efficiency) of underlying brain network topology in the patient group. Therefore, our results are important in understanding cognitive impairment from the theoretical perspective of schizophrenia as a dysconnection syndrome. It is well known that schizophrenia is associated with extensive severe impairment of cognitive function, especially in memory and executive function. Poor cognitive performance has been linked to abnormal functional activation of frontal cortex, prompting development of the concept of “cortical inefficiency” in schizophrenia (31). Yet there is also increasing evidence from neuroimaging and other sources to suggest that brain abnormalities in schizophrenia, whether or not they stem from a primarily focal lesion, are distributed in the form of abnormally integrated or disconnected networks (32–35). Our results are consistent with a relationship between cognitive impairment and abnormal functional network configuration in schizophrenia. Moreover, they extend the prior notion of cortical inefficiency by showing that disease-related impairment of cognition can be quantitatively related to reduced cost efficiency of β -band networks. The frequency specificity of this association between functional network topology and cognitive impairment is potentially important when we recall that there is considerable evidence for abnormalities of inhibitory interneuronal cells, which sustain certain types of both γ - and β -oscillations, in schizophrenia (36, 37). The finding that task performance in people with schizophrenia was most strongly associated with nodal cost efficiency in frontal regions of the β_2 network (whereas performance in healthy volunteers was most strongly associated with parietal regions of the β_1 network) suggests provisionally that local neuronal abnormalities in schizophrenia might differentially affect the generation of these 2 distinct rhythms.

Methodological Considerations. The working memory 2-back task usually imposes a ceiling effect on studies of healthy volunteers because many of them will be able to perform the task at close to 100% accuracy. In the present study, we have excluded all such subjects, but it will be important in future studies to confirm the generalizability of our findings by using a different, more difficult task on which normal variation in performance will encompass a larger dynamic range. It is important to acknowledge that the schizophrenic group were all receiving antipsychotic medication, which could, in principle, provide an alternative mechanistic explanation for the linked changes in working-memory performance and network cost efficiency that we have described. Future studies of unmedicated patients, or the first-degree, nonpsychotic relatives of patients with schizophrenia, will be important to test this alternative interpretation.

Finally, in justifying a relatively complex multivariate approach like graph theoretical network analysis, it is important to confirm that comparable associations with cognitive performance could not be attained by using simpler univariate measures (such as spectral power at each sensor) or bivariate measures (such as correlation, mutual information, or synchronization between a pair of sensors). Previous work using a visual attention paradigm in humans (38) and a delayed matching-to-sample task in monkeys (39) has suggested that both β -band power and β -band phase synchronization can be used to predict accuracy of response to stimuli in target discrimination tasks. However, in the present study, we found that neither spectral power nor mutual information between pairs of sensors in the β -band significantly predicted performance accuracy (see [Figs. S1 and S3](#) and [Table S2](#)). It seems that the neurophysiological correlates of working-memory performance were more clearly identified by economical small-world network metrics than by more elementary univariate or bivariate measures.

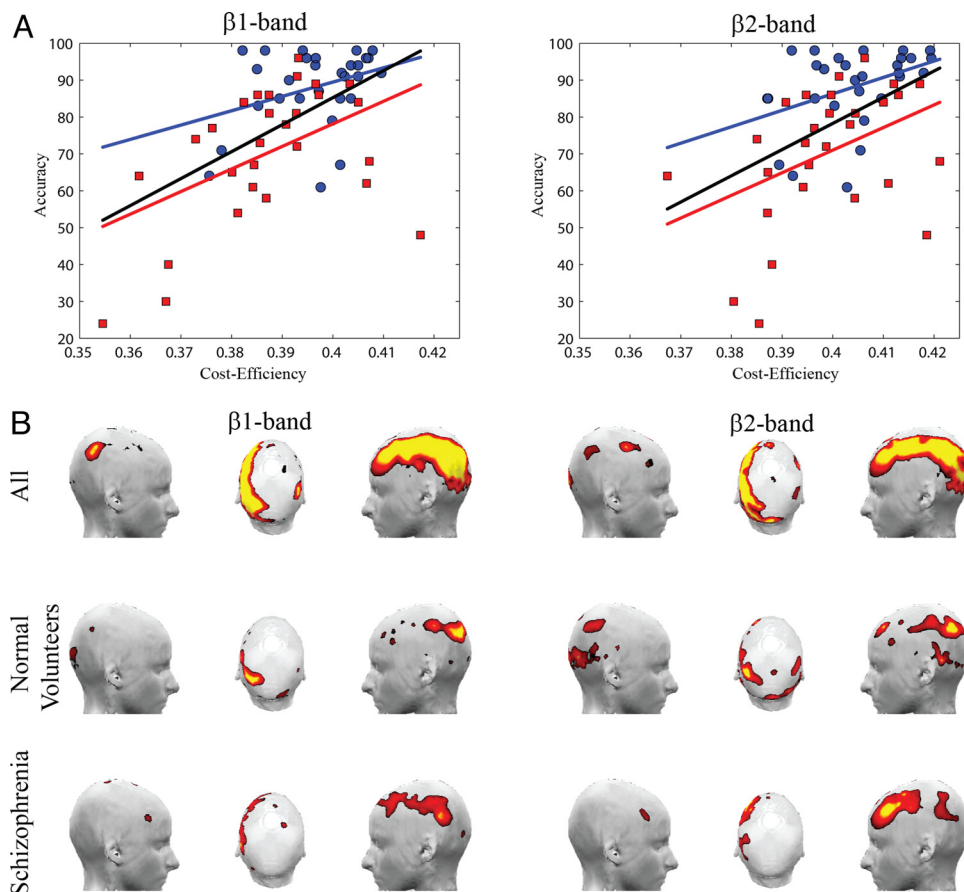


Fig. 4. Associations between cognitive performance and cost efficiency of β_1 and β_2 band networks. (A) Scatter plots of the significant relationships between accuracy and global cost efficiency for the β_1 -band (Left) and β_2 -band (Right) networks including regression lines for healthy controls (blue), people with schizophrenia (red), and both groups together (black). (B) Head surface maps showing regions where nodal cost efficiency in the β_1 -band (Left) and β_2 -band (Right) networks predicted accuracy of task performance across all subjects (Top), in healthy controls alone (Middle), and in schizophrenics alone (Bottom). As in the previous figure, red indicates an association between task accuracy and nodal cost efficiency was significant at $P < 0.05$ uncorrected, orange indicates that the association passed false-positive correction (all $P < 0.0036$), and bright yellow indicates that the association passed FDR correction (minimum $P < 0.00018$).

Conclusion

Our hypothetical prediction was clearly supported by the data: Superior working-memory performance was associated specifically with greater cost efficiency of high-frequency, β -band human brain functional networks. This association was evident both at the level of the whole-brain network and at the level of individual nodes, after controlling for between-group differences and after appropriate correction for multiple comparisons. Although economical small-world properties of high global and local efficiency for low connection cost have been described for many different networks (2, 8), and linked theoretically to optimization of network performance, these results demonstrate directly that optimization of an information-processing system's emergent behavior can indeed depend on finding the topological configuration of the network that maximizes efficiency for minimum cost.

Methods

Twenty-nine healthy volunteers and 28 people with schizophrenia (diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders IV* criteria) were recruited as part of the Clinical Brain Disorders Branch/National Institute of Mental Health Genetic Study of Schizophrenia (National Institutes of Health Study Grant NCT 00001486, Daniel R. Weinberger, principal investigator). Healthy volunteers had no sMRI abnormalities or history of psychiatric illness, depression, or loss of consciousness. All patients were receiving antipsychotic drugs and other medication at the time of the study; none of the healthy volunteers were taking psychoactive medication. Subjects were matched for sex (all male) and age: The age of the healthy control group was

30 years \pm 7.27 (SD), and of the patient group was 33 years \pm 8.42 (SD). The participants gave informed consent in writing, and the protocol was ethically approved by the National Institute of Mental Health Institutional Review Board. MEG data were acquired at the National Institute of Mental Health by using a 275-channel CTF MEG system (VSM MedTech) with a sampling rate of 600 Hz. The experimental paradigm was a 2-back working-memory task using numbers from 1 to 4 (12, 40). Six blocks of trials were performed by each subject, each block containing 11 trials. In each trial, a number was presented visually for 500 msec, and the subject was asked to respond within 1,300 ms by pressing 1 of 4 buttons to indicate the identity of the number seen 2 trials previously. Thus, the number of responses (button presses) is the same for all subjects and for all performance levels. The task was designed in this way to ensure there would be no difference in motor production regardless of working-memory performance.

Raw data were mean corrected and filtered to attenuate background low-frequency noise and line noise at 60 Hz by using a 0.3-Hz-width filter. The axial gradiometers of the CTF machine have source profiles that include information from a wide spatial range, strictly limiting the interpretation of the anatomical location of results. Common source localization techniques such as beam formers and the L2 norm, although allowing greater confidence in localization, change the inherent correlation structure of the time series. To retain the inherent correlation structure of a network of interacting brain regions while gaining localization specificity, we transformed the data into planar space. By using FieldTrip software (F. C. Donders Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands), the planar transform was applied to the data by using the function *megplanar*. The time series were then resampled to 120 Hz to constrain the frequency bands of the wavelet transform to conform to the classical EEG frequency bands. The time series data from each sensor were cropped to the nearest power of 2, $2^{13} = 8,192$ or ≈ 14

s, taken from the middle of the 25-s epoch. A discrete wavelet transform using the Daubechies (4) wavelet could then be applied separately to each time series, with further analysis being performed only on wavelet coefficients at levels 1–6, corresponding approximately to classical EEG frequency bands from γ to low δ ; see Table S1. For secondary analysis of networks operating in the $\beta 1$ (12- to 20-Hz) and $\beta 2$ (20- to 30-Hz) frequency bands, we applied the Fieldtrip software's bandpass Fourier filter to the planar transformed data (rather than a wavelet transform).

Based on prior work showing the greater sensitivity of mutual information as a measure of frequency band-limited functional connectivity (18), we estimated the MI of the wavelet coefficients of each pair of sensors at each frequency interval in each of the 6 blocks of trials. In order for the values of the mutual information to be compared across sensor pairs, we normalized the pairwise mutual information according to Strehl and Ghosh (41). This resulted in a set of normalized MI (association) matrices representing the frequency-specific functional connectivities between all possible pairs of sensors for each subject. The average MI of a network was defined as the average MI over all possible pairs of sensors, N . Each MI association matrix was then converted to a series of adjacency matrices, or graphs G , with variable connection density or cost, C , where:

$$C = \frac{1}{N(N-1)} \sum_{i \neq j \in G} G_{i,j} \quad [1]$$

by applying a range of binary thresholds. Thus, high thresholds were applied to generate sparse or low-cost adjacency matrices with a small proportion of the total number of possible interregional connections represented as edges; whereas low thresholds were applied to generate more densely connected or high-cost graphs.

For each cost in the range $0.01 < C < 1.0$, the regional efficiency $E(i)$ (2, 3) was computed for each node in the graph:

$$E(i) = \frac{1}{N-1} \sum_{j \in G} \frac{1}{L_{i,j}} \quad [2]$$

1. Chen BL, Hall DH, Chklovskii DB (2006) Wiring optimization can relate neuronal structure and function. *Proc Natl Acad Sci USA* 103:4723–4728.
2. Latora V, Marchiori M (2001) Efficient behavior of small-world networks. *Phys Rev Lett* 87:198701.
3. Achard S, Bullmore E (2007) Efficiency and cost of economical brain functional networks. *PLoS Comput Biol* 3:e17.
4. Sporns O, Chialvo DR, Kaiser M, Hilgetag CC (2004) Organization, development and function of complex brain networks. *Trends Cognit Sci* 8:418–425.
5. Salvador R, et al. (2005) Neurophysiological architecture of functional magnetic resonance images of human brain. *Cereb Cortex* 15:1332–1342.
6. Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E (2006) A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *J Neurosci* 26:63–72.
7. Bassett DS, Meyer-Lindenberg A, Achard S, Duke T, Bullmore E (2006) Adaptive reconfiguration of fractal small-world human brain functional networks. *Proc Natl Acad Sci USA* 103:19518–19523.
8. Latora V, Marchiori M (2003) Economic small-world behavior in weighted networks. *Eur Phys J B* 32:249–263.
9. Kaiser M, Hilgetag CC (2006) Non-optimal component placement, but short processing paths, due to long-distance projections in neural systems. *PLoS Comput Biol* 2:e95.
10. Bassett DS, Bullmore ET (2006) Small-world brain networks. *Neuroscientist* 12:512–523.
11. Bullmore ET, Sporns O (2009) Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 10:1–13.
12. Winterer G, et al. (2004) Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. *Am J Psychiatry* 161:490–500.
13. Callicott JH, et al. (2003) Complexity of prefrontal cortical dysfunction in schizophrenia: More than up or down. *Am J Psychiatry* 160:2209–2215.
14. Deiber MP, et al. (2007) Distinction between perceptual and attentional processing in working memory tasks: A study of phase-locked and induced oscillatory brain dynamics. *J Cognit Neurosci* 19:158–172.
15. Pesonen M, Hälämäinen H, Krause CM (2007) Brain oscillatory 4–30 Hz responses during a visual N-back memory task with varying memory load. *Brain Res* 1138:171–177.
16. Missonnier P, et al. (2007) Working memory load-related electroencephalographic parameters can differentiate progressive from stable mild cognitive impairment. *Neuroscience* 150:346–356.
17. Onton J, Delorme A, Makeig S (2005) Frontal midline EEG dynamics during working memory. *NeuroImage* 27:341–356.
18. David O, Cosmelli D, Friston KJ (2004) Evaluation of different measures of functional connectivity using a neural mass model. *NeuroImage* 21:659–673.
19. Goldberg TE, et al. (2003) Executive subprocesses in working memory: Relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch Gen Psychiatry* 60:889–896.
20. Heinrichs RW, Zakzanis KK. (1998) Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology* 12:426–445.
21. Na SH, Jin SH, Kim SY, Ham BJ (2002) EEG in schizophrenic patients: Mutual information analysis. *Clin Neurophysiol* 113:1954–1960.
22. Kitzbichler MG, Smith M, Christensen S, Bullmore ET (2009) Broadband criticality of human brain network synchronization. *PLoS Comput Biol* 5:e1000314.

Here, $i = 1, 2, 3, \dots, N$ indicates the index region, $j \neq i$ denotes a region connected to i , and $L_{i,j}$ is the minimum path length between regions i and j . Thus, regional efficiency is inversely related to minimum path length, and a region with high efficiency will have short minimum path length to all other regions in the graph. The global efficiency is the mean of $E(i)$ over all regions, denoted E . The global cost efficiency is then defined as the global efficiency at a given cost minus the cost, i.e., $(E - C)$, which will typically have a maximum value $\max(E - C) > 0$, at some cost C_{\max} , for an economical small-world network. Likewise, the regional cost efficiency was calculated as the maximum of the function $(E(i) - k)$, where k is the degree or number of edges connecting the i th region to the rest of the network. Importantly, this metric of network topology is independent of an arbitrary, investigator-specified threshold. Instead, the cost-efficiency curve is estimated over a wide range of thresholds, and the behavior of the curve is summarized by its maximum value, which occurs at a data-driven connection density or cost, C_{\max} . Values for $\max(CE)$, as well as for working memory performance, were averaged over the 6 blocks of trials for each subject before further analysis.

All statistical comparisons were implemented in Statistica (StatSoft Inc., www.statsoft.com), and all other computations were performed in Matlab (MathWorks Inc., www.mathworks.com). The scalp-plotting program was adapted for the current use from Delorme, A (2002) Headplot Matlab Code (CNL/Salk Institute, La Jolla, CA). Statistical tests performed on all sensors (such as those shown in Figs. 3 and 4) were reported for 3 levels of stringency: Uncorrected $P < 0.05$, false-positive correction $P < 1/N = 0.0036$, and FDR correction, minimum $P < 0.05/N = 0.00018$. The MEG data preprocessing was performed by using CTF software (VSM MedTech), and FieldTrip software (F. C. Donders Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands).

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23. Attwell D, Laughlin SB (2001) An energy budget for signaling in the grey matter of the brain. *J Cereb Blood Flow Metab* 21:1133–1145.
24. Kopell N, Ermentrout GB, Whittington MA, Traub RD (2000) Gamma rhythms and Beta rhythms have different synchronization properties. *Proc Natl Acad Sci USA* 97:1867–1872.
25. Olufsen MS, Whittington MA, Camperi M, Kopell N (2003) New roles for the gamma rhythm: Population tuning and preprocessing for the beta rhythm. *J Comput Neurosci* 14:33–54.
26. Whittington MA, Traub RD, Faulkner HJ, Stanford IM, Jefferys JG (1997) Recurrent excitatory postsynaptic potentials induced by synchronized fast cortical oscillations. *Proc Natl Acad Sci USA* 94:12198–12203.
27. Roopun AK, et al. (2008) Temporal interactions between cortical rhythms. *Front Neurosci* 2(2):145–154.
28. Kramer MA, et al. (2008). Rhythm generation through period concatenation in rat somatosensory cortex. *PLoS Comput Biol* 4(9):e1000169.
29. Børgers C, Epstein S, Kopell NJ (2005) Background gamma rhythmicity and attention in cortical local circuits: A computational study. *Proc Natl Acad Sci USA* 102:7002–7007.
30. Børgers C, Epstein S, Kopell NJ (2008) Gamma oscillations mediate stimulus competition and attentional selection in a cortical network model. *Proc Natl Acad Sci USA* 105:18023–18028.
31. Tan HY, Callicott JH, Weinberger DR (2007) Dysfunctional and compensatory prefrontal cortical systems, genes and the pathogenesis of schizophrenia. *Cereb Cortex* 17:171–181.
32. Volkow ND, et al. (1988) Brain interactions in chronic schizophrenics under resting and activation conditions. *Schizophr Res* 1:47–53.
33. Weinberger DR, Berman KF, Suddath R, Torrey EF (1992) Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: A magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. *Am J Psychiatry* 149:890–897.
34. Bullmore ET, Frangou S, Murray RM (1997) The dysplastic net hypothesis: An integration of developmental and dysconnectivity theories of schizophrenia. *Schizophr Res* 28:143–156.
35. Stephan KE, Baldeweg T, Friston KJ (2006) Synaptic plasticity and dysconnection in schizophrenia. *Biol Psychiatry* 59:929–939.
36. Gonzalez-Burgos G, Lewis DA (2008) GABA neurons and the mechanisms of network oscillations: Implications for understanding cortical dysfunction in schizophrenia. *Schizophr Bull* 34:944–961.
37. Vierling-Claassen D, Siekmeier P, Stufflebeam S, Kopell N (2008) Modeling GABA alterations in schizophrenia: A link between impaired inhibition and altered gamma and beta range auditory entrainment. *J Neurophysiol* 99:2656–2671.
38. Gross J, et al. (2004) Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. *Proc Natl Acad Sci USA* 101:13050–13055.
39. Tallon-Baudry C, Mandon S, Freiwald WA, Kreiter AK (2004) Oscillatory synchrony in the monkey temporal lobe correlates with performance in a visual short-term memory task. *Cereb Cortex* 14:713–720.
40. Callicott JH, et al. (2003) Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry* 160:709–719.
41. Strehl A, Joydeep G (2002) Cluster ensembles—A knowledge reuse framework for combining multiple partitions. *J Machine Learn Res* 3:583–617.