REVIEW ARTICLE

Cerebral energy metabolism and the brain's functional network architecture: an integrative review

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Recent functional magnetic resonance imaging (fMRI) studies have emphasized the contributions of synchronized activity in distributed brain networks to cognitive processes in both health and disease. The brain's 'functional connectivity' is typically estimated from correlations in the activity time series of anatomically remote areas, and postulated to reflect information flow between neuronal populations. Although the topological properties of functional brain networks have been studied extensively, considerably less is known regarding the neurophysiological and biochemical factors underlying the temporal coordination of large neuronal ensembles. In this review, we highlight the critical contributions of high-frequency electrical oscillations in the γ -band (30 to 100 Hz) to the emergence of functional brain networks. After describing the neurobiological substrates of γ -band dynamics, we specifically discuss the elevated energy requirements of high-frequency neural oscillations, which represent a mechanistic link between the functional connectivity of brain regions and their respective metabolic demands. Experimental evidence is presented for the high oxygen and glucose consumption, and strong mitochondrial performance required to support rhythmic cortical activity in the γ -band. Finally, the implications of mitochondrial impairments and deficits in glucose metabolism for cognition and behavior are discussed in the context of neuropsychiatric and neurodegenerative syndromes characterized by large-scale changes in the organization of functional brain networks.

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BACKGROUND

It is only recently that efforts to understand information processing in the human brain have shifted from the analysis of individual brain regions to the study of the interactions between distributed neuronal ensembles and their large-scale temporal coordination. Accumulating evidence has suggested that the brain is a complex, self-organizing system in which densely interconnected but functionally specialized areas cooperate in ever-changing, context-dependent modules. The dynamic coherence of oscillatory activity in different frequency bands underlies the synchronization of distributed neural responses in both local and extended networks.^{1–3}

Experimentally, synchronous activity fluctuations across the brain are often translated into graphical representations for visualization and analytical purposes. In such network depictions of brain activity, anatomically distinct brain areas that constitute the network nodes are 'functionally connected' to each other if their activity time series correlate above a predefined statistical threshold. Functional connectivity between brain sites is nonuniform and characterized by strong spatial selectivity. Notably, whole-brain analyses of resting-state functional magnetic resonance imaging (fMRI) data in which individual brain voxels serve as network nodes have revealed a collection of spatially segregated areas with markedly elevated functional connectivity to the rest of the brain, often termed 'cortical hubs.' The dense functional connectivity of hub regions is thought to confer them with critical

roles in the efficient routing of information within functional brain networks, as inferred by their high *topological centrality*.^{4,5} That is, cortical hub regions have characteristically elevated values on local centrality metrics derived from graph theory (degree centrality, betweenness centrality, and local efficiency). These measures are assumed to reflect the relative contributions of network nodes to information routing in complex networks of interacting elements, such as the human brain.

Although interregional variability on measures of topological centrality has been well documented in large-scale functional brain networks, considerably less is known regarding the *physiologic significance* of the functional connectivity differences observed across spatially distinct modules in the human brain. Interestingly, it has been shown that regions of elevated topological importance in resting brain networks *also have particularly high metabolic demands*. In a recent whole-brain voxelwise analysis,⁶ it was showed that regional cerebral blood flow (rCBF) measured with arterial spin labeling (ASL) significantly correlated with three nodal topological centrality measures (mean functional connectivity strength, local efficiency, and betweenness centrality) in an extensive resting-brain network estimated from blood-oxygen-level-dependent (BOLD) activity correlations. Given that rCBF is, in turn, closely related to basal cerebral metabolism,^{7,8} the tight association between local centrality measures and rCBF suggests an underlying metabolic basis for highly connected and/or highly centralized functional hubs. Moreover, these

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findings were broadly consistent with an earlier voxelwise analysis of fMRI data that had found a highly significant association between amyloid- β deposition in Alzheimer's disease (AD), a metabolically driven process,⁹ and the nodal degree centrality.⁵

That regions of high topological importance in human brain networks studied with fMRI also have substantive energy demands provides a basis for investigating the relationship between functional connectivity and brain metabolism into greater detail. When examining brain networks derived from fMRI data, it should be kept in mind that hemodynamic signals provide *indirect* measures of neuronal activity¹⁰ and do not immediately reflect electrical events. The electrophysiological dynamics underlying synchronous BOLD fluctuations therefore represent a useful starting point in understanding the energetic demands of functional network connections; information regarding neuronal firing patterns may provide critical insight into the cellular physiological correlates of functional connectivity.

FUNCTIONAL CONNECTIVITY IS ASSOCIATED WITH γ -OSCILLATIONS

Direct electrical measurements of oscillatory dynamics may be collected *in vivo* via a range of invasive and noninvasive neurophysiological methods with high temporal resolution. For safety and ethical reasons, it is not presently possible to *simultaneously* collect direct recordings of neuronal activity and fMRI in the human brain. Very useful insights regarding the electrophysiological basis of BOLD connectivity are nevertheless available, notably from studies combining invasive electrophysiological measurements in patients undergoing presurgical monitoring together with fMRI. Electrophysiological and BOLD connectivity data may be collected in the same subject over separate sessions, or in different groups of subjects. Nir *et al*¹¹ combined intracranial electrocortical recordings (ECoG) from patients undergoing presurgical clinical testing with resting-state fMRI data from healthy volunteers. One of the aims of the study was to determine which ECoG dynamics were the neural correlates of functional connectivity detected with fMRI. Interhemispheric correlations in γ -band ECoG time series in sensory areas showed substantial similarity to the corresponding interhemispheric functional connections detected with fMRI, both in the magnitude and in the spectral profiles of the correlations. In a similar experiment,¹² intracranial electroencephalography (EEG) and fMRI were collected in the same subjects to examine whether γ -band signal correlations in pairs of spatially remote electrodes were related to BOLD signal synchrony between the corresponding anatomic sites. When subjects were in the awakened state, a strong correlation between γ -band ECoG connectivity and BOLD connectivity was indeed found.

The significant correspondence between BOLD functional connectivity and synchronized neuronal activity in the γ frequency band (30 to 100 Hz) revealed by invasive neurophysiological techniques is consistent with earlier investigations of γ -band dynamics in laboratory animals and humans. Niessing *et al*¹³ measured electrical and hemodynamic activity in the visual cortex of anesthetized cats subjected to visual stimulation, and correlated the strength of hemodynamic responses with the oscillation power of several frequency bands. Of all the local field potential frequency bands under study, the strength of hemodynamic responses correlated most strongly with oscillation power in the upper γ -band. Conversely, oscillation power in the θ -, α -, and β -frequency bands were uncorrelated with hemodynamic signals. A similar study¹⁴ examined spontaneous fluctuations (i.e., stimulus free) in the visual cortex of anesthetized monkeys using simultaneous resting-state BOLD and intracortical electrical recordings. Again, spontaneous variation in the hemodynamic signal over time showed the strongest correlation with fluctuations in neuronal spiking activity in the

local field potential γ -band. Finally, Lachaux *et al*¹⁵ showed that regionally specific fMRI activation patterns could predict cross-condition differences in γ -band energy during a cognitive task state in patients undergoing intracranial EEG monitoring. This study provided initial evidence for a relationship between BOLD signals and γ -band electrophysiology in the human cortex, consistent with the earlier results from animal studies.

Taken together, these findings indicate that synchronized γ -power oscillations likely are the primary neural basis of BOLD functional connectivity and the associated network-level architecture traditionally revealed with fMRI. That functional connectivity between spatially remote brain areas strongly depends on γ -oscillations is consistent with the established role of γ -band dynamics in supporting distributed neurocognitive phenomena requiring the coordination of large neuronal ensembles, such as the binding of sensory information into a coherent percept,¹⁶ and memory formation.¹⁷ In this general framework, γ -oscillations may be capable of binding neurons into a common temporal matrix and enable the emergence of functional brain networks.

According to current theory, the synchronous activity of GABAergic interneurons is the major driving force giving rise to γ -oscillations in local circuits. Network oscillations in the γ -band are associated with tightly coupled discharges of inhibitory interneurons, leading to the periodic inhibition of pyramidal cells.¹⁸ The reciprocal connectivity between fast-spiking interneurons and pyramidal cells allows γ -oscillations to synchronize membrane potentials over large ensembles of both inhibitory and excitatory cells (Figures 1A and 1B). GABA-mediated inhibition is both necessary and sufficient for the generation of γ -oscillations experimentally induced by either AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-kainate or metabotropic glutamate receptor agonists. Thus, the generation of γ -oscillations predominantly depends on GABA receptor-mediated inhibition.¹⁹

Fast-spiking basket cells that express parvalbumin (PV cells), a subclass of GABAergic interneurons, are particularly essential

Figure 1. (A) Schematic representation of the reciprocal connectivity between pyramidal neurons (PNs) and fast-spiking inhibitory interneurons (INs) that underlies the generation of γ -frequency oscillations (adapted from Bartos *et al*¹⁹). (B) Anatomic rendition of synaptic connectivity between a pyramidal cell (left) and inhibitory basket cell (right). (C) Synchronous high-frequency oscillations across spatially remote regions give rise to complex functional brain networks whose topology may be represented graphically and analyzed with graph theoretical measures. (D) The metabolic demands of high-frequency neural oscillations result in *regionally specific* oxygen and glucose consumption across the brain that may be estimated with fluorodeoxyglucose positron emission tomography and arterial spin labeling (ASL). The metabolic demands of neuronal populations correlate with their topological importance in functional brain networks.

to the generation of γ -oscillations.^{19,20} Indeed, inhibition of PV interneurons using optogenetic techniques selectively suppresses γ -oscillations.²¹ Conversely, activation of these fast-spiking interneurons via periodic stimulation of light-activated channels selectively amplifies γ -oscillations.²² According to some authors, the key involvement of PV cells in generating γ -oscillations is thought to represent one of the strongest cases made so far for the importance of a specific cell type to sustain rhythmic electrophysiological activity in the brain.²²

Inhibitory PV cells are well-suited for this specialized role for several reasons. First, basket cells form dense connections to one another in the neocortex^{23,24} that results in an extensive local network capable of synchronizing activity with temporal precision. Second, they display divergent coupling to each other, and to pyramidal cells.²⁵ This suggests that inhibitory synapses between basket cells could synchronize activity within the basket cell network, while inhibitory synapses between basket cells and pyramidal cells may then distribute this synchronized activity to neighboring pyramidal neurons.¹⁹ Moreover, GABA receptor-mediated inhibitory postsynaptic potentials (IPSPs) display strikingly rapid kinetics in basket cells. The IPSPs at basket cell-to-basket cell synapses are approximately twice as fast as IPSPs at basket cell-to-pyramidal neuron synapses. The IPSPs rise almost instantly and decay with a time constant of ~ 2 ms.^{19,26} As such, rapid inhibition at postsynaptic GABA interneurons is instrumental to the generation of high-frequency oscillations.¹⁸

The excitatory drive to interneurons required to sustain γ -frequency oscillations is commonly thought to arise from pyramidal cells^{27,28} but evidence for gap junction-mediated excitation across interneurons also exists.²⁹ In agreement with this view, AMPA-mediated principal neuron-to-interneuron excitatory synapses have been identified in the neocortex and hippocampus, and the associated postsynaptic currents have a particularly rapid time course³⁰ indicative of functional specialization to facilitate rapid oscillations. Moreover, *N*-methyl-D-aspartate (NMDA) R1 receptor deletion in GABAergic interneurons results in a loss of neuronal synchronization in slices,³¹ and glutamatergic synapses on interneurons are stronger than those on principal neurons,¹⁹ also consistent with a directional role in providing tonic excitatory inputs to PV cells.

Although the neuronal mechanisms underlying γ -oscillations have been studied extensively, comparatively little is known regarding the potential contributions of astrocytes to high-frequency network oscillations. It has notably been shown that the inhibition of astrocytes by fluorocitrate selectively suppresses extracellular EEG rhythms in the γ -band in anesthetized rats.³² Although the specific processes by which astrocytes may modulate γ -oscillations remain generally unknown, initial evidence suggests that SB100 calcium-binding protein secretion by astrocytes can increase pharmacologically induced γ -oscillations *in vivo* via the activation of metabotropic glutamate receptors.³³ Furthermore, given the high sensitivity of γ -oscillations to metabolic changes, astrocytes may also be capable of influencing γ -oscillations by regulating the coupling between synaptic activity and cellular energy metabolism;³⁴ however, this particular hypothesis has not yet been investigated.

LONG-RANGE SYNCHRONY AND PHASE SCATTERING

As discussed above, the association between γ -oscillations and long-range network connectivity estimated via BOLD signal correlations has been established. However, the specific mechanisms by which local coherent oscillations generate long-range phase synchrony in the human brain remain unclear and are a matter of intense investigation.

The temporal coupling between different neural oscillators is required for the genesis and control of higher mental functions. Distinct mental states are defined in a specific manner by

sequential epochs of neural activity across multiple cortical and subcortical areas, formed by cooperation and expressed in spatial patterns.³⁵ Patterns of cooperation by phase synchronization intermixed by periods of phase scattering are the prototypical network processes allowing for information to be transferred across neural modules. Rodriguez *et al*³⁶ were the first to show, using EEG in humans, that patterns of long-range synchrony in the γ -frequency range observed in a particular cognitive state (task of facial recognition) were followed by periods of strong desynchronization, marking the transition between the moment of perception and a task-required motor response.

Interestingly, it has been reported that the relative phase of γ -oscillations measured across widely separated brain areas is near zero.^{36–38} From a purely anatomic perspective, the zero-phase lag of distant neural oscillators is surprising given that axonal conductance and synaptic transmission should involve nonnegligible delays, especially over large physical distances.³⁹ Although long-range structural projections between populations of GABAergic cells are thought to help distribute neural pacemaker dynamics,⁴⁰ mechanisms beyond direct anatomic connectivity must also be involved in synchronizing high-frequency oscillations across distal brain sites.

Evidence has been coalescing around the idea that the long-range synchrony of electrical oscillations in the brain is self-organized.³⁵ Self-organization naturally emerges from the dynamics of a system without the need of any external intervention. In a simple analogy, self-organization may be depicted as a series of independent oscillators, such as metronomes, separately oscillating at the same frequency. If a weak physical connection is established among them, as can be achieved by placing the devices on a slightly flexible wooden board, the independent metronomes will start ticking in phase within a matter of seconds. Interestingly, similar phenomena are commonly observed in Nature. Wherever one looks, networks of cells/organism can be found whose collective activity can be modeled as an ensemble of coupled oscillators. As soon as an interaction is switched on between the independent oscillators, synchronization can occur. This interaction then becomes part of the system, such as the wooden board in the metronomes example above. It is the combination of oscillation and weak coupling that can generate waves of synchronized activity that expand over long distances. Mathematical models of such network dynamics, as the Kuramoto phase oscillator, are now routinely used to describe the coupling of neuronal ensembles.⁴¹

An emerging view that has been extensively adopted in experimental work at the micro-, meso-, and macro-scales expands on biophysical models of synchronous brain function to further state that neural activity is of fractal nature, and that the brain is a self-organized critical system (SOC).^{42–44} Systems in a critical state are poised on the cusp of a transition between ordered and random behavior, and show complex patterning of fluctuations at all scales of space and time.

Bak *et al*⁴⁵ originally suggested that a simple cellular automaton could produce several characteristic features observed in natural complexity (fractal geometry, $1/f$ noise, and power laws) and that this critical behavior emerged in a robust manner irrespective of the fine-tuning of the system. Since then, the SOC paradigm has been used to explain the emergence of dynamic synchronous behavior across diverse fields including geophysics, cosmology, evolutionary biology, ecology, and economics. As postulated by Turing⁴⁶ and more recently articulated by Chialvo,⁴⁷ the brain can be viewed as a dynamic system that naturally develops into a critical state. It has indeed been observed with experimental techniques ranging from single-neuron avalanche sensing to multimodal neuroimaging that dynamic waves of synchronous activity take place among neuronal units at every scale, from individual neurons to large cortical units, generating brain

rhythms with a $1/f$ power spectrum in space and time typical of a system at criticality.^{48,49}

Recent evidence has suggested the brain's critical organization may prove advantageous for information processing. It is generally accepted that hypercorrelated brain dynamics produce behavioral states of limited functional value, and weakly correlated dynamics prevent information flow.³ Criticality confers the brain with an intermediate regime characterized by power-law correlations. Moreover, critical brain dynamics exhibit an optimal dynamical range for information processing,^{50,51} as phase transition is a perfected mechanism for rapid switching between cooperative neuron collectives⁵² and is also able to display efficient learning of complex rules via plastic adaptation.⁵³

In sum, the self-organization of brain activity into a critical state may enable local γ -band activity to become synchronized across anatomically distant neural oscillators in the brain, and thereby enable functional integration in large-scale networks. The presence of long-range anatomic projections between neural modules and the brain's small-world network architecture⁵⁴ likely facilitate the emergence of critical properties and long-distance neural synchrony with near-zero phase lag.

ENERGY DEMANDS OF HIGH-FREQUENCY NETWORK OSCILLATIONS

The energetic load of γ -activity reflects on the brain's overall metabolic demands. Although the brain only accounts for 2% to 3% of total body mass, it has, by a considerable margin, the highest metabolic activity of all organs. In the awakened state, the human brain consumes $\sim 20\%$ of the body's oxygen supply and 50% of its glucose supply even in the absence of experimental task demands.

It is expected that the maintenance of ionic homeostasis across neuronal cell membranes during high-frequency network oscillations significantly drives local energy consumption in the brain. During γ -oscillations, the elevated firing rate of PV cells results into a very high incidence of excitatory postsynaptic potentials (EPSPs) and IPSPs associated with dynamic alternating ion fluxes through the neuronal cell membrane. Excitatory pyramidal cells also display heightened firing rates during γ -oscillations, but their spiking is intermittent and overall lower than in basket cells. To maintain ionic homeostasis, PV cells rely on adenosine triphosphate (ATP)-dependent ion pumps and transporters including the Na^+/K^+ -ATPase, Ca^{2+} -ATPase, and the $\text{Na}^+/\text{Ca}^{2+}$ exchanger.⁵⁵ The rate of ATP production is tightly coupled to neuronal activity by both intracellular calcium concentrations and the ATP/adenosine diphosphate (ADP) ratio.^{56,57} To counterbalance local ATP consumption during γ -oscillations, PV neurons likely rely on oxidative phosphorylation in the mitochondria; the metabolic process underlying most of the brain's ATP production.^{58,59} Accordingly, the maintenance of γ -oscillations is expected to require strong performance of the mitochondria, and correspondingly elevated local oxygen and glucose consumption.

Several lines of evidence support the above model of function. First, pharmacological inhibition of the respiratory chain selectively disrupts γ -oscillations *in vitro*. Oxidative phosphorylation is carried out by over 100 proteins arranged into five respiratory chain enzyme complexes, and their inhibition compromises ATP synthesis. Rotenone, a Complex I inhibitor, causes rapid decreases in the power of γ -oscillations in mouse hippocampal slices.^{60,61} Similarly, inhibition of Complex IV by potassium cyanide and interference with the mitochondrial electrical gradient by protonophores also cause significant reductions in γ -power.⁶¹ Importantly, other electrically evoked forms of oscillatory activity are more resistant than γ -oscillations to treatment with rotenone,⁶⁰ which highlights the particular sensitivity of γ -band dynamics to metabolic disruptions. Moreover, concentrations of mitochondrial inhibitors that cause no significant effect on the

resting potential of pyramidal cells can induce a marked depolarization of inhibitory basket cells.⁶¹ This result reinforces the notion that it is largely the activity of PV cells that drives the local energy demands associated with γ -oscillations. It is also consistent with the observation that basket cells contain particularly high concentrations of mitochondria.⁶² Cytochrome c (CC) staining that labels mitochondria at the ultrastructural level has indeed revealed the ubiquitous presence of mitochondria in PV cells, as reflected by strong CC signals in the somata, dendrites, and axo-axonic terminals. Mitochondrial staining in PV cells is stronger than in pyramidal cells across all cellular compartments, and this observation has been attributed to the comparatively lower average firing rates of principal neurons.⁶²

Complementary to mitochondrial inhibition experiments, direct measurements of local interstitial partial oxygen pressure (pO_2) also provide insight regarding the energy demands of high-frequency network oscillations *in vitro*. Kann *et al.*⁶⁰ investigated oxygen consumption during γ -oscillations in mouse acute slices. Absolute values of pO_2 in a given slice were obtained during spontaneous network activity and during γ -oscillations that were induced by bath application of acetylcholine. Oxygen consumption was significantly increased during γ -oscillations, as reflected by a rapid and sustained decrease in interstitial pO_2 . These data suggest that γ -oscillations require high O_2 consumption because of enhanced oxidative energy metabolism. Similarly, in rat organotypic hippocampal cell cultures used after 7 to 10 days *in vitro*, γ -oscillations were associated with a significant decrease in pO_2 ; more than twofold of that observed during applied electrical stimulation (10 s, 20 Hz), indicating increased oxygen consumption.⁶⁰ These findings are consistent with earlier *in vivo* work that showed a correlation between γ -oscillation power and the strength of hemodynamic signals.¹³ Finally, changes in mitochondrial redox state during γ -oscillations have been investigated in slice cultures using live fluorescence imaging of nicotinamide adenine dinucleotide and flavin adenine dinucleotide. Combining this technique with electrophysiological recordings,⁶⁰ it was shown that further electrical stimulation of hippocampal cells undergoing γ -oscillations at baseline resulted in a significant attenuation of the additional oxidation of dinucleotides relative to γ -oscillatory behavior alone. This observation suggests that, during γ -oscillations, the electron transport chain may already operate near limit, thus barely permitting a further increase in mitochondrial oxidation.

The results from human clinical studies also reflect the metabolic demands of γ -oscillations. Notably, Nishida *et al.*⁶³ combined subdural electroencephalography with fluorodeoxyglucose positron emission tomography to show a strong correlation between γ -spectral amplitude and cortical glucose metabolic patterns in patients with nonlesional focal epilepsy. Importantly, this association was specific to the γ -band and a linear correlation was *not* found between regional glucose metabolism and ECoG measures of δ -, β -, θ -, and α -frequency bands. Furthermore, administration of the NMDA receptor antagonist ketamine, which has been shown to enhance the power of γ -oscillations *in vivo* in a mouse model,⁶⁴ also increases the metabolic rates of glucose in the human cortex in a regionally specific manner.⁶⁵

It is well established that synchronized network activity is spatially selective, and that the topological importance of anatomically distinct areas is nonuniform across the cortex.^{4,5,54} Thus, it would be of interest to identify specific biochemical features that might explain the differential capacity of neuronal populations to sustain high-frequency network oscillations. In this regard, the cellular machinery supporting mitochondrial functions holds particular relevance. Regarding γ -oscillations, arguably the best-characterized component of the mitochondrial respiratory chain is Complex I (NADH/ubiquinone oxidoreductase). Complex I is composed of ~ 42 polypeptides encoded by both nuclear and mitochondrial DNA, and is rate limiting for oxygen consumption in

the nerve terminal.⁶⁶ As mentioned above, pharmacological inhibition of Complex I results in the selective suppression of γ -oscillations.⁶⁰ Within the CA3 subfield of the hippocampus, mRNA expression of Complex I subunits correlates with both γ -oscillation power and γ -associated oxygen consumption.⁶⁰ Moreover, expression of Complex I subunits is higher in the CA3 hippocampal subfield than the CA1 subfield. The latter observation is particularly important because cholinergically induced γ -oscillations are consistently more prominent in CA3 than in CA1, independent of the type of preparation or the species under study.⁶⁰ Furthermore, the magnitude of spontaneous CA3 oscillations *in vitro* correlates strongly with the magnitude of γ -oscillations observed *in vivo*.⁶⁷ Taken together, these findings indicate that Complex I expression may be a key determinant of the ability of neuronal populations to engage in high-frequency network oscillations. Future studies should examine the effect of other metabolic parameters on γ -band dynamics, with special emphasis on interregional comparisons.

METABOLIC DEMANDS OF HIGH-FREQUENCY NETWORK OSCILLATIONS: FUNCTIONAL IMPLICATIONS

Mitochondrial Performance

A crucial implication of the large energy demands associated with high-frequency network oscillations is that metabolic alterations may influence functional integration, cognitive performance, and behavior. Based on the evidence discussed above, neuronal mitochondrial function and glucose metabolism can modulate the oscillatory dynamics and, consequently, the functional connectivity of neuronal populations (Figure 1). Thus, the importance of metabolic processes in the brain is not limited to sustaining basic events required for the survival of neural tissue; some metabolic parameters may actually contribute to shaping the brain's functional network architecture. The γ -band dynamics have been implicated as a cellular correlate for several higher brain functions including sensory processing, memory formation, and consciousness.^{19,68,69} Fast neuronal oscillations in the γ -band are thought to provide a temporal matrix for the binding of information arising from distributed neural sources, and thereby enable various mental operations. In recent years, an emerging body of work has begun to provide mechanistic insight on the relationship between brain energy metabolism, network activity, and cognitive functioning.

Roubertoux *et al*⁷⁰ elegantly showed the influence of mitochondrial DNA on cognition in mice, and its possible relationship to γ -oscillations. The authors performed cross-breeding experiments to develop strains of mice congenic regarding mitochondrial DNA (mtDNA), and investigated the animals' behavior on learning and exploration paradigms. In laboratory learning tasks, the behavior of the congenics was intermediate to that of the parental strains, and performance was as expected according to the origin of their mtDNA. In tasks of exploration, mtDNA cross-transfer yielded new phenotypes, with lower exploratory activity in the congenic strain than either donor strain. Deficits in exploratory behavior were assessed by counting the number of holes explored by the mice in an automated hole-board during a 10-minute period. These cognitive/behavioral differences were solely attributable to mtDNA cross-transfer, as the study tightly controlled for the potential behavioral influences of maternal DNA, and the mtDNA substitution had no significant effect on the expression levels of mitochondrial genes encoding polypeptides. It should also be noted that mtDNA transfer did not result in significant morphologic changes to the hippocampus, a region strongly involved in learning and memory. However, meaningful variations in mitochondrial gene sequences of Complex I and Complex IV proteins were found in the congenics. This finding is of particular interest, as recent experimental results

(see the section 'Energy demands of high-frequency network oscillations') have highlighted the contributions of these same enzyme complexes to the generation of γ -band oscillations *in vitro*. It is therefore plausible that the behavioral differences induced by mtDNA substitution resulted from changes in high-frequency network oscillations in turn modulated by Complex I and/or Complex IV activity.

Clinical studies have also provided evidence for a relationship between mitochondrial performance, high-frequency network oscillations, and cognition. Disruptions of fast-spiking interneuron function and γ -oscillatory dynamics have been described in brain disorders including schizophrenia, Parkinson's disease, and AD.⁷¹ Interestingly, several inherited mitochondrial disorders are characterized by related clinical features including encephalopathic psychoses, Parkinsonism, and dementia.⁷² Although primary genetic mitochondrial disorders are relatively rare, this observation raises the possibility that more subtle metabolic disruptions induced by commonly inherited polymorphic variants and/or environmental triggers might compromise the functional integrity of fast-spiking inhibitory interneurons and disrupt synchronous oscillatory activity across the cortex in various brain disorders.⁷³ In agreement with this view, changes in mitochondrial activity have been identified in patients with isolated neurologic and psychiatric disorders. Notably, mutations to the ND5 subunit of Complex I have been reported in idiopathic Parkinson's disease,⁷⁴ and post-mortem studies of the parkinsonian brain have revealed significant decreases in Complex I activity.^{66,75,76} Similarly, post-mortem analyses of the Alzheimer's brain have found that activity of Complex IV was reduced by ~30% in the cerebral cortex and ~50% in the hippocampus relative to controls.^{77,78} Altered cerebral energy metabolism has also been suggested to play an important role in the pathophysiology of schizophrenia.⁷⁹ Notably, Dror *et al*⁸⁰ found that Complex I enzymatic activity is increased in blood platelets of schizophrenic patients relative to controls, and strongly correlates with the severity of positive symptoms. In this same study, mRNA levels for two of the three Complex I subunits being analyzed were significantly higher in patients than controls, which indicates that alterations in Complex I are expressed at the level of transcription and translation in psychosis. Moreover, a positive correlation has been reported between peripherally measured Complex I activity and regional hypermetabolism of glucose in the thalamus and basal ganglia of schizophrenics with elevated positive symptoms,⁸¹ regions that also show aberrant BOLD connectivity to the cerebral cortex in schizophrenia.^{82,83} Future studies are needed to determine whether such functional connectivity deficits directly arise from metabolic dysfunction.

Glucose Supply

In addition to strong mitochondrial performance, continuous cerebral glucose supply is also critical for the maintenance high-frequency network oscillations because of the brain's limited capacity for energy storage in glycogenic form. This suggests that deficiencies in glucose transport and/or homeostasis may play a role in brain disorders of functional integration characterized by disruptions in the synchronized activity of distributed networks. Alterations in the topological configuration of functional brain networks have been well documented in AD and schizophrenia.

Alzheimer's disease has been associated with a reduced proportion of long-range connectivity, greater path length, and reduced network efficiency^{84,85} that may precede pathologic findings of fibrillar amyloid plaque deposition.⁸⁶ In graph theoretical studies, an increase in the global average path length of a graph signifies that, on average, the speed at which information emitted from a given node can reach each of the other nodes in the network decreases; a greater number of edges must be traveled to go from one node to another. It has been

proposed that the net effect of these topological changes is the lowering of metabolic connection costs,⁵⁴ which may be an adaptive response to decreased cerebral glucose supplies. Consistent with this idea, a reduction in cerebral glucose use is one of the earliest signs of Alzheimer's disease.⁸⁷ Alzheimer's disease patients have impairments in glucose transport and in the insulin signal transduction cascade⁸⁸ to the extent that a 'type 3' diabetes has been coined to describe brain-based disturbances in insulin signaling in AD-related dementias.⁸⁹ Furthermore, type-2 diabetes mellitus is an established risk factor for both AD and mild cognitive impairment (MCI), and population-based studies have associated MCI with earlier onset and longer duration of type-2 diabetes mellitus.⁹⁰ Relative to healthy controls, type-2 diabetes mellitus patients show reduced functional connectivity in resting-state networks. These functional connectivity changes are in turn correlated with the severity of insulin resistance,⁹¹ and similar to those observed in the early stages of AD before cognitive dysfunction. Taken together, these findings suggest that impaired glucose uptake early in the course of AD may trigger the reorganization of synchronized network activity to a topological configuration that is less metabolically expensive, but at the cost of integration capacity.⁵⁴

Schizophrenia is characterized by a 'subtle randomization' in the global topology of functional brain networks and associated cognitive deficits.⁹² The development of metabolic syndrome contributes to a reduction in the average life expectancy of individuals with schizophrenia. It is unclear whether this association reflects an unhealthy lifestyle, side effects of atypical antipsychotic medications, or disease-inherent derangements. However, *in vivo* fluorodeoxyglucose positron emission tomography imaging studies of unmedicated schizophrenic patients have shown prefrontal cortical gray matter hypometabolism and hippocampal hypermetabolism⁹³ that may reflect a metabolic adaptation to increase glucose sources⁹⁴ and compensate for cognitive hypofunction. It has indeed been suggested as part of the 'selfish brain theory' that, to sustain higher-order mental functions in certain pathologic states,⁹⁴ the brain may overactivate the sympathoadrenal system to increase its glucidic supply, causing long-term damage to other organs by induction of insulin resistance, obesity, and hypertension.^{95,96}

Future studies are needed to determine cause-and-effect relationships between pathologic changes in glucose metabolism and topological disruptions of network dynamics in a disease-specific manner. For instance, because reduced glucose use in AD is evident early in the course of the disease, it is plausible that functional brain networks in AD patients adjust to a less metabolically expensive organization in response to decreased glucose supplies that ultimately leads to cognitive impairments. In this context, aberrant glucose metabolism may be the *cause* of pathologic changes in the functional architecture of the brain. In contrast, in schizophrenia, the brain may require additional glucose use to compensate for a suboptimal functional network architecture shaped by aberrant neurodevelopmental processes, which results in reduced glucose uptake by peripheral tissues and the induction of insulin resistance. Schizophrenia may therefore represent a case where the development of metabolic syndrome is a *consequence* of abnormal network connectivity.

CONCLUDING REMARKS

In recent years, there have been several reports of disrupted functional connectivity and associated topological changes in brain disorders.^{54,85} This growing body of work has provided the basis for a paradigm shift in the study of neuropsychiatric syndromes. Novel measures of the brain's functional organization have emphasized the importance of temporal coding and coordinated neuronal oscillations in distributed networks,⁹⁷ interactions that cannot be captured by examining the activity

of individual brain regions in isolation. The relevance of this emerging perspective to patient care has become evident,⁹⁸ with recent studies examining topological changes in functional brain networks in the context of specific clinical hypotheses pertaining to symptomatology,⁹⁹ medication effects,¹⁰⁰ and disease progression.¹⁰¹ It follows that patient outcomes may be improved by restoring oscillatory dynamics in affected circuits to a target range observed in healthy functioning. The development of effective circuit-based therapeutics requires in-depth knowledge of the neurobiological underpinnings of synchronous network oscillations, which is presently lacking. This review aimed to integrate findings from neuroimaging, electrophysiology, biophysics, and cellular biology to illustrate the importance of integrative approaches in the study of functional brain networks and their energetic demands.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

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