BRAIN
A JOURNAL OF NEUROLOGY

SCIENTIFIC COMMENTARIES

Mitochondria and cortical gamma oscillations: food for thought?

Increasingly, modalities such as functional MRI and positron emission tomography are finding their place in clinical neurological practice. These techniques provide a unique window into the collective behaviour of neuronal networks; and provide useful information concerning both physiological and pathophysiological modes of operation in particular regions of the brain. A contentious issue is whether or not inferences can be made about neuronal spiking or synaptic activity from measurements of brain-blood flow and energy metabolism (Logothetis and Wandell, 2004). In order to obtain this level of information, electrophysiological techniques such as intracranial EEG, using subdural and/or depth electrodes, are needed. However, this type of invasive approach is not widely used, being suitable only in patients suffering from intractable epilepsy. Recently, a number of research groups have combined techniques such as functional MRI with EEG. This powerful combinatory approach permits experimenters to overcome limitations in terms of discriminating spatial, temporal and spectral features when compared with EEG recordings alone. Such an approach has been fruitful in revealing a significant positive correlation between a particular type of EEG rhythm and haemodynamic responses in the visual cortex (Niessing *et al*., 2005). This particular EEG rhythm, the gamma frequency oscillation (γ-oscillation), occurs in many cortical regions and is suggested to play a role in several cognitive processes including memory formation (Fell *et al*., 2001), attention (Fries *et al*., 2001) and perception (Fries *et al*., 2007; Uhlhaas *et al*., 2008). The γ-oscillations are therefore highly likely to be important in a wide range of human diseases disrupting normal brain function.

At the level of the cortical microcircuit, γ-oscillations are generated through an interplay between cortical inhibitory (gamma-aminobutyric acid releasing) interneurons and excitatory (glutamate releasing) principal neurons. Both *in vivo* (Atallah and Scanziani, 2009) and *in vitro* (Traub and Whittington, 2010) studies have demonstrated that, via a tightly synchronized action potential output, inhibitory interneurons recruit pyramidal cells by inhibitory post-synaptic potentials. In turn, the inhibitory post-synaptic potentials synchronize pyramidal cells and limit the ability of these neurons to generate action potentials. Thus, the local field potential γ-oscillations that underlie the EEG signal are dependent on high rates of interneuronal spiking and population inhibitory synaptic activity. However, although functional MRI/EEG approaches have demonstrated a global relationship between neuronal oscillations and brain metabolism, many questions relating to neuronal metabolism and network function remain unanswered at the circuit level. Several research groups have focused on the contribution of synaptic and cellular components to the production and maintenance of γ-oscillations, but there have been few mechanistic studies aimed at determining the interaction between neuronal metabolism and organized network oscillations in health or disease.

At the heart of the matter is the role of mitochondrial energy production during organized brain activity. Adenosine triphosphate (ATP) is the principal source of intracellular energy within neurons and most is generated within mitochondria through the process of oxidative phosphorylation. Oxidative phosphorylation is carried out by over 100 proteins encoded by nuclear DNA and intra-mitochondrial genes (mtDNA). These proteins are arranged into five respiratory chain enzyme complexes, and their disruption will compromise ATP synthesis. The rate of ATP production is known to be tightly coupled to neuronal activity by both intracellular calcium concentration and the ADP:ATP ratio (Nicholls *et al*., 2003; Kann and Kovacs, 2007). Given that high rates of interneuronal spiking are seen during γ-oscillations, it would be expected that in order to maintain the balance of sodium and potassium ions across the neuronal cell membrane, these cells would have a greater metabolic capacity than pyramidal cells that display intermittent firing patterns. Anatomical studies support the concept of a functional heterogeneity of interneurons with respect to metabolic demands (Gulyás *et al*., 2006). Nevertheless, to date, a detailed description of the relationship between physiological and pathophysiological network activity, mitochondrial gene expression and oxidative metabolism has been lacking.

In this issue of *Brain*, Kann *et al*. (2011) provide this evidence by examining the relationship between γ-oscillations, mitochondrial gene expression and oxidative metabolism *in vitro*. Using the ability to induce γ-oscillations pharmacologically in acute and slice cultures of the hippocampus, the authors provide detailed mechanistic information concerning neuronal energy consumption and γ-oscillation. In particular, they illustrate using oxygen-sensing electrodes that γ-oscillations correlate with a reduction of interstitial partial pressure of oxygen. As the final electron acceptor for

the mitochondrial respiratory chain, oxygen consumption is widely used indirectly to measure cellular oxidative metabolism and ATP synthesis. The authors then demonstrate within the hippocampus that the γ-oscillation-associated oxygen consumption is largest in the CA3 subfield and correlates with the highest expression of mRNA encoding complex I subunits of the mitochondrial respiratory chain. This finding may have important functional implications given that the CA3 area is capable of generating an intrinsic γ-oscillation (Middleton *et al*., 2008; Colgin *et al*., 2009) that can then entrain or drive γ-oscillations in CA1 of the hippocampus. This is particularly important because the magnitude of spontaneous CA3 γ-oscillations (in the absence of a strong depolarizing drive) *in vitro* correlate strongly with the magnitude of γ-oscillations observed *in vivo* (Buzsáki *et al*., 2003; Lu *et al*., 2010).

Given its central role in oxidative phosphorylation, possibly as a rate-limiting step, what are the functional implications of disrupting complex I activity? To address this, the authors concurrently monitored the interstitial partial pressure of oxygen levels and γ-oscillations with and without the specific complex I inhibitor, rotenone. This pharmacological manipulation of mitochondrial function showed that γ-oscillations are critically dependent on complex I activity. Interestingly, the same manipulation does not have the same magnitude of impact on electrically stimulated synaptic activity or pathological epileptic events. Exploring this issue further, Kann *et al*. (2011) then used a variety of non-invasive indicators of neuronal metabolism. Insight into the redox state of neuronal mitochondria can be gained by measuring alterations of nicotinamide adenine dinucleotide phosphate fluorescence in brain slices, flavin adenine dinucleotide and rhodamine-123 (an indicator of the membrane potential of the inner membrane of mitochondria). Combining this technique with electrophysiological recordings provides a powerful window into neuronal metabolism during particular types of organized network activity *in vitro*. Applying this approach, Kann *et al*. (2011) dissected out the contribution of mitochondrial function for γ-oscillations in the hippocampus. They show that mitochondrial oxidative phosphorylation is essential to maintain maximal neuronal firing rates during γ-oscillations. Taken together, these data provide substantial evidence for the critical relationship between optimal mitochondrial performance and hippocampal γ-oscillations—and particularly complex I activity, which is disrupted in a wide range of inherited and sporadic human brain diseases.

As with any illuminating paper, these findings are thought-provoking and suggest additional intriguing questions. While not directly demonstrated, the work intimates that a particular type of inhibitory interneuron may be sensitive to disruption of mitochondrial function. This type of interneuron can be distinguished by the expression of a particular calcium-binding protein, parvalbumin. Indeed, recent selective optogenetic manipulation of these parvalbumin-containing interneurons has highlighted their importance in generating cortical γ-oscillations (Cardin *et al*., 2009). Exquisite metabolic sensitivity of parvalbumin-positive interneurons would fit with previous anatomical evidence showing higher levels of mitochondrial cytochrome *c* oxidase (respiratory chain complex IV) in the interneuron population when compared with principal neurons (Gulyás *et al*., 2006). Overall, these findings suggest that energy consumption is apportioned between the various classes of neurons that are critically important for the generation of γ-oscillations.

In keeping with this analysis, disruption of parvalbumin-positive interneuron function is observed in a number of common neuropsychiatric disorders including epilepsy, schizophrenia, Parkinson's disease and dementia. Importantly, in all of these conditions, disturbances in the synchrony of γ-oscillations have also been observed (Uhlhaas and Singer, 2006). It is therefore intriguing that inherited genetic mutations resulting in disruption of complex I synthesis and function can cause epilepsy both in isolation, or as part of a multi-system primary mitochondrial disease (Zsurka *et al*., 2008; Zsurka and Kunz, 2010); and encephalopathic psychoses, Parkinsonism and dementia are key components of several inherited mitochondrial disorders (McFarland *et al*., 2010). This raises the possibility that the disruption of γ-oscillations is responsible for several disabling features of these neurogenetic diseases.

As a group, primary genetic mitochondrial disorders affect ~1 in 5000 of the population and thus are considered relatively rare disorders (Schaefer *et al*., 2004). However, there is emerging evidence that secondary mitochondrial dysfunction is a key component of the more common sporadic forms of epilepsy, psychosis and neurodegenerative disease. This raises the possibility that a more subtle disruption of complex I activity, perhaps due to common inherited polymorphic variants or an environmental trigger, might compromise parvalbumin-positive interneurons to such an extent that the disruption of γ-oscillations causes a neurological disease. In epilepsy, for example, the critical role of parvalbumin-positive interneurons in shaping physiological hippocampal network function (Fuchs *et al*., 2007) and evidence for their disruption in seizures (Wittner *et al*., 2009) suggest that compromised energy metabolism in this neuron class may be responsible.

The results now provided by Kann *et al*. (2011) strengthen the case for linking studies of mitochondrial DNA mutations to those of neuronal oscillations. Constructing a detailed framework of the interaction between mitochondrial dysfunction and neuronal oscillations should improve our diagnostic capabilities and provide insights into an increasingly varied range of neurological disorders that have abnormalities of structure and function of mitochondria as their basis. By targeting neuronal mitochondria, that knowledge ought to reveal novel therapeutic interventions.

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doi:10.1093/brain/awq382

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Pathological network activity in Parkinson's disease: from neural activity and connectivity to causality?

Pathophysiological changes in the basal ganglia thalamocortical loops, first described ~20 years ago by Alexander *et al*. (1990), are commonly assumed to underlie key symptoms of Parkinson's disease. In their model, Alexander *et al*. (1990) described a large network of inhibitory and excitatory connections between different subnuclei of basal ganglia, thalamus and cortex. In the normal (i.e. physiological) state, two distinct loops regulate basal ganglia activity: a direct loop between the striatum and the internal segment of the globus pallidus; and an indirect loop between this structure and the striatum (in this loop, activity is relayed via the subthalamic nucleus). In the healthy state, these two loops are balanced resulting in well-regulated activity of the internal segment of the globus pallidus and the tightly connected pars reticulata of the substantia nigra. Besides its influence on brainstem activity, the 'output-region' of this basal ganglia network is assumed to project to the thalamus, thereby modulating thalamo-cortical interactions. Albeit simplistic, the degeneration of dopaminergic neurons in the pars compacta of the substantia nigra is to date considered the key neuropathological change underlying Parkinson's disease. Based upon neuropathological findings, after degeneration of dopaminergic cells in the substantia nigra the Alexander *et al*.'s (1990) model proposes affection of the indirect loop leading to reduced inhibition of the subthalamic nucleus, and stronger excitation of the internal segment of the