

● PERSPECTIVE

How and why does photobiomodulation change brain activity?

The concept that certain wavelengths of light can change regional brain activity as well as influencing the functional connectivity between different brain centers, is rather striking. Such a concept goes beyond that of a function for light stimulating specialized retinal ganglion cells to entrain circadian rhythms but extends this to include light having a direct influence on all neurons to potentially influence a range of core higher-order brain activities. In this perspective, we explore how light may influence such core brain activities, together with why it should do so in the first place. We propose that the effect of light on brain activity has evolutionary links, relating to a basic survival strategy against any potentially dangerous situation.

A key feature of brain function that has emerged over recent years is that higher-order activities, for example cognition or attention, develop after extensive intercommunications between a number of different centers. There is a cooperation between different centers, comparable to that evident among different sets of musical instruments in an orchestra. With the use of several different methods, such as functional magnetic resonance imaging or electroencephalography, several different networks of cooperation have been identified, each associated with distinct day-to-day functional activities. These include, memory, salience, cognitive (executive), emotional and default mode networks. The latter network has by far and away been afforded the most attention by authors (Raichle, 2015) and will be a focus of this perspective.

The default mode network was discovered, somewhat by accident, after elevated levels of activity in a set of brain structures were found in individuals who were seemingly at rest, not engaged in any specific mental task. At these times of idle rest, an individual tends to have focus on so-called internal thoughts, such as daydreaming, recalling memories, envisioning the future and mind-wandering. Individuals are just “thinking”, but not about anything in particular. They are not even thinking about thinking (Raichle, 2015)! This default mode network is made up of a number of distinct brain centers, including the midline located medial prefrontal, posterior cingulate and precuneus cortices. In addition, some authorities indicate the more lateral inferior parietal and lateral temporal cortices and the hippocampus as part of the network. While these centers show elevated activity when an individual is at rest, their activity lowers when the individual is engaged in a particular task, such as focusing attention on something in the external (e.g., visual tasks) or internal (e.g., meditation) environments (Raichle, 2015). Such “focusing” by an individual, appears to deactivate the network, or parts thereof, so that the various networks associated with attention, such as the salience and central executive ones, can operate (Raichle, 2015). Indeed, it is thought that individuals who cannot deactivate this network when performing a task will perform the task more poorly (Raichle, 2015).

In this context, some recent findings using photobiomodulation, the use of red to near infrared light ($\lambda = 600\text{--}1000\text{ nm}$) on body tissues, have indicated that, quite remarkably, it can not only influence the survival and functional activity of any type of neuron (Hamblin, 2016; Mitrofanis, 2019), but after transcranial application, it appears to influence the functional connectivity of large scale networks such as the default mode network (Naeser et al., 2020). Transcranial photobiomodulation (henceforth referred to as “light”) has been reported to reduce activation and resting connectivity strengths between cortical regions responding to a simple finger-tapping task, including parts of the default mode network in healthy control subjects (El Khoury et al., 2019). Further, in patients suffering from either chronic stroke or Alzheimer’s disease, both of which have abnormally functioning networks, light can strengthen and influence functional connectivities within the default mode network itself, together with its connectivity with other networks, for example the salience and central executive ones. In essence, in these damaged and/or diseased states, light may help correct the imbalance of functional connectivity, restoring the connectivity between cortical regions to “normal” levels (Saltmarche et al., 2017; Chao, 2019; Zomorodi et al., 2019; Naeser et al., 2020).

So, how does this happen? How can light change brain activity? Although the precise mechanisms are not clear, the central target for light within individual neurons is the mitochondria (Figure 1A). In fact, light has been shown to increase mitochondrial fusion and fission, as well as mitochondrial biogenesis. Light is absorbed by a chromophore and the best charac-

terized one is cytochrome c oxidase, unit IV in the mitochondrial electron transport chain. This molecule has two haeme and two copper centers that absorb light within two bands across the red to near infrared range. The mechanism involves light dissociating nitric oxide from its haeme and copper binding sites in the cytochrome c oxidase, thereby allowing the binding of oxygen. Thereafter, electrons are transported along the respiratory chain and a translocation of protons across the mitochondrial membrane occurs. This produces a proton gradient, one that drives ATP (adenosine triphosphate) synthase. The result is an increase in the mitochondrial membrane potential and a surge of ATP. There is also a release of nitric oxide that also triggers the vasodilation of nearby blood vessels, increasing cerebral blood flow. Such an effect has been considered short-term, in operation mainly when light is being applied to the neurons. After activation of cytochrome c oxidase, small amounts of reactive oxygen species are released (within normal levels), that then stimulate transcription factors in the nucleus, leading to the expression of various functional genes. This latter effect has been considered longer term, in operation well after the application of light has ceased (Hamblin, 2016).

There is evidence that, in addition to cytochrome c oxidase, there must be other photoacceptors within neurons. For instance, an increase in ATP levels has been reported after light has been applied to mouse and human cell lines lacking cytochrome c oxidase altogether (Lima et al., 2019). It has been suggested that a key, in fact main, photoacceptor within the mitochondria is water. Layers of nanowater, referred to as interfacial water, are found within the highly folded membranes of the mitochondria (Figure 1A) and these tend to get viscous, much more so than bulk water. This increase in viscosity of the interfacial water, due largely to the cramped interface of the membranes and/or an abnormal increase in the levels of reactive oxygen species within the neurone, impedes the function of ATP synthase and hence the translocation of protons and production of ATP. In this context, application of light has been related to a decrease in the viscosity, as well as an increase in volume (presumably due to a small increase in temperature), of interfacial water. This then results in an increase in the efficiency of ATP synthase, increased translocation of protons, higher levels of ATP and lower levels of reactive oxygen species (Sommer et al., 2015). This ability of light to change the composition of water has been suggested to have been critical to the very beginnings of life, relating to a fundamental interaction between the elements, namely between light and water (Pollack et al., 2009).

There is also evidence that chlorophyll metabolites may act as photoacceptors (Figure 1A). That it is not only plants - but animals also - that use chlorophyll to absorb light. When incubated with a metabolite of chlorophyll, isolated mammalian mitochondria have higher levels of ATP after exposure to light, compared to those that are not. Further, when rodents are fed a chlorophyll-rich diet, the chlorophyll metabolites have been shown to enter the circulation, become incorporated within body tissues and concentrate within mitochondria. Hence, the chlorophyll ingested by animals can be converted into metabolites that become incorporated within mitochondria across a number of body tissues. These chlorophyll metabolites, when exposed to light, can catalyse the reduction of coenzyme Q, leading subsequently to cytochrome c oxidase activation and an increase in mitochondrial activity and ATP production (Xu et al., 2014).

Finally, other wavelengths across the light spectrum have been reported to be absorbed by yet other chromophores. For instance, blue (450–490 nm) and green (520–560 nm) light has been shown to activate opsins (non-retinal), such as encephalopsin (OPN3), panopsin (OPN3) or neuropsin (OPN5), leading to opening of light-gated ion channels such as members of the transient receptor potential family of calcium channels (Hamblin, 2016).

But why? Why does light appear to target the activity of neurons including those within the default mode network? Of course, there is no clear answer to this question, but it is tempting to speculate. From a transcranial approach, light can penetrate down to the level of the cerebral cortex (Hamblin, 2016; Mitrofanis, 2019). Therefore, light, being an electromagnetic wave, can potentially influence the activity and frequency of neurons in the large-scale neural networks, for example to influence the functional connectivity within the default mode network, as well as within and with the other networks, such as the central executive and salience ones (Figure 1B). The significance of why light would have such an effect on these networks perhaps subserves a key survival strategy for the organism. With the evolution of the encased vertebrate brain, and the development of higher-order activities such as cognition and attention, it would be of some advantage to the organism if, when exposed to light and the environment, the brain could focus attention quicker, particularly to any potential dangerous situation (Figure 1B). That

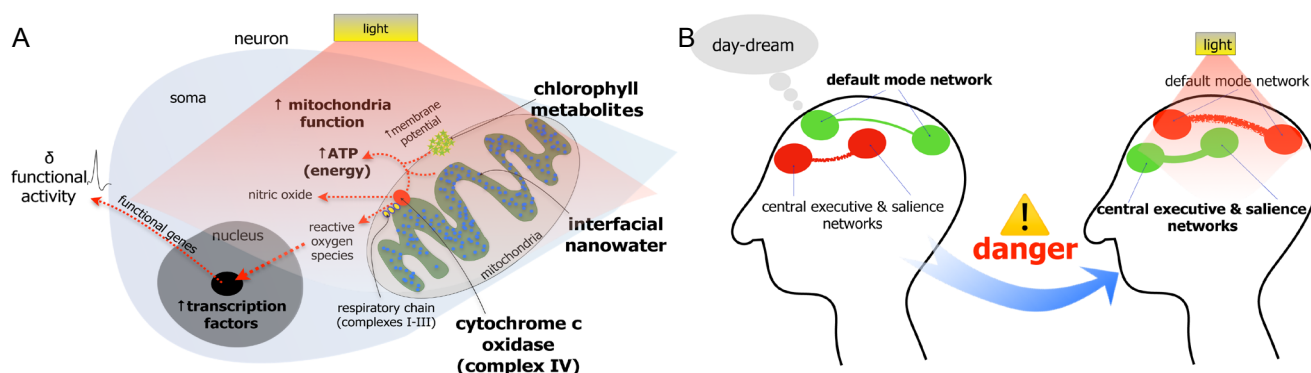


Figure 1 The impact of photobiomodulation on brain function.

(A) Schematic diagrams of the mechanisms behind how photobiomodulation (light; $\lambda = 600\text{--}1000\text{ nm}$) may influence neuronal activity. When light hits the neurones “flush”, it activates various intrinsic cellular mechanisms. Light is absorbed by a chromophore (accumulated chlorophyll metabolites, interfacial nanowater and/or cytochrome c oxidase) that then prompts mitochondrial activity and hence ATP levels. This then leads to an activation of transcription factors associated with a change in functional activity (via functional genes). (B) Schematic diagrams of the potential significance of the effect of photobiomodulation (light) on brain activity. Transcranially, light can only reach, at best, the cerebral cortex and the large-scale networks. It has been suggested that light alters functional connectivity in the default mode network and other networks (e.g., central executive and salience). We suggest that the significance of this effect has evolutionary links, subserving a survival strategy; with exposure to light and outdoors, the brain can switch attention to any potentially dangerous situation more readily. The light does not necessarily switch the default mode network off (red) and the others on (green and bold text), but it would alter the efficacy of the process by influencing the functional connectivity between regions (thicker connecting lines). The light source has been shown as red (e.g., 670 nm) for the sake of clarity of presentation, but any light within the red to near infrared range should have a similar effect.

light - by influencing the functional connectivity within the default mode and other networks - would help the brain switch from a state of idle rest and mind-wandering to a state of focused attention more readily. Light may not necessarily be the trigger for the switch between the networks, but it would serve to alter the efficacy of the process by influencing the functional connectivity between regions. In this context, it is perhaps relevant that the midline cortical regions of the default mode network (medial prefrontal, posterior cingulate and precuneus) are very well-placed to sample light levels; further that different wavelengths of light (e.g., red and near infrared) could be more effective on the network activity at different times of the day, for example at sunrise and/or sunset (i.e., orange-red wavelengths). Other animals, including rodents, carnivores and non-human primates, have been shown to have a default mode network also (Raichle, 2015), so light may well have a similar influence on their large-scale networks. It should be noted that, even though these animals are quadrupeds, the midline regions of their default mode networks are still in a key position to be influenced by light levels.

In conclusion, light has a considerable influence on brain activity. It does so by stimulating mitochondrial function within individual neurones either by an activation of cytochrome c oxidase, a change in the composition of interfacial water, and/or a stimulation of any accumulated chlorophyll metabolites. It remains to be determined which of these mechanisms is, in fact, the most dominant across different types of cells and whether different situations or cell types rely on one mechanism over another. Such an interaction, between light and mitochondria, helps to preserve the homeostasis of neurons, maintaining their proper function when in a healthy state or aiding their survival when in distress or after damage (Hamblin, 2016; Mitrofanis, 2019). As to why light, from a transcranial approach, influences the neurones of the default mode network, we suggest that there are evolutionary links, relating to a survival strategy for the organism against any potentially threatening or dangerous situation.

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John Mitrofanis^{*}, Luke A. Henderson

Department of Anatomy, School of Medical Sciences, University of Sydney, Sydney, Australia

***Correspondence to:** John Mitrofanis, PhD, john.mitrofanis@sydney.edu.au.

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