Illuminating the Brain: Pipedream or Impending Reality for Minimally Invasive Neurostimulation?

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Optogenetics has revolutionised the field of neuromodulation by enabling the monitoring and control of neural cell activity through the expression of light-sensitive proteins. However, the high absorption of visible light by the skin and skull presents a major obstacle for non-invasive modulation of neurons. We demonstrate a significant advancement in overcoming this challenge by employing near-infrared (NIR) light sources and exploiting the nonlinear photoconversion properties of phytochrome.

Firstly, the study delves into how visible and NIR light interacts with *ex vivo* mouse head tissues, highlighting the advantages of the NIR biological windows for deeper tissue penetration and reduced light absorption and scattering (Fig.1a). Our computer simulations and experimental results demonstrated that over 12% of initial light irradiation passes through skin and skull, reaching the brain cortex, potentially enabling minimally invasive neural activation [1]. Furthermore, our pioneering work in the two-photon (2P) photoconversion of novel genetically engineered monomeric variants of phytochrome demonstrates the 2P photoswitching efficiency of up to 71% in the NIR-II range (Fig.1b) and 2P NIR fluorescence using NIR-I laser radiation (Fig.1c,d). The excitation, fluorescence emission, and photoconversion NIR wavelengths indicate the potential use of new monomeric *Deinococcus radiodurans* bacterial phytochrome as a sensitive biological tool for high-resolution imaging, detection and treatment of neurological diseases [2].

Additionally, we introduce a versatile ultrashort pulsed fibre laser designed to operate within the NIR-I and NIR-II wavelength ranges. The laser is characterized by its remarkably low repetition rate of 600 kHz, resulting in high-peak-power pulses of 82 kW with an average power of 250 mW [3,4]. Since the laser has a compact size and high pulse stability, the source can be used for *in vivo* optogenetic research. These discoveries unveil possibilities for advanced biomedical applications in neurostimulation, promising enhanced tissue penetration and a non/minimal invasive approach.

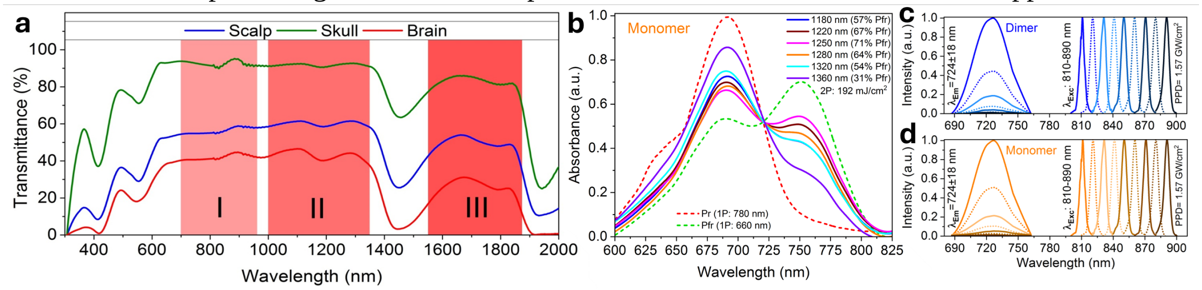

Figure 1. (a) Transmission spectra of mouse head samples; (b)1P and 2P Pr→Pfr conversion of monomeric bacterial phytochrome; 2P NIR fluorescence of (c) dimeric and (d) monomeric phytochromes.

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