Blueprint for Neurostimulation with Intranasal Light therapy

Lew Lim
MedicLights Research Inc
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This is a private document and a work-in-progress at this date.

Introduction

Intranasal light therapy achieves neurostimulation by irradiating the various parts brain (“brain stimulation” or “neurostimulation”) with red or near infrared-red (NIR) light through the nasal cavity (intranasal). The process involves inserting a small light source clipped temporarily to the nose. See Figure 1 below.

Figure 1: Intranasal light therapy in use

This paper reviews various existing methods of neurostimulation and proposes intranasal light therapy as a safe and effective neurostimulation method with strong scientific bases. Even intranasal light therapy has many possible combinations of specifications that may draw desired outcomes. The discussions below leads to a 3 different sets of specifications that would
lead a good complementary collection of different models of intranasal light therapy devices that promises to cover a comprehensive array of indications. The most potent of these for neurostimulation in particular could be the near infrared red (NIR) light from a light emitting diode (LED) pulsed at 10 Hz.

**Review of neurostimulation methods**

The following are the major methods being deployed to stimulate the brain, or for neurostimulation.

**Electroconvulsive therapy (ECT)**

Brain stimulation techniques of various kinds have been part of the neuroscience world for many decades, based on the fact that the neural system have always responded to these in some ways. Most of these are based on electrical and magnetic impulses. See Figure 2 below.

![Figure 2: Electroconvulsive therapy](source: http://www.humanillnesses.com/Behavioral-Health-Br-Fe/Electroconvulsive-Therapy.html)

One of the oldest, electroconvulsive therapy (ECT) is used to electrically induce seizure in anesthetized patients to treat difficult cases of severe depression, mania and catatonia.¹ The mechanism of action of this method is still not fully understood and there is no consensus on the treatment protocol. Furthermore it carries the risk of damaging the brain, represented by cognitive deficits.² In addition, the consequent loss in IQ and memory from the therapy is also significant.³

**Cranial electrotherapy stimulation (CES)**
Another electrical brain stimulation technique involves cranial electrotherapy stimulation (CES). This method applies a small pulsed electric current across the patient’s head. See Figure 3.

Figure 3: Cranial electrotherapy stimulation (source: http://www.jandacri.com/A_acuscope_Neuroscope.htm)

Some medical practitioners claim that CES helps with conditions such as stress, anxiety, depression and insomnia but it is still an experimental technique. The proposed mechanism of action is that the pulses of electric current increase the ability of the neural cells to produce serotonin, dopamine, DHEA, endorphins and other neurotransmitters that stabilize the neurohormonal systems. Skeptics believe that CES may help relieve certain stress-related symptoms but it has not been studied sufficiently to determine whether its use is practical and cost-effective.

Deep brain stimulation (DBS)

Deep brain stimulation (DBS) implants work by delivering measured doses of electrical stimulation via a thin electrode surgically inserted through a small hole in a patient's skull, with its tip implanted in a targeted brain area. See Figure 4.
The U.S. Food and Drug Administration (FDA) has approved these devices for a disorder called essential tremor in 1997, for Parkinson’s disease in 2002, and for dystonia (a disorder involving sustained muscle contractions) in 2003.

Despite the success of this method, it can cause overactivity, which can trigger dizziness, tingling, and other side effects. Researchers also do not fully understand the underlying mechanism of DBS.

Lately, Alzheimer’s Disease is reported to also respond to DBS.

Transcranial light therapy (TLT)

Transcranial light therapy (TLT) is enjoying more attention in recent years due to the increasing understanding of the underlying mechanism of action, successful outcomes, lack of side-effects and being non-invasive. This method involves directing light to the brain from the outside of the skull. The source of light can be light emitting diodes (LED) or low level laser, usually in the red or near infrared-red (NIR) part of the spectrum. The NIR band would be the choice to provide deeper penetration through the meninges, cranial material and then through the brain matter in order to reach the deeper parts of the brain. Recent research supports TLT’s potential for treating stroke, traumatic brain injury, Parkinson’s disease, mild cognitive impairment, Alzheimer’s disease, depression, and some other cognitive issues.

The TLT devices are available commercially. The most commonly available device consists of a hand-held piece about the size of a hair dryer that contains the lens, connected by optic fiber to
a control unit about the size of a small printer. The hand-held piece can also be in the form of a “cluster head” containing an array of LED diodes. See Figure 5 below.

Figure 5: Transcranial light therapy (source: http://topnews.us/content/237119-transcranial-light-therapy-may-help-tbi-patients)

Ear canal transcranial light therapy

The ear canal transcranial light therapy was developed following a study in Finland that demonstrated that when bright light is directed into the ears, it helps to treat seasonal affective disorder (SAD) or winter depression. See figure 6.

Figure 6: Ear canal transcranial light therapy (source: http://lighting.com/led-light-therapy-ears/)

The commercial device has diodes in the form of ear buds with very bright white LED attached by cables to a controller unit. It is consumer-friendly and appears effective for SAD. There is potential to expand discovery from the use of red light with this modality.
Optogenetic neurostimulation (Optogenetics)

In the optogenetic neurostimulation (optogenetics) process, researchers introduce a gene for a light-sensitive molecule, called channelrhodopsin 2 (ChR2), into a specific subset of neurons. Shining blue light on these neurons through an implanted light probe inserted into the brain interact with the gene, which then causes the neurons to fire. See Figure 7.

Figure 7: Optogenetic neurostimulation (source: http://seedmagazine.com/content/article/light_mind_control/)

One advantage of this approach is its specificity - only the neurons with the gene are activated. It also provides a way to shut neurons off; by introducing a different molecule, halorhodopsin (NpHR), an inhibitor. Yellow light also silences the cells. The combination of these elements makes the technique very exact for achieving specific neuro-outcomes.

Research with optogenetics can draw important understanding in relating anatomical locations of the brain with predictable behavioral outcomes. The exactness of how behaviour can be manipulated has great appeal or advancing neuroscience. However, at this time, the challenge is to translate animal experiments into practical human applications. It is very much in the laboratory domain, involving small animals (mainly rats and mice). It is a highly invasive method, connecting the targeted brain area to a controller unit via a catheter holding an optic fiber. It also requires the introduction of ChR2 into the specific areas of the brain to have the desired neurons fire.

In 2010, optogenetics was chosen as the Method of the Year across all fields of science and engineering by the interdisciplinary research journal Nature. At the same time, optogenetics was highlighted in the article on “Breakthroughs of the Decade” in the scientific research journal Science. The precision of the method is highly appealing to scientists but it is expected to stay in the research laboratory domain for the foreseeable future.
Today, over 500 laboratories are applying optogenetic tools to animal models of Parkinson's, blindness, spinal injury, depression, narcolepsy, addiction, and memory.\textsuperscript{11}

Summary

There are good data supporting the efficacy of all these methods, confirming that the brain responds to light, bringing about therapeutic outcomes in various forms. They are all different ways of stimulating the brain. Most are either deployed in laboratory conditions on animals, or if deployed on human beings, largely have to be administered under clinical supervision. The method group that has the potential to treat a wide range of conditions, the transcranial method, has yet to reach a state where it can be mass produced at a low cost, and thus offer the convenience of a consumer-friendly product. It inherently suffers some disadvantages by way of mass appeal. The optogenetics method understandably has attracted a great deal of attention in the physiology community because of the exactness in which it can extract neural outcomes through precise anatomical manipulation of the brain. However, the invasiveness and set-up required restricts it to the laboratory domain. The method to date that has the potential as a consumer-friendly product, the ear canal transcranial method, is specifically for treating seasonal affective disorder as there is no publication to show its efficacy beyond this application.

The intranasal pathway as a solution

The intranasal method (directing light to the brain) through the nasal cavity has the potential to overcome the disadvantages of the present brain stimulation methods. In the past, the challenge of this modality was making the applicator small enough to fit comfortably and safely with the restricted size of the nostril. However, all things being equal, it should enjoy all the credibility of the transcranial method because the scientific principles are the same.

This challenge has been overcome by the invention of MedicLights Research Inc (MedicLights), branded as “Vielight”. The issue is now shifted to selecting the correct specifications for desired outcomes. Clinical studies show that there is no one universal set of parameters for all indications, although it is safe to say that red or near infrared-red light stimulates cellular activities in general. It is now a question of being specific.

Summary of device specifications proposed for neurostimulation

In summary, based on relevant literature and ensuing discussions, the devices proposed for neurostimulation are:
1. LED device with 633 nM wavelength, 8mW power, continuous wave, 25 minute exposure time.
2. Low level laser device with 655 nM wavelength, 5 mW, 10 Hz pulsing, 30 minute exposure time.
3. LED device with 820 near infrared red (NIR), 8 mW, 10 Hz pulsing, 30 minute exposure time.

The bases for these different models are expounded below.

**Potential Impact of Intranasal Irradiation**

**Key Targeted Areas**

Specific parts of the brain govern specific functions of the mind and body. The diencephalon (roughly around the mid-brain) is the seat of some of the most essential survival functions, and holds some keys to the physical well-being of the person. This is a hard-to-reach region for access from the outside the skull but is more easily reached by a light source in the nasal cavity. Among the sub-regions here, the hypothalamus is the control center for many autonomic functions. It is connected with structures of the endocrine and nervous systems to support its vital role in maintaining homeostasis throughout the body. It is part of the limbic system that influences various emotional and pleasure responses, storing memories, regulating hormones, sensory perception, motor function, and olfaction. The other components of the limbic system are the amygdala, cingulated gyrus, hippocampus, olfactory cortex and the thalamus.

Whilst the mid-brain area could be a primary target, the divergent light rays will also illuminate some of the other parts of the brain to achieve wider spread benefit. The effect is then rapidly distributed throughout the brain through the neural network. The substantia nigra (its dysfunction lead to Parkinson’s disease) located at the bottom of the mid-brain area or in another case, the prefrontal cortex in a separate location, could be targeted to improve higher order cognitive functions.

**The anatomical advantages of intranasal irradiation**

Compared to the other methods that endeavor to irradiate the brain, a light source that is inserted into the nasal cavity will be in close proximity (about 3 inches of mainly air cavity and soft tissue) to the mid-brain area. See Figure 8.
When the light source 1 in this position is pointed towards this area, it requires little energy for effective irradiation because much of the physical pathway to the brain is air cavity 2. For the purpose of illustration, the mid-brain areas highlighted are the amygdala 3, hippocampus 4, hypothalamus 5, septal area 6 and the cingulated cortex 7. The portion of the neo-cortex that is easily illuminated by the light source is the prefrontal cortex 8.

The brain is encased inside a bony skull. Other than the area of the brain stem 9 which connects the spinal cord to the brain, the thinnest part of the protective skull is the thin perpendicular plate of the ethmoid bone 10. As testament to its low barrier to the brain, it is also the part of the skull that is broken during the ancient Egyptian mummification process to drain out the brain materials. There is some tissue material as part of the nasal septum wall in the pathway leading to the mid-brain region but is of low density.

Having little tissue between the light source and the targeted areas matters because red and infrared red penetration as covered by Beer-Lambert law, suffer optical power decay of up to 80% at 1 mm from the surface. 12

Based on 810 nm low level laser irradiation done transcranially on mice, Ando T et al measured the average penetrative power, which showed that only 15% of the of the laser power was transmitted through the skin and 6% of that penetrated through a combination of skin and skull, despite the relatively better penetrative quality of this wavelength. 13 The intranasal pathway only has the much thinner perpendicular plate of the ethmoid bone between the brain and the
light and little of everything else, hence allowing more light penetration into the brain, given that all other parameters remain the same.

**The engineering advantages of intranasal irradiation**

The above anatomical advantages now allow for a system that contains a low energy, single diode with the correct electromagnetic wavelength light source pointing in the direction as illustrated in Figure 8. Once this can be achieved, it becomes the basis for a small and convenient personal-use device.

**Scientific Bases and Evidence for use for neurostimulation**

**Recent relevant research evidence**

A summary of recent research into the beneficial in vivo transcranial effects of low-level light therapy on the brain is shown in Table 1 below. In animal studies, the technology has been found to be promising for treating anoxic brain injury, atherothrombotic stroke, embolic stroke, Parkinson’s Disease, mild cognitive impairment and Alzheimer’s Disease. In human studies, it has been found to be promising for improving on the effects of ischemic stroke, traumatic brain injury, depression and functions of the prefrontal cortex.

The potential for addressing more outcomes may be demonstrated by more future research on selected indications. For the time being, an understanding of the mechanism of action could reveal the potential for the technology.

**Table 1**

<table>
<thead>
<tr>
<th>Source</th>
<th>Wavelength</th>
<th>Dose</th>
<th>Effect</th>
<th>Relevance</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser</td>
<td>808 nm</td>
<td>1.6 w/cm², 4320 J/cm²</td>
<td>Increased cerebral blood flow and decreased hippocampal and cortical neuronal death after unilateral BCCAO (mouse)</td>
<td>Anoxic brain injury</td>
<td>Uozumi et al</td>
</tr>
<tr>
<td>Laser</td>
<td>808 nm</td>
<td>7.5 mw/cm², 0.9 J/cm², 2 minutes per point</td>
<td>Improved neurological recovery, increased subventricular neural proliferation after MCAO (rat)</td>
<td>Atherothrombotic stroke</td>
<td>DeTaboada et al, Oron et al</td>
</tr>
<tr>
<td>Laser</td>
<td>808 nm</td>
<td>25 mw/cm², 15,000 J/cm², continuous</td>
<td>Improved motor function and reduction in effective clot dose for stroke 3 hours after clot injection (rabbit)</td>
<td>Embolic stroke</td>
<td>Lapchak et al</td>
</tr>
<tr>
<td>Laser</td>
<td>808 nm</td>
<td>25 mw/cm²,</td>
<td>Increased cortical ATP, decreased</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Mechanism of action and its far-reaching impact**

The intracellular mechanism of low level light therapy is illustrated by Table 2 below. The key to the response of the brain lies in the presence of a photoacceptor respiratory enzyme in all cellular mitochondria called cytochrome oxidase. It represents the best known intraneural marker of metabolic activity and is tightly coupled with free radical metabolism, cell death pathway and glutamatergic (a neurotransmitter related) activation, important for learning and memory.  

Photoacceptors, unlike photoreceptors found inside the eyes, do not process light but are part of metabolic pathways. They are sensitive to light in the visible red and near-infrared parts of the spectrum, and convert the absorbed light into cellular energy adenosine triphosphate (ATP). When light with these wavelengths at low energy hit the cells (including nerve cells), it modulates the cells into metabolism (photobiomodulation) by regulating mitochondrial function, intraneuronal signaling systems, and redox states. With the brain affecting virtually all

<table>
<thead>
<tr>
<th>Laser</th>
<th>808 nm</th>
<th>1 J/cm² per point</th>
<th>Improved clinical outcome at 90 days after ischemic stroke (human)</th>
<th>Ischemic stroke</th>
<th>Lampl et al. 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser</td>
<td>808 nm</td>
<td>10 or 20 mw/cm²/point</td>
<td>Improved motor behavior 5 days after closed-head injury, and decreased brain lesion size from 12.1% to 1.4% at 28 days after injury (mouse)</td>
<td>Traumatic brain injury (acute)</td>
<td>Oron et al. 22</td>
</tr>
<tr>
<td>LED</td>
<td>633 nm and 870 nm</td>
<td>LED cluster</td>
<td>Improved cognition of two patients with chronic mild traumatic brain injury after 2–4 months of treatment (human)</td>
<td>Traumatic brain injury (chronic)</td>
<td>Naeser et al. 23</td>
</tr>
<tr>
<td>Laser</td>
<td>670 nm</td>
<td>40 mw/cm², 2 J/cm² in four fractions</td>
<td>Reduction in substantia nigra dopaminergic cell loss after MPTP toxicity (mouse)</td>
<td>Parkinson’s disease</td>
<td>Shaw et al. 24</td>
</tr>
<tr>
<td>Laser</td>
<td>1072 nm</td>
<td>6 minutes × 10 days</td>
<td>Improved acquisition of working memory for spatial navigation in middle-aged mice (mouse)</td>
<td>Mild cognitive impairment, Alzheimer’s disease</td>
<td>Michalikova et al. 25</td>
</tr>
<tr>
<td>LED</td>
<td>810 nm</td>
<td>250 mw/cm², 60 J/cm</td>
<td>Decreased depression scores, increased prefrontal blood flow (human)</td>
<td>Depression, prefrontal functions</td>
<td>Schiffer et al. 26</td>
</tr>
</tbody>
</table>

**Abbreviations:** ATP, adenosine triphosphate; BCCAO, bilateral common carotid artery occlusion; LED, light-emitting device; MCAO, middle cerebral artery occlusion; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

functions of the body, the impact of exposing neurons to light (photoneurobiomodulation) could consequently affect the entire well-being of the human being.

Table 2: Intracellular mechanism of action of low level light therapy

Source: Rojas JC, Gonzalez-Lima. Low-level light therapy of the eye and brain. 2011:3 49-67 (modified)
The sensitivity of cytochrome oxidase to red and near infrared red light can be explained by the role of a chromophore in the protein structure. This chromophore is an organic cofactor that is present in all photoreceptors, such as the those in the eyes that give us the perception of colors. These chromophores will absorb particular wavelengths and reject the others, and those in the cytochrome accept red and infrared red light.

These facts express the potential impact of light that could be correctly directed to the various parts of the brain, resulting in both therapy for, and prophylaxis against nervous disorders. At low energy levels, the therapeutic effects are not accompanied with any major side effect. Experiments show that photoneurobiomodulation of electrical activity in neurons can also be achieved independently of thermal effects.\(^{28}\)

**Photoacceptors in the nervous system**

Although earlier animal experiments suggested the presence of photoacceptors in the brain, it was experiments in year 2000 that demonstrated that isolated mitochondria are sensitive to irradiation with monochromatic light in the red and near infrared red spectrum. For example, illumination of isolated rat liver mitochondria with red low-powered lasers increased ATP synthesis and oxygen consumption.\(^{29}\)

It has been demonstrated that impaired mitochondrial oxidative metabolism is associated with neurodegeneration.\(^{30}\) Rat neuronal cultures exposed to low level red light showed increases in cytochrome oxidase activity.\(^{31}\) Therefore an intervention such as this invention, that is aimed at improving mitochondrial metabolism is hypothesised to benefit the function of both the diseased and normal brain. It is also clinically tested to be able to relieve pain in humans.\(^{32}\)

The effects of the light irradiation on the brain are observed in a wavelength-specific range. The data also suggest that the primary photoacceptor mediating the effects of the light is not only localized to the mitochondria; the molecules that absorb the light in cells are probably part of the respiratory chain.\(^{33}\)

**Cellular Equilibrium and homeostasis**

There is a point when the photoacceptors such as cytochrome oxidase do not respond to further photostimulation: when the cytochrome oxidase is fully reduced or fully oxidized. It responds only when it is in its intermediate stage.\(^{34}\) Therefore further sequential low power irradiation will not yield further metabolic activity from these photoacceptors. This is indicative that cells in the body have coded action potential when they are ex-homeostasis. In this state the neurons would thus have the potential to respond positively to light irradiation until they reach homeostasis.
Potential Indications

Based on the scientific evidence, there are many potential indications that can be derived from the irradiation of the brain. There are direct response indications such as stroke and neurotrauma, Parkinson's disease, cognition and emotional states. The human and animal studies that are related to these are well documented.\(^{35}\)

The brain being the control center of systemic body health, also implies that brain health has a direct impact on body health. The health of the hypothalamus for instance, being the key regulating gland for systemic homeostasis, has a profound impact on overall body health.

Since intranasal light therapy stimulates the hypothalamus, its added convenience and easy administration should generate more interest in potential indications.

Some specific indications that are already tested in related studies are discussed below.

**Stroke and neurotrauma – protection and therapy**

Investigations into brain irradiation has extensively covered stroke and neurotrauma. Recent studies by Uozemi et al demonstrated that low energy light delivered transcranially was able to increase blood flow by 30%.\(^{36}\) That would help prevent ischemic strokes. The outcomes have also been accompanied with significant increases in nitric oxide production, a mechanism that is associate with the relaxation of vascular walls to achieve improved blood circulation. The cerebral blood flow was increased in both treated and untreated hemispheres. Also, subjects pretreated with irradiation showed improved blood flow during the period of occlusion, with stable body temperature, heart rate and respiratory rates. Application of the modality during a stroke event also includes significant decrease in apoptotic (death of) cells.

Regular irradiation with low level near infrared red (NIR) light has also been found to be associated with significant neurological recovery after stroke events.\(^{37}\) Furthermore, these effects were associate with increased neuronal proliferation and migration in the subventricular zone (which plays a role in neurogenesis).\(^{38}\)

The studies on the effect of NIR on human stroke patients will continue to grow,\(^{39}\) and with the evidence available, we also understand better how light irradiation therapy on the brain may affect other conditions.

**Traumatic brain injury**

Studies have provided in vivo evidence that the effects of low level red to NIR light irradiation on cytochrome oxidase and nitric oxide play a major role in the neuroprotective action of light irradiation therapy; not just for ischemia, but also traumatic brain injury.\(^{40}\)

**Parkinson's disease**
Irradiation of the brain has been found to support neurogeneration. If applied appropriately, it may impact neurodegenerative diseases like Parkinson’s disease, which is specific to the substantia nigra, a part of the mid-brain area located behind the hypothalamus that may be reached with NIR through the nasal pathway.

In a study with small animals like mice, it was found that low level light irradiation at 670 nm wavelength, helps prevent the loss of dopaminergic cells in the substantia nigra. Longer wavelengths like NIR may be more feasible for the much larger human being.

**Dementia and Alzheimer’s disease**

Neurodegeneration can lead to cognitive impairment that is often identified with dementia. Improved blood flow with this invention demonstrates potential for addressing vascular dementia.

Alzheimer’s disease although a form of dementia, could have different causes, though full knowledge is still lacking. The early signs of this neurodegenerative condition is revealed in the form of regional brain metabolic deficits in the form of reduced cytochrome oxidase activity – which is a sign for potential risks for Alzheimer’s disease. The record that brain irradiation has with the red and infrared red lights on activating cytochrome oxidase makes intranasal light therapy a potentially good candidate to help manage the onset of a full Alzheimer’s disease.

**Depression and emotional deficits**

Phenotypic expressions of mood disorders such as depression and post-traumatic stress disorder (PTSD) have been shown to be associated with decreased metabolic capacity in the prefrontal cortex region. Electrical stimulation of the prefrontal cortex has antidepressant effects. Irradiation of the same area with red and near infrared red light is expected to have at least similar outcomes, as well as the potential for being neuroprotective of these conditions. Indeed, a pilot study showed that when the foreheads of patients with major depression and anxiety are irradiated with low level light with 810 nm wavelength, the blood flow to the frontal cortex increased and induced a 63% reduction in depression scores.

**Memory and learning deficits**

It has also been found that irradiation of the prefrontal cortex with near infrared red light of 1072 nm wavelength, also improved working memory. As this condition is common among the more elderly, using a relevant light irradiation method to irradiate the prefrontal cortex will help with an aging-related problem of working memory deficits.

Furthermore, the therapy may stimulate a reversal in learning and memory deficits because of indications that it could proliferate neural progenitor cells in the subventricular zone. These cells and are known migrate to the olfactory bulb and are then to the hippocampus, an area that supports memory and learning, and then mature into interneurons.
Summary

The science and evidence supports the intranasal pathway to be as efficacious, if not more than the alternative neurostimulation methods. The potential of its apparent ability to activate neurogenesis to achieve cellular homeostasis could form the bases of new studies that may uncover new indications. There neural conditions yet unexplored include epilepsy, migraine, chronic fatigue syndrome, encephalitis, multiple sclerosis, anxiety disorder, attention deficit disorder, schizophrenia, and perhaps even learning disability.

Bases for System Specifications / Dosimetry

The relevant specifications that govern a light therapy modality include the wavelength, coherency, energy (in Joules (J)), Power (in Watts (W) or milliwatts (mw)), Irradiance (W/cm²), Radiant exposure (J/cm²), Exposure time (seconds), Wave type (continuous vs pulsed), Fraction protocol (number of component sessions), Aperture (area of landed beam), and Delivery distance.

Determination of therapeutic wavelengths

The wavelengths shown to be most effective at inducing in vivo beneficial effects in cells that do not have specialized photopigments, have been in the optical window of the red and infrared red range (NIR) of the spectrum, between 600 – 1100 nm. Successful experiments with brain irradiation have mainly been carried out at 633-670 nm (red) or 808 - 1072 nm (NIR) in both animals and humans. This matches the luminous range of energy that excite susceptible intracellular molecules. This activation affects cellular metabolism. The longer the wavelength, the lower the energy required.

It is also a fact that the longer the wavelength, the deeper the penetration. In the case of brain irradiation through the nasal cavity, the shorter red wavelength may be able to perform as well as the NIR wavelengths, as often tested with the transcranial method. It has been recognised that it is this range of wavelengths that draw the greatest mitochondrial response as opposed to the need to have this wavelength for tissue penetration. Having stated this, when tested on rats, photons between 630 nm and 800 nm have been shown to penetrate up to 28 mm even in layers of tissues with relatively low transparencies such as skin, connective tissue, muscle, bone, and spinal cord (even though much is already dissipated after the initial 1 mm) with about 6% of the total energy density being detectable at the ventral surface. Therefore, should depth of penetration be a factor for the indication, NIR should be considered for use.

Penetration of light into tissues depends not only on the wavelength but also on the optical properties of the target tissue. The maximal penetration of light in the gray and white matter of the brain occurs at wavelengths at the NIR spectrum.
In this respect, in neural tissues, cytochrome oxidase is the most abundant metallaprotein; its wavelength peaks in its absorption spectrum (670 nm and 830 nm) highly correlate with its peaks in its catalytic activity and with ATP in vitro.\textsuperscript{52}

Another important protein that is a photoacceptor for red and near infrared red light is the flavoprotein, reduced nicotinamide adenine dinucleotide (NADH)-dehydrogenase.\textsuperscript{53} Enzymes involved in NADH are found to be attractive targets for drug discovery against a variety of human diseases, including cancer, multiple sclerosis, neurodegeneration and Huntingdon’s disease.\textsuperscript{54}

Terminal oxidases and endogenous antioxidant enzyme superoxide dismutase (SOD) also show absorption peaks under exposure to light at 670-680 nm.\textsuperscript{55} SOD is a key enzyme in neutralizing free radicals that are constantly created during endogenous activities.

It is also in our favour to select a single monochromatic wavelength for a single application. Based on the above research, it should be around 670 nm (visible red) or 830 nm (near infrared red). It has been found that simultaneous dichromatic irradiation changes the ratio of the reduced and oxidized form of the enzyme; suggesting that the invention should select pure monochromatic wavelength light source for every application.\textsuperscript{56}

However, literature review of successful research studies guides this invention to select specific wavelengths in the region of 633 to 670 nm (for general brain irradiation) or 808 to 1072 nm (to reach the deeper regions of the brain). The systems in this invention can embody separate devices to cover selected wavelengths, but not limited to these, to accommodate future discoveries. In the preferred embodiments, the selected wavelengths are 633 nm, 655 nm and 820 nm, all falling within the ranges in discussion. The selection are around the recognised wavelength peaks in the absorption spectrum, frequently tested as efficacious, and also takes into consideration the convenience and economy of available semi-conductor diodes.

**Coherent vs non-coherent (or laser vs LED)**

Lasers feature coherent electromagnetic radiation that is unidirectional, hence allowing more concentrated energy. With high energy input, they become surgical instead of therapeutic tools. Modern therapeutic laser sources are usually in low intensity semi-conductor form, with a built-in divergence that allow for a high degree of safety (often about 57 degrees divergence). The lasers have the advantages of higher tissue penetration, efficient optic coupling and high monochromaticity. Where deeper penetration is required, given the same parameters of wavelength, energy dosage and intensity, the lasers are more desirable over LEDs. However, for most therapeutic applications this coherency is not required, and where greater tissue penetration is asked for, it is better met with light with a longer wavelength.

LEDs are also being used for photobiomodulation, gaining increasing recognition in more recent years as viable fully-safe alternatives to lasers. Prominent photobiologists postulate that the photoacceptors (particularly cytochrome oxidase) do not discern the coherency of the photons
that are received. Therefore, given the same wavelength, energy dosage and intensity input received at the receptors, the outcome should be similar. Although penetration with LED is shallower, it has the advantage of giving wider area irradiation coverage.

The systems in this invention recognize the differences and offer options for both, preselecting the optimum combination for particular purposes. For example, where there is an advantage in irradiating specific areas of the mid-brain, say, the more deeply located pineal gland for restoring circadian rhythm and addressing sleep disorder, the laser option may be preferred. As alternative, the use of a longer wavelength in the NIR range and longer session time make up for the loss of penetration when compared to lasers.

Whereas the NIR 810 nm laser would be most favoured based on recent discoveries because of its deeper tissue penetration, it is invisible to the human eye – staring at a laser may damage the retina. The user has no visible light to trigger blinking as an autonomic defence mechanism. Hence the device utilizing this wavelength that is intended for unsupervised use, should be available to the public in the safe LED version only; and reserve the laser version for use in the research domain or in a supervised environment. Alternatively, a visible red laser say at 655 nm wavelength could be made available to benefit from the penetrative advantage of lasers and yet provide the safety aspect of visibility.

The non-coherency of the LED light creates very negligible amount of heat. This allows brain tissue longer exposure to “therapeutic” wavelengths at relatively low power densities while allowing modulation of neural metabolism, even if the treatment time is prolonged. For this reason, the LED may be favored over laser to treat traumatic brain injury which requires prolonged exposure to the light without the risk of thermal injury.

In summary, we may desire NIR for its penetrative quality to reach deep-lying regions of the brain such as the substantia nigra to treat Parkinson’s disease, pineal gland to regulate the circadian rhythm, and to draw a stronger response from the hypothalamus for systemic homeostasis. If we use NIR, our overriding preference would be for the safe non-coherent LED. A LED NIR diode would have a large footprint that would cover the whole brain while it is able to reach deep lying glands too.

Low level lasers based only on visible red light may be preferable as a lower cost solution to NIR. Its footprint may be targeted at the mid-brain area that include the limbic system. This would cover issues involving emotional stability, anxiety, long-term memory, motivation, olfaction and pleasure (through release of dopamine). Other glands in that region of the brain would include the substantia nigra and the pineal gland. Because of the shorter wavelength, it may not be as potent as NIR.

Visible red LED would be the lowest cost option but has a larger footprint than lasers, although not as penetrating. It may be used for general therapy and popular preventive medicine. This covers conditions related to cognitive functions, general neurogeneration to overcome trauma lesions, vascular dementia, migraine, pain, memory deficits, improved regulation of the
immune system and maintaining homeostatic balance. NIR LED would should be able to cover the same areas as visible red LED but for the lay user, its invisible nature may be unsettling.

**Therapeutic energy and other parameters**

Energy is measured in Joules (J) = Power (W) x Time (seconds). For brain stimulation, very little energy is required to stimulate mitochondrial activity although a definitive threshold is yet to be established. A reference is the time-tested intravenous light irradiation method (involving light being directly injected into the vein – used mainly in Russia, Germany and many countries around the world for decades). This modality normally employs lasers with wavelength of 632.8 nm, power of 1.5 mw, time of 30 minutes per session. Treatment is usually spread over once a day for the first three days and then once every two days until a total of ten sessions is reached. For each session, dosage energy of 2.7J (1.5/1000W x 30 minutes x 60 seconds) is delivered.

When blood irradiation with a laser (of similar wavelength) is applied indirectly through the nasal pathway, we have to deal with additional tissue materials. This can be overcome by increasing the power by several order of magnitude, say 5 mw for 25 minutes, giving an energy output of 7.5J (5/1000W x 25 minutes x 60 seconds).

Pushing greater power to a pulsed light source delivers more energy, which can activate more ATP, as demonstrated in a study on rabbits. However, this compromises on usability in an intranasal embodiment. The preferred pathway for this invention would be to achieve the required energy dosage by extending the dosage time instead.

A reference power parameter for the laser invention is to limit the power to 5 mw to keep it at the low risk level of Class 3R as classified by the US Food and Drug Authority (FDA). A revised set of parameters for the laser diode could offer power of 5 mw, duration of 25 minutes for each treatment session, to deliver the desired energy. As with blood irradiation therapy (see www.mediclights.com) which attempts to reach the blood circulatory system, in neurostimulation, we are also attempting to irradiate the underlying subcutaneous materials; although in this instance, the brain and related neural system are the targets. In principle, the parameters ought to remain the same.

The LED diode light source is mostly divergent. In using the LED diode, we can increase the energy output by say, another 60% to 12 J. This calls for a higher power at 8 mw (12J / (25 minutes x 60 seconds) x 1000mW).

In summary, for intranasal light therapy; for a laser diode the energy to aim for is 7.5J (5/1000W x 25 x 60 seconds). For a LED diode, the energy to aim for is 12 J (8/1000WX 25 x 60 seconds).

However, these configurations will be further fine-tuned after taking into consideration the discussion on the delivered wave forms of continuous wave versus pulsed frequency in the next section.
Continuous wave (CW) vs Pulsed frequency

Using 808 nm lasers on rabbits, researchers demonstrated that pulsed lasers at 100 Hz and 1000 Hz produced superior results to continuous wave (CW).\(^6^0\)

Later researchers tested 810 nm laser that pulsed at 10 Hz produced even greater recovery from traumatic brain injury than 100 Hz. They suggested that the antidepressant activity of the light therapy was a contributing factor.\(^6^1\)

Pulsed lasers can penetrate the tissues more deeply if we increase the peak power. However, to maintain the FDA laser safety classification of 3R, the power output at 5 mw should be maintained. The pulsing duty cycle of 50% duty cycle at 10 Hz is recommended, to duplicate the evenness of the pulses as observed from the brainwaves. This would reduce the energy output accordingly. However, the treatment session will be extended by 5 minutes to 30 minutes. With this, the energy output is calculated at 4.5 J/cm² (5/1000W X 50% X 30minutes X 60 seconds).

The answer as to why pulsing at 10 Hz works better than 100 Hz (or any other frequency) is a matter of hypothesis: 10 Hz is the frequency of the alpha brain waves. Therefore the pulsation at 10 Hz resonates with the whole brain at rest.

Furthermore, the hippocampus region also functions at waves in the 4-10 Hz. The hippocampus is responsible for memory, emotional well-being, behavioral management, spatial memory and navigation. It also is one of the regions that suffer damage in Alzheimer’s disease. A study showed that transcranial light therapy using a 808 nm laser diode attenuated amyloid plaque development in the transgenic mouse model, implying the possible efficacy of this therapeutic method for Alzheimer’s disease in humans.\(^6^2\)

In summary, for brain therapy, particularly to the mid-brain region, a 10 Hz pulsed model promises efficacious related outcomes. We may combine this with the NIR 810 mw light source which gives good penetration depth but only in the LED embodiment for safety reasons.

However, we may pulse a laser light source that is in the visible red spectral band, say 655 nm. It may not have the penetration quality of NIR but since the pulsed frequency is the factor that carries the real value, it is efficacious for stimulation of the mid-brain region.

Overall Invention Parameters

The above discoveries shape the specifications for viable intranasal light therapy devices for brain therapy and stimulation. Given the semi-conductor diodes that are commercially available, MedicLights are making available 3 different models that cover different price ranges and take a flexible approach to neurological conditions. The sub-systems that these models represent are set out in Table 3 below.
Table 3: Model parameters

<table>
<thead>
<tr>
<th>Model:</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proposed indications</strong></td>
<td>For general well-being and non-specific healing, including (general guide only): Preventive medicine, systemic homeostasis, facial area and systemic pain (eg fibromyalgia), cognitive performance, working memory, age-related neurodegeneration, chronic fatigue, early vascular dementia, depression, PTSD, pain.</td>
<td>For more specific, acute and chronic disorder, particularly mid-brain related, including (general guide only): Acute and chronic neurological disorders, Parkinson’s disease, Alzheimer’s disease, anxiety disorder, sleep disorder, acute fatigue, emotional disorder, memory deficiency</td>
<td>For deeper penetration and wider irradiation; covers most areas of the brain (general guide only): Intended for healing over being just preventive. Covers the indications of the other 2 versions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wavelength</th>
<th>633 nm (visible red)</th>
<th>655 nm (visible red)</th>
<th>820 nm (near-infrared red)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode</td>
<td>LED</td>
<td>Laser</td>
<td>LED</td>
</tr>
<tr>
<td>Power</td>
<td>8 mw</td>
<td>5 mw</td>
<td>8 mw</td>
</tr>
<tr>
<td>Single session duration</td>
<td>25 minutes</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Wave/pulse mode</td>
<td>Continuous wave</td>
<td>10 Hz pulse</td>
<td>10 Hz pulse</td>
</tr>
<tr>
<td>Duty cycle</td>
<td>Not applicable</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Exit energy per session</td>
<td>12 J</td>
<td>4.5 J</td>
<td>7.2 J</td>
</tr>
<tr>
<td>Direction</td>
<td>Angled to cover general brain area</td>
<td>Angled mainly at mid-brain area</td>
<td>Angled to cover general brain area</td>
</tr>
</tbody>
</table>

The above relationship between the system options and indications serves as a guide only and will be revised from time to time to incorporate new discoveries and understanding.

The Model 1 light pathway is represented by Figure 9 below: The model is a LED light source delivering 633 nm light. The light rays are generally unimpeded and dispersed over a wide area. The penetration into the brain is relatively shallow but the extensive neural network distributes the signal throughout the brain. It targets the prefrontal cortex although it covers the brain in general. However, the light source can be angled to point at any region of the brain as desired.
Figure 9: LED 633 nM, continuous wave

Figure 10: Laser 820 nM, pulsed at 10 Hz

Figure 11: LED 820 nM NIR, pulsed at 10 Hz
The Model 2 light pathway is represented by Figure 10 above: The model is a low level laser light source delivering light of 655 nm wavelength. The light rays from the laser light source generally stay coherent within a smaller dispersion footprint. The penetration is deeper relative to the 633 nm LED model in Figure 9. The extensive neural connections will still distribute some of the energy to throughout the other regions of the brain.

The model 3 pathway is represented by Figure 11 above. The model uses a 820 nm LED light source. It is NIR and is invisible to the human eye. The light rays from the LED light source delivered over a wide area. The penetration is deeper relative to the 633 nm LED model in Figure 9 and the dispersion (and coverage) is wider than the 655 nm laser in Figure 10. It more easily covers the depth and breadth the other two models cannot, including the deeper lying areas. It features the features of the other 2 models. For ease of-use, the presence of the invisible light can be detected by a infrared red sensor.

Conclusion

In conclusion, an analysis of the neurostimulation technologies vis-a-vis intranasal light therapy has revealed the inherent advantages the intranasal light therapy method has over the others. This is particularly so from the perspective of ease-of-use and effectiveness for the user. Many studies point to the efficacy of the technology. The diversity of light source used in published studies have yielded positive outcomes for numerous disorders.

It then becomes an issue of incorporating the most appropriate specifications for different indications. The 3 models with different combinations of specifications are: the 633 nM continuous wave model, the 655 nM low level laser model pulsed at 10 Hz, and the 850 NIR model pulsed at 10 Hz. Based on its penetrative qualities, Model 3 with the NIR LED light source could be the most potent; potentially able to deliver improvements for most neural disorders.

References


Schiffer F (2009). “Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety”. Behav Brain Funct. 5:46.


