Published in final edited form as:

*Trends Neurosci*. 2018 May ; 41(5): 252–254. doi:10.1016/j.tins.2018.03.002.

# Light Therapy in Parkinson's Disease: Towards Mechanism-based Protocols

**Karim Fifel**[1,2,*] and **Aleksandar Videnovic**[3]

[1]Department of Molecular Cell Biology, Neurophysiology unit, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands [2]International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan [3]Movement Disorders Unit and Division of Sleep Medicine, Massachusetts General Hospital, Harvard Medical School, 165 Cambridge Street, Suite 600, Boston, MA 02446, Boston, Massachusetts, USA

## Abstract

A growing body of work is investigating the safety and efficacy of light in Parkinson's disease (PD). Here we discuss the potential of this emerging therapy to improve both motor and non-motor symptoms of PD. We also highlight directions for future basic, translational and clinical research that is critical for the development of mechanism-based protocols of light therapy in PD.

### Keywords

Chronotherapy; Non-motor symptoms; Bright light

## Main text

### Parkinson's disease and the rational of light therapy

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder. PD is diagnosed primarily by progressive and age-dependent deterioration of motor functions (i.e. bradykinesia, resting tremor, muscular rigidity and postural instability) [1]. Despite the primacy of this motor dysfunction in the clinical diagnosis of PD, patients with PD display also a wide range of non-motor symptoms (NMS) including sleep disturbances, cognitive deficits, sensory impairments, as well as psychiatric problems such as depression, anxiety and psychosis [1]. In fact. at advanced stage of the disease, NMS tend to dominate the clinical picture of PD and become the main determinants of the overall quality of life of PD

*Correspondence: fifel-k@hotmail.com (K. Fifel).
ORCID for Karim FIFEL: 0000-0001-6259-9336.

**Conflict of interests**

The authors declare no conflict of interests.

patients and decisions on their institutionalization [1]. Currently, therapies that effectively target NMS are lacking, and are therefore the second key unmet clinical need in addition to disease-modifying treatments [1]. These challenges are in stark contrast to the highly efficacious therapies currently available for motor aspects of the disease [1]. In view of this, growing interest is currently underway in the development of alternative treatment modalities for PD. Light therapy is one of these novel therapies [2–6]. The rationale of introducing light therapy to PD clinic resides in the well-documented therapeutic effect of bright light in other neurological and neuropsychiatric disorders [7], some of which co-exist in PD patients [1]. Here, we briefly summarise the results of the early studies that assessed the efficacy and safety of light therapy in PD, and discuss caveats, which future clinical and fundamental research efforts need to address. We also highlight the potential of these fundamental insights in helping the development of more efficacious and mechanism-based protocols of light therapy in PD.

## Therapeutic effects of light in PD

As a salient alternating environmental cue, light acts as one of the most powerful signal that influences our behaviour and health [7]. As such, over the last three decades, exposure to bright light has been used as a therapy to treat several disorders including mood disorders, cognitive disabilities, circadian misalignment, and alterations of sleep/wake behaviour [7]. Building on this experience, bright light therapy (BLT) has been recently introduced to PD with the perspective of improving the quality of life of PD patients. So far only four studies have assessed the efficacy and safety of BLT in PD patients [2–5]. Bright light pulses of intensities and durations ranging from 1.000 to 10.000 lux and 30min to 1.5h respectively were used daily either in the morning (1h after awakening [3]) or in the evening (1h before bedtime [2,4]) or twice daily [5] over varying periods, from one week to several months [2–5]. Efficacy of BLT was assessed using both routine clinical examination of PD patients over time and several validated instruments and questionnaires that evaluate both motor and NMS in PD patients. Taken together, these studies have demonstrated that BLT significantly improves motor dysfunction including bradykinesia, rigidity, tremor, nocturnal movements, dyskinesia and postural imbalance [2–4]. Improvements in motor functions were also captured with actigraphy, an objective measurement of overall physical activity in the most recent study [5]. Like in other forms of depression [7], bright light had anti-depressant and anti-anxious effects in PD patients. Several alterations of sleep behaviour were improved. These included insomnia, excessive daytime sleepiness and the overall fragmentation of sleep/wake cycle [3–5]. The rate of improvement of these symptoms was variable; both anxiety and insomnia improved quickly within days while motor functions improved slowly over months to years [2–5]. Near-infrared light (NIr; 670nm) therapy has also been tested in the context of PD. Although still in its pre-clinical stage, when applied intracranially just above the midbrain, NIr light reduced clinical signs and offered neuroprotections against MPTP intoxication in a non-human primate model of PD [13]. In summary, these results suggest that light has a substantial therapeutic potential for both motor and NMS of PD. However, the field is still in its infancy and further investigations are needed. For example, in many ways, current understanding of both the mechanisms of light therapy and PD pathology are not incorporated in the design of light therapy protocols. In the next section,

we highlight these shortcomings and provide directions for future research that might improve the benefits that light therapy may have for the PD population.

## Towards mechanism-based bright light therapy for PD

Since light exerts its effects primarily through the eyes, the efficacy of BLT will depend on the functional capacity of eyes. The non-visual effects of light are mediated by intrinsically photosensitive melanopsin-containing retinal ganglia cells (mRGCs) [8]. Although constituting a small subset (1–2%) of visual retinal ganglion cells, these cells are at the origin of the retinohypothalamic tract through which they project to several subcortical areas [8]. Several studies have described retinal neuropathology in PD including dopamine depletion and neurodegeneration affecting RGCs and optic nerves [9]. However, whether mRGCs are affected in PD is currently unknown. Interestingly, a recent study using chemogenetic activation of mRGCs in dark-housed mice, which simulates the excitatory effects of bright light, has indicated that the non-visual effects of light are selectively mediated by mRGCs [8]. Circadian phase resetting, mood and vigilance state modulation are among these light modulated physiological effects [8,9]. In line with the anatomy of mRGCs, the study also showed that mRGCs mediate the activation of several brain structures involved in the regulation of widespread aspects of physiology and behaviour that are dysfunctional in PD [8]. Elucidation of the anatomical and functional integrity of mRGCs in PD will facilitate our understanding of the afferent pathways of light signalling in PD. Furthermore, full examination of the temporal dimension — and the extend — of dysfunction of the different projections of mRGCs over disease progression will be crucial in adjusting light parameters over time to maintain maximum therapeutic benefit.

The efficacy of LT depends also on the timing, intensity, duration and wavelength of the received light [7]. They collectively represent “the dose” of LT that should be appropriately prescribed to patients. For PD patients, the optimal values for each of these dosing parameters is unknown. Studies conducted so far used intensities from 1.000 to 10.000 lux and durations of 30min to 1.5h. Only polychromatic white light was used and the timing of administration was not based on the chronotype of patients [2–5]. This last point is pertinent given that one mechanism by which light exerts its therapeutic effect is by reinforcing circadian patterning of the internal physiology and its appropriate entrainment to the external world [7]. Alterations of the circadian system and their heterogeneity in PD patients make the calibration of light parameters challenging [9]. Further complicating the matter is poor understanding of the pathophysiology of the neuronal circuitry underlying circadian rhythms in PD. Such fundamental knowledge is essential in order to design protocols of light therapy that should also incorporate mechanistic understanding of PD-specific neurodegeneration. To gain such knowledge, future research should take advantage of the rapidly evolving technologies that allow temporal and genetically-specific manipulation of neuronal networks in animal models of PD as well as in vivo imaging of widespread aberrant neuronal networks. In clinical settings, large scale multi-center trials with multiple treatment arms are needed.

The synchronization of circadian rhythms is not the only mechanism of LT. In patients suffering from seasonal depression, it has been shown that the correlation between the

magnitude of circadian consolidation and the anti-depressive effect of light accounts for only 14% of the variance, suggesting that the main action of LT is mediated by non-circadian mechanisms [7]. Currently, the mechanisms of light therapy in PD are unknown. The results of an ongoing double-blind clinical trial are expected to shed some light on the relative contribution of circadian-mediated vs non-circadian processes to the therapeutic effects of light in PD patients [6]. However, two of the four trials conducted so far have shown that PD patients receiving supplemental light are able to reduce the amount of L-DOPA to 50% while maintaining therapeutic efficacy, compared to a 17% increase in L-DOPA requirements in untreated patients [2,4]. These observations suggest that BLT could mediate its therapeutic effects by enhancing dopamine (DA) neurotransmission, although more direct evidence would be needed to support this possible link. Consistently with this hypothesis, electrophysiological studies in rodents showed that DA neurons respond to light [10]. Additional research on how light influences DA signalling – including the possibility of potential interference with the progressive DA neurodegeneration – will be crucial in advising, for instance, on the time (early or late) and the nature (acute or chronic) of interventions with light in PD. This possibility is particularly pertinent given the non-invasive nature of BLT and the emerging strategies used to identify people at high risk of developing PD [1,7].

Another potential, yet not systematically studied, mechanism of BLT in PD is the neuroplastic remodelling of brain circuits. Neuroplastic changes, defined as adjustment through neuronal re-organisation, have been shown in the DA system following chronic regimes of exposure to [11] or deprivation from light [12]. In principle, these plastic changes could operate in other brain structures including all targets of mRGCs. Future research on the impact of light on DA and non-DA circuits in PD holds the promise of extending the scope of light therapy to alleviate several NMS of PD such as cognitive dysfunctions.

## Concluding remarks

For over 30 years, LT has been used as adjuvant therapy in several medical conditions. In addition to its well-established therapeutic effects, this intervention has an unusually benign side-effect profile. Given the paucity of efficacious treatments for NMS in PD, the safety and therapeutic benefits of BLT is currently investigated in the PD population. Although the results of several initial trials are promising, we argue that future trials should leverage knowledge about the mechanism of action of light in the context of PD-specific neurodegenerative process. At the fundamental level, future research should aim at investigating underlying mechanisms of BLT in both PD patients and animal models of PD. The implementation of these mechanistic insights in the design of BLT protocols in clinical setting is expected to yield better outcomes in improving the quality of life by either alleviating symptoms or perhaps by modulating the disease biology and slowing down disease progression.

## Acknowledgments

K.F. gratefully acknowledges support during the writing of this article from the European Community's Marie Sklodowska-Curie IEF Programme under contract 655135, "The Role of Dopamine in the Regulation of Sleep and

Circadian Rhythms (CIRCADOPAMINE).” A.V. received research grant support from the National Institutes of Health (R01NS099055).

## References

1. Schapira AHV, et al. Non-motor features of Parkinson disease. Nat Rev Neurosci. 2017; 18:435–450. [PubMed: 28592904]
2. Willis GL, Turner EJ. Primary and secondary features of Parkinson’s disease improve with strategic exposure to bright light: a case series study. Chronobiol Int. 2007; 24:521–537. [PubMed: 17612949]
3. Paus S, et al. Bright light therapy in PD: a pilot study. Mov Disord. 2007; 22:1495–1498. [PubMed: 17516492]
4. Willis GL, et al. A historical justification for and retrospective analysis of the systematic application of light therapy in Parkinson’s disease. Rev Neurosci. 2012; 23:199–226. [PubMed: 22499678]
5. Videnovic A, et al. Timed Light Therapy for Sleep and Daytime Sleepiness Associated With Parkinson Disease: A Randomized Clinical Trial. JAMA Neurol. 2017; 74:411–418. [PubMed: 28241159]
6. Rutten S, et al. A double-blind randomized controlled trial to assess the effect of bright light therapy on depression in patients with Parkinson’s disease. BMC Psychiatry. 2016; 16:355. [PubMed: 27769202]
7. Wirz-Justice, A., et al. Chronotherapeutics for affective disorders: a clinician’s manual for light and wake therapy. Basel: Karger; 2013.
8. Milosavljevic N, et al. Chemogenetic Activation of Melanopsin Retinal Ganglion Cells Induces Signatures of Arousal and/or Anxiety in Mice. Curr Biol. 2016; 26:2358–2363. [PubMed: 27426512]
9. Fifel K. Alterations of the circadian system in Parkinson’s disease patients. Mov Disord. 2017; 32:682–692. [PubMed: 27859638]
10. Dommett E, et al. How visual stimuli activate dopaminergic neurons at short latency. Science. 2005; 307:1476–1479. [PubMed: 15746431]
11. Tsai HY, et al. Sunshine-exposure variation of human striatal dopamine D(2)/D(3) receptor availability in healthy volunteers. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35:107–110. [PubMed: 20875835]
12. Gonzalez MM, Aston-Jones G. Light deprivation damages monoamine neurons and produces a depressive behavioral phenotype in rats. Proc Natl Acad Sci U S A. 2008; 105:4898–4903. [PubMed: 18347342]
13. Moro C, et al. Effects of a higher dose of near-infrared light on clinical signs and neuroprotection in a monkey model of Parkinson’s disease. Brain Res. 2016; 1648(Part A):19–26. [PubMed: 27396907]