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Review

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Review: Circadian disruption, chronotherapy, and deep brain stimulation (DBS) in Parkinson's disease (PD)

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Disruption of sleep and circadian rhythms is a pervasive symptom of Parkinson's disease with a severe impact on quality of life. We review existing therapies for Parkinson's disease and circadian disruption (chronotherapies), and we argue that modern deep brain stimulation technology presents a novel treatment pathway for these symptoms—it has the potential to continuously monitor and/or adaptively modulate sleep and circadian rhythms.

Parkinson's disease (PD) is the world's second most common neurodegenerative disorder, with an estimated global prevalence of 11.8 million in 2021, and is the fastest growing neurological disorder causing disability and death[1,2]. It is often termed a movement disorder due to prominent motor symptoms like rest tremor, muscle rigidity and bradykinesia (slowness of movement)[3–5]. However, PD also leads to significant non-motor symptoms including sleep disturbances, excessive daytime sleepiness (EDS), cognitive impairment, and mood disorders[3,5]. Almost all of these non-motor symptoms may be linked together by one common factor—the disruption of *circadian rhythms*[3,6,7]. This issue is not currently addressed by conventional PD treatments (e.g. via dopaminergic medication) and presents a potential new avenue for therapy. A new class of *chronotherapies* seeks to address circadian disruption directly through targeted scheduling of light exposure, behaviours, or drug intake. Among these approaches, deep brain stimulation (DBS) technology may be particularly suitable as a candidate platform for the delivery of more advanced chronotherapy, owing to its potential to support continuous monitoring of the brain and the circadian system, bespoke temporal patterning of stimulation, and algorithmic therapy adjustments. We explore how DBS systems might track and modulate circadian rhythms (considering available biomarkers, anatomical targets and algorithmic approaches), and sketch out a road map towards the clinical investigation and translation of such bioelectronic chronotherapies for PD.

Background

Circadian rhythms

Circadian rhythms are physiological and behavioural variations with a periodicity of approximately 24-h, which persist in a constant environment[8]. They are involved in almost every bodily function and enable the human body to prepare for predictable changes in its environment (e.g. light/dark)[9]. Prominent examples of circadian rhythms are the sleep-wake cycle, the secretion rhythms of hormones (e.g. melatonin), and the daily variation of core body temperature (CBT)[9]. They are generated endogenously in tissues throughout the body and brain, via what are known as transcriptional-translational feedback loops (TTFLs)—molecular feedback loops that involve the transcription/translation of specific genes (known as clock genes) with a near 24-h periodicity[10]. Key clock genes include *CLOCK*, *BMAL1*, *PER1* and *PER2*, *CRY1* and *CRY2*[11]. These TTFLs around the body are driven, synchronised, and coordinated by the suprachiasmatic nucleus (SCN), the central circadian pacemaker located in the hypothalamus of the brain[10]. The SCN entrains (synchronises) to the external environment by receiving inputs that contain information on environmental time-cues known as zeitgebers (German for "time giver")[9]. The strongest zeitgeber is light (received via direct connections from intrinsically photosensitive retinal ganglion cells (ipRGCs) in the retina), but non-photic zeitgebers such as physical activity, and dietary schedules, play an additional role in synchronising the SCN, and thus peripheral TTFLs, to the environment (Fig. 1)[12].

It should be noted that many overt 24-h rhythms are generated by a combination of circadian rhythmicity and exogenous or behavioural factors.

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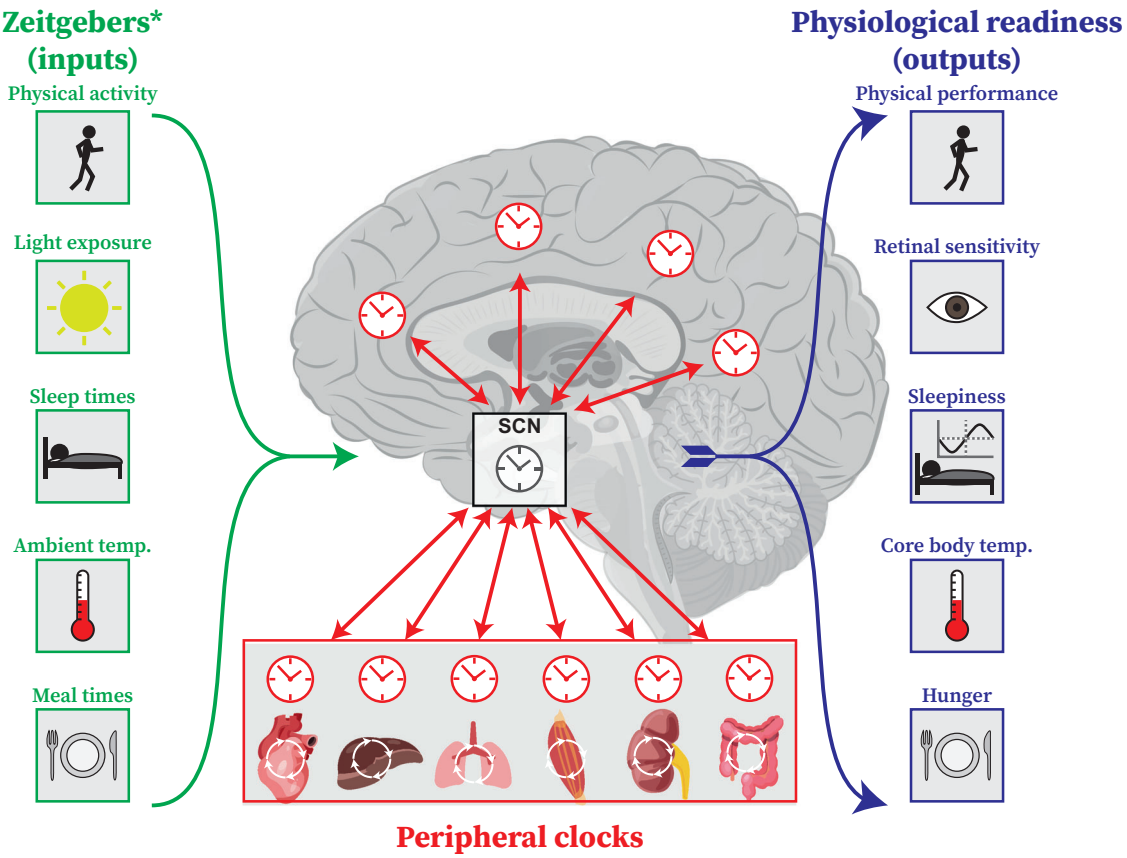


Fig. 1 | A high-level diagram of the circadian system with examples of established and putative zeitgebers feeding into the circadian system, and examples of impacts on physiological readiness. The illustration of the brain is adapted from Injurymap at https://www.injurymap.com/free-human-anatomy-illustrationsand all other organ illustrations are adapted from drawings by John Chilton on SciDraw.io.

For example, the amplitude of the CBT rhythm is large when sleep occurs at night, but smaller when participants stay awake during the night, and even smaller when sleep occurs during the day[13]. As sleep lowers body temperature[13], the overt rhythm observed is generated by a combination of circadian rhythmicity and behavioural effects (e.g. sleep). Thus, the disruption of rhythmicity may be related to the disruption of circadian mechanisms or other factors. Throughout this review, we will use the term "circadian rhythms" to refer to the total observed diurnal rhythms of a physiological/behavioural measure, and "disruption" to refer to any disturbance of these rhythms[14].

Circadian disruption in PD

Given the critical role of circadian rhythms in many key physiological processes and coordinating them[11], it follows that their disruption can have a detrimental impact on sleep[15], metabolism[16], cognition[7], mood[16], mortality[7], and overall quality of life[7,16]. Sleep disorders are common in PD and include insomnia, excessive daytime sleepiness (EDS), restless leg syndrome (RLS), and REM sleep behaviour disorder (RBD)[17]. These disorders can be viewed as a disruption of circadian organisation, with some of them directly related to the circadian system, while others may be related to sleep regulatory mechanisms downstream of the circadian timing system, such as RBD. RBD presents as a loss of normal muscle atonia/paralysis and patients acting out their dreams during REM sleep[17]. While REM sleep propensity is under control of the circadian pacemaker in the SCN[18,19], RBD itself is related to changes in the subcoeruleus nucleus or sublaterodorsal nucleus[20]. RBD is very common among PD patients (up to 50%) and often precedes the clinical manifestation of PD motor symptoms by several years[21,22]. Motor activity (and motor symptom severity), CBT, heart rate, retinal contrast sensitivity, and hormone (melatonin and cortisol) secretion also show abnormal diurnal fluctuations in PD patients[3,7]. Specifically, many circadian rhythms (including the melatonin rhythm) exhibit diminished amplitudes (and sometimes even complete loss of 24-h variation), with little to no changes in the timing of these rhythms (phase) or their period[3,7]. These observations suggest that while expression (amplitude) of the circadian rhythms may be reduced in PD, core aspects of rhythm generation may be conserved. The reduced amplitude of circadian rhythmicity may be related to a disruption of various outputs of circadian (SCN or peripheral) oscillators.

Anatomical origins of circadian disruption in PD

PD develops as a consequence of the misfolded protein aggregates (primarily composed of the protein α-synuclein) building up in formations known as inclusion bodies that invade neural cells and eventually cause cell death[23]. Inclusion bodies accumulating in areas like the substantia nigra (SN), which regulate motor function via the release of the neurotransmitter dopamine (DA), are the primary cause of PD's cardinal motor symptoms which include rest tremor, muscle rigidity and bradykinesia (slowness of movement)[23]. On the other hand, understandings of anatomical mechanisms underlying circadian disruption in PD are less established, though many studies suggest they may be complex and multifactorial. Understanding these mechanisms is key to developing treatments which can address these issues.

Firstly, PD seems to affect the SCN directly. One study observed inclusion bodies in the SCN of 9 out of 13 PD patients examined post-mortem[24]. These findings are supported by two studies using transgenic α-synuclein-overexpressing (ASO) mice, which both found significant α-synuclein accumulation in the SCN[25,26]. One of the studies observed an accompanying impairment in the photic entrainment of locomotor

rhythms, but no significant changes in locomotor rhythms under constant darkness[26]. The other study, on the other hand, found no significant impairments in photic entrainment and no changes in SCN PER2 expression, but observed altered sleep-wake rhythms and fragmented locomotor rhythms with reduced amplitude under a 24-h artificial lighting regime simulating the day-night cycle (skeleton photoperiod)[25]. Both studies showed no changes in the period of locomotor rhythms[25,26]. In other animal models of PD which affect circadian rhythms (MPTP and rotenone), mRNA expression rhythms of multiple clock genes (*Per1, Per2, Cry1, Cry2, Bmal1*) in the SCN were significantly altered[27,28]. While these findings are sparse and do not yet make clear how, exactly, circadian rhythms are affected by degeneration of the SCN, they do seem to suggest some level of SCN degeneration in (a subset of) PD patients, and potential effects on the SCN's molecular clockwork, regulation of behaviour, and/or entrainment. Further research is required to clarify the involvement of SCN degeneration in PD's circadian disruption.

Efferent pathways from the SCN could also be disrupted. In ASO mice, reduced daytime SCN neuronal firing rates were observed concurrently with fragmented locomotor rhythms[25]. These findings were also concurrent with observations of unaffected locomotor rhythm period, photic entrainment, and SCN PER2 expression, which suggest that the underlying pacemaker and entrainment systems are unaffected in ASO mice. Therefore, the authors conclude that the reduced firing rates indicate weakened outputs from the SCN, which may be the primary cause for the fragmented locomotor rhythms. While this inference is drawn from results of a single animal experiment, it is consistent with PD showing a widespread accumulation of inclusion bodies across the brain, which may disrupt the many complex signalling pathways that allow the SCN to communicate with peripheral clocks[7].

Afferent pathways into the SCN also show disruption. In particular, impairment of photic entrainment pathways is the mechanism currently supported by the strongest evidence. Compared to age-matched controls, PD patients show thinner inner retinal layers[29], reduced density of ipRGCs[30], and reduced complexity of ipRGC dendrites[30], likely related to the impaired contrast sensitivity and pupillary light reflexes commonly seen in PD patients[3]. As a consequence, photic entrainment may be impaired. The depletion of DA in PD may contribute to these phenomena as the mRNA expression of melanopsin (a key light-sensitive protein located in ipRGCs enabling photic entrainment) is regulated by DA[31]. In addition to affecting photic entrainment, animal studies have suggested that DA also regulates sensory functions of the olfactory bulb (OB)[32] and may contribute to regulating the endogenous diurnal variations[33] in its responsivity to odours[34], neuronal firing rates[35], and *PER1* expression levels[35]. Thus, DA depletion in PD can impair olfactory function[36] and thus entrainment to odorous zeitgebers[37], as well as disrupt the OB's endogenous rhythms, consequently compromising its regulation of rhythms in other brain structures such as the piriform cortex[34]. Animal studies have shown that DA depletion is also likely to affect clock gene expression in other parts of the brain like the striatum[38,39], which has shown connections to the SCN in mice[40].

Finally, significantly reduced clock gene expression (*BMAL1, CLOCK, CRY1, PER1, PER2*) has been observed in peripheral blood cells[41]. Since this change is observed even in early stages of PD[41], it may be related to observations of α-synuclein pathology in the gastrointestinal tract, early in PD development[42].

Motivation

Many recent studies have hypothesised that these circadian disruptions may have a bidirectional relationship with PD—not only does PD cause circadian disruption, but circadian disruption can also exacerbate PD progression via numerous mechanisms[3,7]. Firstly, symptomatic associations have been observed between disrupted sleep and neurodegeneration - disrupted sleep not only further disrupts circadian rhythms, but also shows associations with increased neuroinflammation[43,44] and pathological build-up of α-synuclein[43,44] in both human[43] and animal[44] studies. Similarly, mice with misaligned circadian rhythms (forced desynchrony or altered light-dark cycles) show elevated inflammatory markers in blood[45], and reduced dendritic length and complexity in prelimbic prefrontal cortex neurons[46]. Secondly, mechanistic hypotheses have been posited that because the hormone melatonin has shown antioxidant and anti-inflammatory effects in many animal studies[47], its disrupted secretion rhythms in PD patients may weaken its neuroprotective effects, accelerating neurodegeneration[3]. Lastly, another mechanistic hypothesis can be posited that the aforementioned damage to ipRGCs (and the resulting dysfunction of retinal contrast sensitivity) may hinder the SCN's ability to receive photic zeitgebers, exacerbating circadian disruptions[3]. This hypothesised bidirectional relationship between circadian disruption and PD could create a positive feedback loop that brings about rapid neurodegeneration[7]. The evidence and hypotheses presented above further highlight the importance of targeting circadian disruption in PD treatment: addressing circadian disruption has the potential to combat these positive feedback loops, as well as alleviate numerous PD symptoms and improve overall quality of life for patients. Nonetheless, additional detailed longitudinal studies are required to definitively establish the existence of such a bidirectional relationship and make the case for any truly disease-modifying effects of treatments addressing circadian disruption. Furthering this research may also be beneficial for the treatment of other neurodegenerative diseases such as Huntington's disease (HD), Alzheimer's disease (AD), and frontotemporal dementia, all of which exhibit circadian disruption, though the type of circadian disruption may differ[7].

Impact of existing treatments for PD and circadian disruption

Levodopa

The first line of treatment for PD typically involves the administration of L-3,4-Dihydroxyphenylalanine, a DA precursor, also known as levodopa or L-dopa[48]. While L-dopa very effectively alleviates motor symptoms for most PD patients[49], its impact on circadian rhythms is currently unclear.

Some results in Parkinsonian mice (6-OHDA model) have suggested that L-dopa administration has the ability to partially restore blood pressure, heart rate, and temperature variation[50,50]. Meanwhile, other results have suggested that L-dopa has no significant effects on temperature and physical activity rhythms (in the same animal model)[50]. L-dopa is also known to advance the melatonin rhythm, with one study finding that the delayed phase/timing of the melatonin rhythm in 6-OHDA-lesioned rats could be restored to that of control subjects by L-dopa treatment, via a phase advance[51]. However, L-dopa was also found to reduce overall melatonin levels below that of control subjects, and increase overall cortisol levels beyond that of control subjects[51]. Furthermore, in the case of cortisol, the peak of secretion was unchanged by 6-OHDA, but delayed by 6 h on L-dopa[51]. In combination with the increase in overall levels, L-dopa ultimately worsened the divergence of cortisol rhythms from the control group[51].

Results have also been mixed regarding the effects of L-dopa on sleep in PD patients. While studies reported an improvement in insomnia, sleep-disordered breathing, and RLS on L-dopa, EDS and RBD generally worsened[52]. Most significantly though, one study found that L-dopa substantially increased total melatonin secretion and delayed sleep onset relative to the time at which melatonin secretion began (also known as dim light melatonin onset or DLMO)[53]. This result was not only due to the aforementioned phase advance in the melatonin secretion, but also due to a delay in sleep onset (with respect to clock time)[53]. This increase in the phase angle between sleep onset and DLMO indicates an altered alignment between circadian and sleep-wake rhythms, which may contribute to the various sleep disturbances observed among PD patients. Strikingly, the melatonin secretion level and time difference between sleep onset and DLMO was not significantly different between control and unmedicated PD groups, suggesting that some sleep-circadian disruptions may not result from PD, but from L-dopa[53,54].

Animal studies also assessed the expression of key clock genes and their proteins involved in TTFLs. In the striatum, the brain region most affected by DA depletion in the mouse models used, one study observed the partial

restoration of expression level and rhythmicity of the clock proteins BMAL1 and CLOCK following administration of L-dopa. However, another study observed that rhythms of transcripts (RNA) of the clock genes *BMAL1* and *PER2* in the SCN could not be restored by L-dopa once abolished by the Parkinsonian model (6-OHDA). Their expression levels remained reduced[51]. The study also found that, in the striatum, phases of the transcripts of four clock genes *BMAL1*, *RORα*, *CLOCK*, and *PER2* were significantly delayed on L-dopa, despite the Parkinsonian model itself having no effect on phases of these transcript rhythms. The overall result was that these four clock gene transcript rhythms were significantly altered by L-dopa beyond the Parkinsonian model[51].

Deep brain stimulation (DBS)

When patients no longer respond well to L-dopa, or they experience disabling tremor, deep brain stimulation (DBS) is a treatment option[55]. In DBS, electrodes are implanted deep within the brain, and electrical pulses, generated by an implantable pulse generator (IPG), are applied to great therapeutic effect[56]—many patients report "regaining independence and self-confidence with DBS-[49]. In PD, electrodes are commonly implanted in the subthalamic nucleus (STN) or globus pallidus (GP)[56,57], or in rare cases, the pedunculopontine nucleus (PPN) if patients experience severe freezing of gait (FoG)[58]. Stimulation parameters (amplitude, frequency, pulse-width) are typically programmed while patients are in the clinic to optimise motor symptom alleviation, and will remain unchanged for long periods (weeks/months)[59]. This approach is commonly known as conventional, 'open-loop,' or continuous DBS. Recently, alternative open-loop stimulation patterns have been explored to varying degrees of success, including cycling DBS (periodic alternation between stimulation ON and OFF), and ramped frequency stimulation (frequency is periodically increased or decreased between two extremes)[59]. Simple closed-loop, adaptive DBS (aDBS) paradigms have also been studied in recent years for PD, where measured biomarkers for the severity of motor symptoms are used to modulate the stimulation amplitude[60–62]. Several of these aDBS approaches have successfully shown greater suppression (reduced severity and duration) of motor symptoms without increased dyskinesia[61–63], improvements in overall well-being[61,62], and between 38-73% savings in power consumption compared to conventional DBS, though some studies have not been able to show significant improvements[59]. Outcomes depend greatly on implementation details[59].

Several studies have investigated the effect of DBS on sleep. Human studies have shown that conventional STN-DBS may significantly improve insomnia, daytime sleepiness, and overall sleep quality[17,64]. However, RBD, RLS, and nocturia (repeated sleep disruption due to the need to urinate) do not seem to show measurable improvements following conventional STN-DBS[64]. DBS in alternative implantation sites like the pedunculopontine nucleus (PPN) shows even more promise for modulating sleep-wake cycles. Some clinical studies have found that PPN-DBS administered during sleep significantly increased total REM duration throughout the night[65,66]. One clinical study, administering PPN-DBS while patients were awake in the day, found that high-frequency PPN-DBS (~80 Hz) can have a sedating effect, while low-frequency PPN-DBS (10-25 Hz) can heighten alertness[58]. These findings may be expected in view of the PPN's role in the regulation of sleep (particularly REM sleep)[67–69]. A more recent trial further found that, during PPN-DBS, cortical beta (13–30 Hz) and gamma (>30 Hz) waveforms are significantly phase-locked to 40 Hz (the PPN stimulation frequency), and to harmonics at half of that frequency[70]. While these effects of STN- and PPN-DBS on sleep could be, in part, mediated by mechanisms involving the circadian system, they could also be due to a variety of other mechanisms, including but not limited to improvements in nocturnal motor symptoms, reduced L-dopa dosages on DBS (which would reduce aforementioned side-effects on DLMO), and/or improvements in mood[71]. Thus, it should be noted that effects of DBS on sleep do not necessarily indicate a modulatory effect on the circadian system.

There are only two studies exploring the effects of DBS, specifically, on circadian rhythms. One human study corroborated previous findings on improvements in sleep, but also found that there were no changes to clock gene expression in peripheral blood after continuous STN-DBS[72]. On the other hand, a mouse study showed that stimulation of the pontine nuclei (including the PPN) can shift the phase of activity rhythms and augment the level of neurotransmitters acetylcholine (ACh) and/or glutamate (Glu) in the SCN[73]. These effects depended on stimulation parameters (amplitude, frequency, pulse-width) and where in the circadian cycle stimulation was applied[73].

Chronotherapy

Given the severe sleep and circadian disruption in PD and their hypothesised links to symptomatology and disease progression, there have been a number of efforts to target circadian disruption in PD patients directly. Many of these efforts fall under the label of chronotherapy, which broadly refers to the practice of accounting for circadian rhythms in the treatment of a disease[74]. Many chronotherapies (particularly for circadian disruption in PD) involve the regulation of a zeitgeber in order to exert a positive synchronising pressure on the circadian system and are covered in the following sections.

Bright light therapy (BLT). Light is well-known as the zeitgeber with the strongest synchronising effects on the circadian system. This effect is mediated by the direct pathway between the retina and the SCN: when photons are absorbed by melanopsin in ipRGCs and opsins in other photoreceptors located in the retina, a signal is sent directly to the SCN via the retinohypothalamic tract, one of the main afferent pathways to the SCN[3,7]. This pathway can be utilised very effectively to influence the SCN (and thus the wider circadian system) to restore regular/healthy circadian rhythms and alleviate some circadian disruptions. In bright light therapy (BLT), patients experiencing circadian disruption are exposed to bright light (1000–10,000 lx) for 0.5–1.5 h, typically 1 h before bedtime and/or after awakening (often depending on whether the patient experiences sleep maintenance insomnia or sleep onset insomnia respectively). Sometimes the light exposure is combined with other treatments such as cognitive behavioural therapy and/or drugs (e.g. doxepin)[75]. Most trials administering BLT to PD patients administered light before sleep[75], demonstrating an improvement in insomnia[76,77], subjective sleep quality[78], sleep fragmentation[77], RBD[77], and depression[76,78], as well as bradykinesia[78], and rigidity[78]. Studies applying brighter light (4000–6000 lx) an hour before bedtime additionally showed improvement in tremor, nocturnal movement, dyskinesia, balance, and anxiety[75,76]. A preliminary study ($n = 18$) administering light after awakening in the morning also showed an improvement in depression and a slight reduction in tremor, but the study's short duration limits the conclusions that can be drawn[79]. Another small study ($n = 16$) applying 10,000 lx, twice daily (morning and afternoon), showed significant improvements in insomnia, EDS, sleep consolidation, motor symptoms, and increased physical activity. Remarkably, improvements in EDS persisted for 2 weeks after stopping BLT[80]. These beneficial effects of BLT on both motor and non-motor symptoms (including those not directly related to circadian disruption like depression and anxiety) seem to further suggest a close link between PD's pathology and circadian disruption, showing promise for chronotherapy as a treatment for not just PD's immediate symptoms, but also for its disease progression.

In early studies of BLT as a treatment for seasonal affective disorder (a disorder also linked to circadian disruption[81,82]), BLT's benefits were assumed to be mediated purely by instantaneous phase shifting of circadian oscillators by light[83]. This inference was primarily based on early experiments in nocturnal animals[84,85], but also in humans[86,87], showing that light exposure can induce phase shifts of different magnitudes and directions, depending on the circadian time of light exposure—morning light phase advances rhythms and late evening light induced delays[88]. Thus, BLT's primary mechanism of action in PD was hypothesised to be via resynchronising the timing of the SCN and its outputs to the 24-h day via phase shifts[78,89]. However, studies in other patient populations have shown benefits

of BLT, such as a reduction in the fragmentation of the sleep-wake cycle, even though phase shifts were not observed[90]. In other studies, reduced sleep-wake fragmentation was observed even when light exposure occurred at a time not expected to cause a phase shift[91]. These findings suggest other mechanisms may also be at play and are increasingly studied in the circadian field. One of these possible mechanisms may be mediated by light's modulation of circadian amplitudes[92]. Clinical studies have shown that light exposure, depending on circadian time of application, can enhance or diminish amplitudes of CBT[93] and melatonin rhythms[94]. Recent animal experiments have also shown that light can significantly increase spontaneous firing rates in the SCN, alongside enhancing amplitude and robustness of locomotor rhythms[95]. Such effects may reverse the blunted circadian amplitudes often seen in PD patients[7]. Another mechanism by which BLT may exert positive effects relates to total light exposure throughout the day. Increasing the total amount of light exposure during wakefulness has been shown in healthy humans to increase the total duration and intensity of NREM[96,97] (indicated by increased total EEG delta power (0.5–4 Hz)[98]), accelerate dissipation of homoeostatic sleep pressure[96,97] (indicated by faster dissipation of delta power[99]), reduced wake after sleep onset, and improved subjective sleep quality[96]. The positive effects of BLT may also be mediated by light's alerting effect, which has been demonstrated by numerous human studies using different measures of alertness[100,101]. Finally, mechanisms unrelated to circadian rhythms could also be at play such as light's effects on mood[102], and/or modulation of DA[75]. One study observed higher striatal DA activity in healthy individuals who were exposed to more sunlight[103], consistent with findings that human striatal DA activity is up-regulated during the summer[104]. Studies in a diurnal rodent further found that different light exposure patterns could affect day-night DA neurotransmission rhythms in the nucleus accumbens and dorsal striatum[105]. These findings may explain the BLT studies showing improvements in PD motor symptoms and reduced dependence on L-dopa[78]. Whatever BLT's mechanisms of action, its efficacy further supports the evidence that impaired photic input to the brain is a significant contribution to the aetiology underlying circadian disruption in PD.

Currently, information is lacking on the optimal dosage, timing, frequency, and intensity of light for this therapy[75]. Another significant limitation is that an individual's circadian phase (timing of the internal circadian system relative to local clock time) cannot easily be taken into account, since there are no accurate, non-invasive methods for measuring it. Circadian phase is likely to factor into how a patient responds to BLT. In addition, effects of light are often implied to primarily involve changes in timing or phase of circadian rhythms, and effects of light on amplitude are not considered[95]. Until all aspects of BLT are optimised, the limits of what BLT can achieve will remain unknown. Further investigations into the mechanisms of BLT (i.e. whether it is related to effects of light on circadian phase, amplitude, or other 'non-circadian-phase' effects of light) will also be important in the future[75]. However, overall, BLT shows considerable promise at this early stage of development, seemingly improving many motor and non-motor symptoms with minimal and transient side-effects (headache, hypomania, agitation, sleepiness, fine tremor)[75], while also being non-invasive, simple to implement, and cost-effective.

Sleep scheduling. The two-process model of sleep regulation posits that propensity for sleep ("sleep drive") is made up of two components: a homeostatic, or sleep pressure component which builds up during wake and decreases exponentially during sleep, and a circadian component which varies periodically, such that sleep propensity is high during the night and low during the day and early evening[18,106]. The circadian component is driven by the SCN, which communicates with various sleep-wake centres in the brain[107]. This relationship has also been observed in the other direction as the SCN also receives information about sleep/vigilance state. In rodents, sleep-state was shown to affect SCN neuronal activity/dynamics[108], sleep-wake rhythms affected the SCN's response to photic zeitgebers[109], and in humans, sleep restriction has been observed to affect peripheral clock gene expression (*PER1*, *PER2*, *Rev-Erbα*, *Rev-Erbβ*, *BMAL1*)[110]. Human studies have also suggested that sleep may act as a zeitgeber, albeit a weak one. Altering the sleep-wake cycle affects CBT and melatonin phases in blind patients[111] and shift workers[112], gradual shifts in sleep time can cause shifts in CBT and melatonin phases under continuous near-darkness conditions (<0.2 Lux)[113], sleep deprivation causes shifts in melatonin rhythms of healthy individuals[114], and entrainment to 24-h sleep-wake cycles is possible under dim-light settings[115]. However, it is difficult to completely remove the influence of light[116]. In many of these studies, manipulations of the sleep-wake cycle were confounded by changes in light exposure (e.g. when people close eyelids during sleep) and in the studies with blind patients[111] or patients under dark/dim-light settings[113–115], phase shifts observed were small. Thus, while sleep by itself may act as a zeitgeber, it is likely a weak one[113]. Nonetheless, since scheduling sleep also inevitably includes scheduling of other variables like light exposure, posture, and eating, it is, from a practical perspective, less relevant to this context whether it is sleep, per se, or environmental and behavioural changes associated with sleep that is the zeitgeber. In fact, scheduling sleep may be an effective way to regulate light exposure and induce circadian phase shifts as daytime naps in healthy individuals have been shown to phase delay or advance DLMO and other hormone rhythms (thyrotropin) depending on whether the nap was during the morning or evening respectively[117]. In other words, the effects of naps, which are equivalent to an absence of light input to the SCN, are opposite to those of light exposure at these times.

However, at present, there have not yet been any human studies exploring sleep scheduling as a chronotherapy. Some rodent studies have shown promise. In one study, the circadian rhythms in a murine Huntington's disease (HD) model (R6/2) were analysed[118]. The model caused the activity-rest rhythms of the mice to become progressively incoherent and irregular, leading eventually to a near-complete loss of defined rhythms. The SCN also showed reduced expression of mPER1 and mPER2 proteins and a significantly reduced peak of mProk2 expression, indicating impaired clock gene function. Some of these mice were then given the sedative Alprazolam (injection) every morning between 9:00 and 10:00 AM, the beginning of their sleeping periods (mice are typically nocturnal). The R6/2 mice given alprazolam daily showed improved cognitive performance on a two-choice visual discrimination task, greater rousability in the morning (pre-injection), improved overall health according to the SHIRPA test, and longer survival, all accompanied by improved clock gene expression that was previously impaired. Meanwhile, the wild type mice showed no significant changes on alprazolam. Although alprazolam's anti-anxiety effects could've contributed to these improvements, this possibility was ruled out as anti-anxiety effects were not observed in the R6/2 mice treated. Thus, the researchers concluded that the cognitive improvements must result from the pharmacological imposition of a regular sleep/wake cycle[118]. The same team verified these results 2 years later, observing cognitive improvement in R6/2 mice administered alprazolam and the stimulant modafinil to impose regular sleeping and waking times, respectively[119]. This study additionally found that using alprazolam and modafinil in combination improved cognitive performance better than when used individually, suggesting that it may also be important to impose both regular sleep and waking times[119]. Nonetheless, these results should be taken with caution as alprazolam and modafinil may have had additional effects which were not controlled[119]. While these studies show promise for scheduling sleep/wake as a chronotherapy in PD, much additional research is required to observe whether scheduled sleep/wake can also improve cognitive function in humans with PD, and whether any other tangible improvements in PD symptoms and/or circadian disruption are observed.

Meal scheduling. Many components of the human gastrointestinal (GI) tract and organs involved in digestion such as the liver and pancreas show circadian variation including DNA synthesis in the mucous membranes lining its insides, gastric acid production, appetite, and speed of digestion (gastric and colonic motility)[120]. The inverse has also been demonstrated -

meals have the capacity to affect the circadian system and act as a zeitgeber.

Animal models have shown that the intake of particular single nutrients and substances can impact the circadian system in various ways. Glucose solution administered to rodents via jugular catheter across 12 h (daytime) has been shown to phase advance *PER2* expression in the SCN and delay it in the liver[121]. Similarly, glucose solution administered orally to rodents enabled entrainment to delayed feeding times[122]. Amino acids (also administered to rodents via jugular catheter across 12 h) were shown to advance *PER2* phase in the SCN even more, but retain *PER2* phase in the liver[121]. High-salt diets increased rats' circadian blood pressure variation amplitudes, and reduced amplitudes of clock gene (*PER2*, *BMAL1*, *DBP*) expression rhythms in the heart, kidney, and liver[123]. Ethanol consumption led to alterations (lengthening or shortening) in the period of activity rhythms[124], impaired entrainment to photic zeitgebers[124], and reduced the amplitudes of *PER2* and *PER3* mRNA expression rhythms in the SCN[125]. Intracerebral injections of caffeine in Syrian Hamsters attenuated activity rhythm shifts by acting as an adenosine antagonist, which itself is hypothesised to reset circadian phases[126]. Thiamine (vitamin B1) deficiency leads to disrupted CBT rhythms[127] and reduced period in activity rhythms[128] in rats. Retinoic acid, a metabolite of vitamin A1, delays peripheral *PER2* expression in mice[129].

Feeding times also act as a significant zeitgeber in animals. When availability of food is restricted to a few hours in the day (known as restrictive feeding or RF), animals adjust their feeding schedule over a few days to consume their daily intake within this period[130]. Animals will also shift feeding-anticipatory behaviours (increased locomotor activity, CBT, corticosterone secretion, digestive enzyme activity, etc) to 2–4 h before mealtimes[130]. RF is even capable of restoring most liver clock gene rhythms in mice without functional TTFLs (double knockout of clock genes *CRY1* and *CRY2*)[131]. However, RF is likely to only affect TTFLs in peripheral tissues (liver, kidney, heart, pancreas), without affecting the SCN[130]. Thus, feeding schedules may be key in coordinating peripheral rhythms with the SCN[130]. In combination with RF, the caloric content can be restricted in calorie restriction (CR), which does entrain SCN rhythms - hypocaloric feeding at midday advanced hormone (vasopressin) rhythms, and *PER1* and *CRY2* mRNA rhythms in the SCN by 2, 1, and 3 h, respectively[132]. The response of *PER1* levels in the SCN to light was also affected[132]. Intermittent fasting (IF), where animals are fed with double the available food quantity, every other day, also led to changes in the SCN[130]. Clock gene expression in the liver would become arrhythmic if IF was implemented with feeding during the daytime, but would lead to similar rhythms as freely-fed mice if fed during the night-time[130]. Although this is in the periphery, the fact that the effect depends on time suggests the SCN is involved[130]. The few human studies completed to date have also shown effects of meal timing on the rhythms of variables such as plasma glucose[133,134], although effects on other circadian markers such as melatonin have yet not been reported in human studies.

Interestingly, CR and IF also show numerous health benefits in animals including improved lifespan, glucose metabolism, neuroprotection, resistance to cancer, and cardio-protection[130]. Improved cardiovascular health has also been shown in humans under RF[135]. Some studies suggest that these health benefits the regimens confer may be related to the effects that they have on the SCN—a specific transgenic mouse model (αMUPA) has been observed to live long, spontaneously eat less, and have high-amplitude, regular circadian rhythms. These factors are all likely connected[136].

However, research on controlling meals as a chronotherapy is currently very limited. In particular, none of the studies so far have been carried out on PD patients. Additionally, studies thus far have primarily used rodents and have been preliminary—little is currently known about how dosage of nutrients, inter-individual variation, mealtimes (absolute and relative to circadian phase), and extent of RF/CR/IF outcomes. If any of the effects are mediated by DA or neural circuits whose functions are altered in PD, the effects on the circadian system may be very different (or even non-existent) in PD patients. Adherence rates to RF can also vary among patients[137], depending on various factors including work/social schedules[137,138], regularity of schedules[137,138], social support[137,138], diet quality[138], mental health[137,138], alignment with other lifestyle aspects[138], self-monitoring methods[138], and improvements/side-effects felt in physical health, energy, psychology, and hunger when following these regimens[137,138]. Adherence rates appear generally quite high. A meta-analysis reviewed 10 human studies involving adults with metabolic syndrome, non-alcoholic fatty liver disease, and overweight/obesity, and found an 82% mean adherence rate and 68-89% range based on self-reporting[139]. However, some studies using more objective measures (e.g. glucose monitoring on healthy, non-obese patients) suggest that true adherence rates may be lower (~63% after 5 weeks)[137]. Furthermore, as these studies were not with PD patients, adherence rates may be different when it is used to treat circadian disruption in PD. Overall, control of meals as a chronotherapy shows promise but requires further research.

Physical activity. Although physical activity is a weaker stimulus for the circadian timing system than light, there is considerable evidence for it acting as a zeitgeber, primarily in animals[140,141], but also in humans[142,143]. In particular, scheduled exercise in humans has demonstrated the ability to advance or delay the phase of melatonin and CBT (even under dim light conditions), depending on the timing of exercise relative to circadian phase[144]. The health benefits of physical exercise (particularly for PD patients) may also make it useful in chronotherapy. Studies have found that regular exercise can improve cognitive function, mood, sleep, motor performance, DA signalling, L-dopa efficiency, osteoporosis, cardiovascular function, constipation, and fatigue in PD patients[75]. Both human and animal studies also suggest that each individual has a time window during which the benefits of exercise will be maximal[75]. For example, in healthy, older adults (aged 70-80), while cognitive abilities were improved by exercise performed at any time, more measures of cognitive ability were improved when exercise was performed in the late-afternoon[145]. However, there are some studies that have suggested that the regularity of exercise performed (whether it's performed at a specific time every day) has no significant bearing on its benefits. For example, one study found that while physical exercise reduced inflammatory agents in mice with tumours, the effect was most significant when the running wheel was made available to the mice to run at any time, rather than when it was made available for specific time periods every day[146]. Physical exercise has additionally been shown in several rodent studies to affect expression levels of clock genes (*CLOCK*, *PER1*, *PER2*, *PER3*, *BMAL1*, *Rev-Erbα*) in SCN and peripheral tissues[146,147]. Overall, physical exercise shows potential within the context of chronotherapy, but the evidence remains incomplete. In future studies, it will also be important to consider anxieties/fear of falling, compliance, and interactions with other chronotherapies (e.g. light)[75].

Dopaminergic medication. Currently, typical treatment of PD with L-dopa already involves a regular, periodic administration of it throughout the day, personalised to the patient, but typically based around L-dopa's average half-life of ~90 min[148,149]. Irregular L-dopa administration can lead to worsening of motor symptoms between administration times[148]. However, this phenomenon can likely be attributed to the short half-life and the "pulsatile" manner in which DA is delivered to the brain in oral L-dopa rather than misalignment with circadian rhythms, as this issue can be significantly remedied via continuous delivery methods (e.g. intraintestinal infusions)[150]. Currently, there are no studies examining the specific impact of different L-dopa administration schedules on circadian disruption, although one clinical study found that L-dopa absorption rate depends on time-of-day[151]. While deviating from regular administration schedules throughout the day may be questionable with regards to efficacy, it may still be worth considering given L-dopa's aforementioned effects on the circadian system.

The relationship between DA and the circadian system is also elucidated by studies involving the administration of methamphetamine (MA) to animals. Chronic MA administration, which increases dopamine release and dopaminergic activity[152], has been shown to desynchronise locomotor activity rhythms from light-dark cycles[153] and significantly phase shift expression rhythms of clock genes (including *PER1*, *PER2*, *BMAL1*, and *REV-ERBα*) in the olfactory bulb[154], striatum[155], parietal cortex[154,156], and SN[154]. However clock gene expression rhythms in the SCN did not show significant alterations[154,156]. In fact, even in SCN-lesioned animals, regular MA administration can induce locomotor rhythms with approximately 24-h periods, which persist for days after stopping MA administration[157]. These findings imply the existence of an oscillatory system outside of the SCN that can be modulated by MA, often referred to as the methamphetamine-sensitive circadian oscillator (MASCO)[158]. The MASCO in rodents has been shown to regulate locomotor, CBT, hormone (corticosterone) secretion, and other behavioural rhythms[159]. Findings from several studies have suggested that the effects of MA on the MASCO may be primarily mediated by DA. MA is a potent stimulant of dopaminergic and noradrenergic systems in the brain[160], MA-synchronised rhythms can be phase-shifted by DA receptor antagonists (haloperidol)[161], and by pre-treating with various DA receptor antagonists, MA-induced locomotor activity and phase shifts in peripheral oscillators are significantly attenuated or even blocked[162,163]. Therefore, administration of L-dopa may exert effects on the circadian system, at least partially, though engaging the MASCO.

Restrictive feeding (RF) shows similar interactions with the circadian system. RF is able to entrain timing of feeding-anticipatory behaviour in SCN-lesioned rodents[164]. Furthermore, in an experiment in which it was observed that *PER2* expression in the rat OB, striatum, parietal cortex, and SN could be phase delayed by MA compared to controls, RF caused phase advances in the same brain areas[156]. Similarly to the MASCO, these findings imply the existence of another extra-SCN oscillator controlling feeding-anticipatory behaviour, often referred to as the food-entrainable oscillator (FEO)[165]. The FEO and MASCO also show interaction with each other. Administration of MA to mice under RF induces a phase delay in food-anticipatory behaviour, and in mice under short-term MA-treatment, RF has been shown to induce an increase in the period of MA-induced locomotor rhythms[165]. These findings are consistent with literature showing that the effects of RF on the FEO may also be significantly mediated by DA. DA and dopaminergic activity was observed to increase in various mouse brain areas during feeding-anticipatory behaviour[166] and following four days of daily palatable meals capable of entraining locomotor activity[167], and DA antagonists showed significant inhibition of feeding-anticipatory behaviour[166].

These findings on the relationships between the FEO, MASCO, and DA suggest that DA may have strong and significant effects on the circadian system, but via extra-SCN pathways (possibly in addition to SCN-related pathways). Further studies are required investigating DA and specifically L-dopa's effects on PD and PD models which show disrupted circadian rhythms, with a special focus on extra-SCN pathways.

Melatonin. Considering melatonin's importance in the circadian regulation of sleep and its key antioxidant and neuroprotective roles[168], its use in the treatment of PD and accompanying circadian disruptions has a reasonable empirical evidence basis.

Results from studies administering <5 mg/day at bedtime found conflicting results. One study with PD patients administered 3 mg/day at bedtime and found improvements in self-reported sleep quality and sleep disorders as assessed by the Parkinson's Disease Sleep Scale (PDSS), though EDS showed no improvement [169]. In this study there were also significant improvements in cognitive function and mood as assessed by the Mini Mental State Examination (MMSE), 5-word test, and Hamilton Depression Rating Scale (HDRS)[169]. Meanwhile, another study with PD patients, administering 3 mg/day (1 hr before bedtime) found a 50% increase in sleep latency, 66% increase in REM without atonia, and 72% reduction in sleep efficiency, though subjective sleep quality seemed to improve[170]. While this study was double-blind, placebo-controlled, and parallel-group, it should be noted that the study also had a very small sample size of $n = 18$. Results were also conflicting for low dosages of prolonged release formulations of melatonin. A study administering 2 mg to PD patients at bedtime, saw no changes in motor symptoms (Unified PD Rating Scale (UPDRS) part III), but observed improvements in subjective sleep quality (Pittsburgh Sleep Quality Index (PSQI)), which was strongly associated with improvements in non-motor symptoms (PD Non-Motor Symptom Scale (NMSS)) and quality of life (the Parkinson's Disease Questionnaire (PDQ-39))[171]. On the other hand, a study administering 4 mg (prolonged release) to PD patients every night found no improvements in RBD[172].

In studies administering higher dosages (≥5 mg/day), results were generally more positive. In one clinical PD study (double-blind, placebo-controlled, cross-over), placebo, 5 mg, or 50 mg of melatonin was administered every night for 10 weeks[173]. During the 5 mg treatment, there was no significant change in sleep duration measured via actigraphy, but there was a significant improvement in overall subjective sleep disturbance (General Sleep Disturbance Scale (GSDS))[173]. During the 50 mg treatment, they observed a 10 min increase in the mean sleep time but non-significant improvements in the GSDS[173]. EDS was not significantly improved by 5 or 50 mg, as assessed by the Epworth Sleepiness Scale (ESS) and Stanford Sleepiness Scale (SSS)[173]. Another clinical PD study, administering 10 mg/day, also found an improvement in sleep quality (Pittsburgh Sleep Quality Index (PSQI)), mood (Beck Depression and Anxiety Inventories), and non-motor symptoms (UPDRS-I score)[174]. The study also reported normalisations in proteins and expression of genes involved in inflammation (C-reactive protein, TNF-α) and antioxidants (total antioxidant capacity) after treatment[174]. Similar findings were observed in a clinical PD study administering 25 mg/day dose of melatonin ($n = 13$), seeing improvements in antioxidant markers and enzymes involved in inflammation (COX-2), alongside a reduction in overall UPDRS score[175]. Considering that inflammation and antioxidants seem to be a key part of PD onset and/or progression, these findings are promising[176]. Finally, and most notably regarding circadian disruption, a study found that 25 mg/day administration led to an overall increase in *BMAL1* levels, though EDS was unaffected[177].

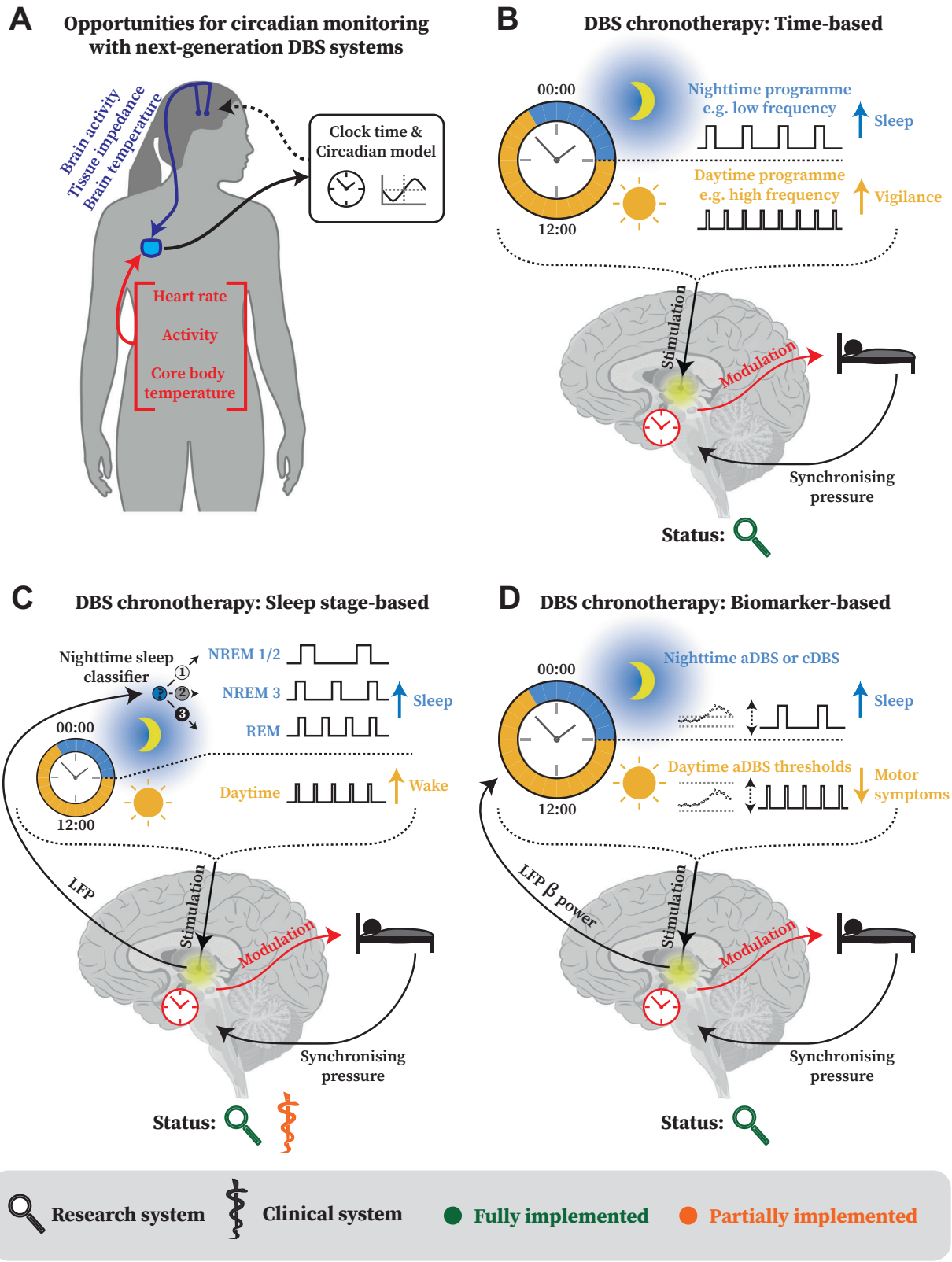
Overall, melatonin shows potential in chronotherapy but has clear limitations (not effective on EDS[177] or RBD[172,178]) and further studies using robust experimental designs are required due to conflicting results. Furthermore, its effects on circadian rhythms other than sleep need further investigation. Its side-effects over long-term administration (particularly on mood) should also be considered as they can be significant[75]. One promising solution is the combination of melatonin with BLT, as it seems to curtail melatonin's side-effects[75]. Generally, the combination of different chronotherapies may be more effective than each of them alone.

DBS and chronotherapy

An advantage of DBS over pharmacological or behavioural approaches is that it affects brain activity in the target area instantly. In theory, this allows for therapy delivery that is precisely patterned in time, making it an ideal candidate for a chronotherapeutic approach. DBS also has very high adherence rates (as stimulation is applied automatically) and enables the integration of (new) circadian therapies directly into traditional treatment. While time-dependent or brain-state-dependent DBS therapy has so far been restricted to manual operation[179] or wireless systems with offline processing[180], recently developed implantable DBS research systems (e.g. the Picostim-DyNeuMo[181–183]) already enable chronotherapy through time-of-day-dependent hierarchical control of continuous or adaptive therapy [184]. This section explores different ways in which such systems could implement DBS as a chronotherapy to ameliorate circadian disruption (Fig. 2).

DBS integration with existing chronotherapies—circadian monitoring with DBS

While the main purpose of DBS is to enact neural modulation, modern DBS devices also increasingly carry sensing capabilities to enable the delivery of



closed-loop DBS[60–62]. Some of these sensing modalities could be used to infer the circadian status (i.e. timing/phase of rhythms, robustness/amplitude of rhythmicity) of the target brain area or even the wider circadian system. These inferences may be useful in understanding the patient's circadian disruption, personalising chronotherapy (external to the DBS system) to an individual, and/or in future, to use these measurements in closed-loop, chronotherapeutic stimulation.

When attempting to assess the state of the circadian system from physiological variables which are considered outputs of the circadian system, the greatest challenge is removing the confounding influence of factors such as physical activity, sleep, and light exposure on these outputs[185,186].

Fig. 2 | . A High-level diagram showing how circadian outputs can be measured from a DBS IPG, and then can be integrated with existing chronotherapies external to the DBS system. It may also be possible, in future, to use the measurements in closed-loop stimulation. **B** Diagram showing a time-based approach to administering chronotherapy with DBS. Stimulation parameters are switched between promoting sleep or vigilance, depending on the time of day. By switching between the daytime and night-time modes at specific times, a positive synchronising pressure is applied to the SCN. This approach has already been implemented on a fully implantable research system (Picostim-DyNeuMo-2c). **C** Diagram showing a sleep stage-based approach to DBS chronotherapy. During the day, stimulation parameters are set to promote vigilance. During the night, LFP measurements from the stimulation site are used to infer which sleep stage the patient is in, which switches the stimulation parameters to those optimal for promoting sleep in that sleep stage. By switching between the daytime and night-time modes at specific times, a positive synchronising pressure is applied to the SCN. Sleep-stage-aware therapy has already been implemented on a research system (Medtronic Summit[180]). Additionally, partially sleep-aware operation has been implemented on a clinically established fully implantable system (Medtronic Percept) using a single LFP biomarker[224]. **D** Diagram showing a biomarker-based approach to DBS chronotherapy. A biomarker derived from LFP measurements in the stimulation target (beta-band power in this case) is used throughout to modulate stimulation parameters. During the day, stimulation is modulated adaptively to alleviate motor symptoms. During the night, thresholds/set-points for measured beta power are adjusted so that stimulation is now continuously modulated to optimise sleep/minimise sleep disruption. By switching between the daytime and night-time modes at specific times, a positive synchronising pressure is applied to the SCN. Time-of-day based adaptive algorithm switching has been implemented on a fully implantable research system (Picostim-DyNeuMo-2c[183]). Switching between an adaptive and sleep-protective open loop algorithm, upon detecting sleep, has been reported with the investigational Medtronic Summit[180,184]. The illustration of the brain is adapted from Injurymap at https://www.injurymap.com/free-human-anatomy-illustrationsand the human outline from Ryan Kissinger at https://bioart.niaid.nih.gov/[258,264].

Thus, the outputs minimally affected by external factors are considered to be the most robust and reliable indicators of circadian rhythms. In a lab setting, the most robust and reliable measure of circadian phase is typically considered to be a 24-h measurement of the concentration of hormones melatonin (in dim light conditions) or cortisol in blood and/or saliva[185]. While wearable devices exist for tracking melatonin and cortisol levels in sweat (with good correlation to salivary measurements), to our knowledge, a safe, practical, and *chronically implantable* lab-on-chip system that can make the required real-time measurements does not currently exist[187]. To track circadian rhythms with a self-contained DBS system (consisting of the stimulating lead and the implantable pulse generator (IPG)), other outputs must be measured (Fig 2A).

Core body temperature (CBT). One of the most commonly used measures of circadian output is core body temperature (CBT)[185], the temperature of the internal organs. CBT has a strong circadian variation and covaries with outputs of the SCN such as the melatonin rhythm in humans[188,189]. CBT ordinarily decreases during the night-time and reaches a minimum at around 5 am. From that point, it will gradually increase during the daytime until eventually reaching its maximum in the late afternoon to early evening[185]. In lab settings, CBT is typically measured by a rectal probe, tympanic infrared sensor, or sometimes an oesophageal probe for greater accuracy[190]. However, these methods cause discomfort, have a high chance of measurement error, or are highly invasive, respectively[190]. Ingestible telemetric sensors can also be used for a high accuracy, but at a greater cost per study[191,192]. In DBS systems, CBT could be measured by adding a temperature sensor (e.g. thermistor-based sensor) to the IPG, which is typically implanted subcutaneously in the chest[193], or in some cases, mounted on the skull[181,194]. Careful placement of the temperature sensor within the IPG package should ensure a separation from heat-generating components and may even be placed outside of the package. In particular, rechargeable IPGs will generate significant heat during its inductive recharge process, and thus temperature measurements may have to pause during that period. Placement of the IPG itself should also ensure a proximity of the sensor to the main arteries in the implantation area, especially for skull-mounted devices, where there are fewer arteries[195]. As IPGs are not implanted deeply, they may be particularly prone to ambient temperature changes and changes in skin temperature. The latter rhythm is very different from the CBT rhythm[196]. CBT measurements are always affected by other non-circadian exogenous factors including sleep, ambient temperature, physical activity, meals, postural changes, and many others[185]. Thus, under most real-life circumstances CBT measures comprises an endogenous circadian component and an evoked component which together form the overt rhythm in CBT. For an assessment of the phase and amplitude of circadian rhythmicity, CBT measures need to be used with care and/or combined with other measures.

Brain temperature. Temperature measured subdurally in the human brain also shows significant circadian variation[197,198]. Similarly to CBT, brain temperature was observed in a study to fall during the night and rise during the day, but showed a much higher average (~38.2 °C compared to ~37.4 °C for CBT) and wider range (~37.0–40.3 °C compared to ~36.0–38.6 °C in CBT)[197]. Brain temperature is primarily determined by heat generated in the brain via metabolism, and heat lost via heat transferred to cerebral blood flow (CBF)[197]. Since the blood flow which cools the brain comes from the body, brain temperature is at least partially dependent on CBT. This may, in part, explain why brain temperature shows a similar diurnal variation to CBT[197]. However, brain temperature is not solely dependent upon CBT, as shown by the observation that brain temperature does not depend on BMI, whereas CBT does[197]. This observation indicates that CBF (especially via means unaffected by fat distribution) is a significant factor that also determines brain temperature[197]. Considering that different factors influence brain temperature and CBT, it may be beneficial as an additional measure to CBT. It should also be noted however, that in mice, brain temperature variation has been found to depend primarily on vigilance state (waking/REM or NREM) and prevalence of wakefulness in the prior 4 h, with a relatively small contribution from time-of-day[199]. Further research is required to understand the contribution of sleep and circadian rhythmicity to human diurnal brain temperature variation. To measure brain temperature, the design of the DBS electrodes would need to be modified to include a thermocouple along the leads. Caution would be required to ensure that placement of the thermocouple along the leads is sufficiently distant from stimulating electrodes as stimulation could have a notable local heating effect[200].

Local field potentials (LFPs) and brain tissue impedance. Local field potentials (LFPs) are aggregate potentials measured from an electrode surrounded by a population of neurons. LFPs measured in the STN show a measurable diurnal variation, specifically in the beta band (13–30 Hz) power, which was observed to increase during the day and decrease during the night-time[201]. However, much of this variation may be attributable to the sleep-wake cycle[202,203]. Although only correlations have been observed thus far and no causal links have been established, beta power appears suppressed during NREM compared to wakefulness and lies between NREM and wakefulness during REM[202,204] (though there is high within- and between-subject variability[204], and some studies have found beta power during REM is sometimes higher than during wakefulness[205]). Beta power is also highly dependent on severity of motor symptoms[206,207] and sleep disturbance[208]. Thus, the circadian contribution of diurnal LFP variation is currently uncertain. Nonetheless, it is likely that the circadian component is still significant and separate to the sleep-wake component, as this is the case for EEGs[209,210]. Furthermore, even if diurnal variation of beta power primarily comes from the patient's sleep-

wake cycle, considering that the sleep-wake cycle itself is a behavioural output of the circadian system, tracking beta power would still provide useful information about the circadian system, especially since measurements are taken across multiple days.

Mechanistically, a factor contributing to the diurnal LFP variation may be the circadian variation of brain tissue impedance[211]. Brain tissue impedance can be measured by simply running a current between DBS electrodes and measuring the voltage across them. The measured impedance is made up of two primary components: the impedance of the electrode-tissue interface, and impedance of the fluid-filled extracellular space (ECS) through which ionic currents can flow[211]. This total impedance reaches a maximum during the daytime and minimum during night-time with a peak-to-peak amplitude of up to $48.94 \pm 16.43\Omega$[211]. It is hypothesised that changes in ECS volume throughout the day cause a change in tissue impedance, leading electrical dynamics in the brain to change, and therefore, contributing to a circadian LFP variation[211]. However, since ECM volume and impedance are also highly dependent on vigilance state, these results must also be interpreted cautiously[212]. Nonetheless, both impedance and LFPs are worth consideration as circadian biomarkers.

A final point to note is that many DBS systems pick up information about cardiovascular activity when recording LFPs. Chest-implanted IPGs can directly pick up electrical activity generated by the heart, with LFP activity containing an electrocardiographic (ECG) component[213,214]. Even when the electrical component of cardiac activity is absent in LFPs, cardiac activity may affect low-frequency components of the LFP signal through interactions of pulsatile blood flow with brain tissue and implanted electrodes[215,216], potentially generating readouts of variables such as heart rate, heart rate variability, and intracranial vascular pressure and compliance[216]. These variables are all potentially informative about the circadian rhythm[217].

Activity/acceleration. In animal studies, activity (e.g. wheel-running) is a very established measurement of circadian rhythm[185]. A similar measurement can be taken in human studies from a wrist-worn accelerometer throughout the 24-h day[185]. This measurement is known as actigraphy. While it is influenced by many non-circadian factors and is prone to artefacts[185], actigraphy can act as a useful addition to other measures of circadian rhythms and shows a reasonable correlation with sleep-wake, melatonin, and CBT rhythms[185,218] (although this may not be the case under some circumstances e.g. if the individual is blind[219]). A similar measurement may be taken from an accelerometer integrated into an IPG device. Although measured accelerations will have a smaller dynamic range than a standard actigraphy as IPGs are typically implanted in the chest or on the skull, these placements may enable measurements which are more difficult on wrist-worn devices. For example, using a direct readout of trunk or head position, these accelerometers can more easily infer postural information. Additionally, measures of physiological function such as a ballistocardiogram (BCG) may become possible, which measures motion resulting from contraction/expansion of the heart and pumping of blood through the body[220]. While a wrist-BCG is affected by arm stiffness, spinal damping, and arm mass, the head and chest are appropriate locations for BCGs[220]. In fact, studies have shown that head-worn and chest-worn accelerometers can estimate sleep parameters more accurately than wrist-worn devices[220,221]. Additional research is required for measuring circadian rhythms using accelerometers with these placements, but it will act as an important addition to the other measures outlined. In fact, multimodal approaches are among several novel approaches that show promise for more reliable estimations of circadian rhythmicity[186,222].

DBS as a chronotherapy

Chronotherapy via sleep regulation. As previously explained, sleep scheduling shows potential as a chronotherapy. While past studies have modulated sleep/wake using pharmacological sedatives and stimulants, it may also be possible to do so via DBS. Conventional STN-DBS already seems to significantly improve insomnia, EDS, and subjective sleep quality[17,64]. Although research is still preliminary, PPN-DBS even shows promise in clinical pilot studies for modulating alertness/vigilance[58] and REM sleep via frequency-dependent effects[70]. However, since the stimulation currently applied in conventional DBS is continuous, the improvements in sleep quality are unrelated to time, and are unlikely to be optimised for any synchronising effects on circadian clocks. Furthermore, since the stimulation waveform is specifically programmed to improve motor symptoms, it could be suboptimal for modulating/improving sleep. This limitation may contribute to why many sleep disorders such as RBD, RLS, and nocturia do not show measurable improvements following conventional DBS[64]. For DBS to be an effective chronotherapy, the stimulation waveform should be modulated to optimally promote sleep at a specific time every night, and vigilance at specific times in the day. As a result, a specific, circadian sleep-wake cycle is imposed, which can have a positive synchronising pressure on the circadian system. The following programs of modulating the waveform can be considered:

1. Time-of-day-based stimulation—the stimulation parameters are switched between promoting wakefulness at specific times during the day, and promoting sleep at specific times in the night (Fig 2B). Granularity of this scheme may be increased by applying parameters that promote specific sleep stages at specific times of the night (i.e. promoting a specific sleep architecture)[223]. One study applying this approach in the PPN has observed an improvement in daytime sleepiness[70]. While the therapy schedule can be informed by a patient's personal preferred daily rhythm ('chronotype'), this remains essentially a prescriptive approach that incorporates no feedback from the patient's actual sleep-wake cycle or circadian rhythm.
2. Sleep-stage-based stimulation—sleep stage (awake, non-REM, REM, etc) can be predicted using LFP recordings from brain nuclei such as the basal ganglia (including STN), using machine learning (ML) algorithms[180,184,224]. Throughout the night, the optimal stimulation parameters for supporting a detected sleep stage can be administered. Sleep-stage based stimulation can be implemented on some investigational DBS systems[180], and one recent study programmed a clinically-available aDBS device to approximate sleep-aware stimulation using a single power band estimate[224]. Alternatively, it may be desirable to continuously adapt stimulation parameters through the night, in a closed loop, to achieve particular sleep stages at specific times, enforcing a specific sleep architecture. This modulation between sleep stages may induce changes in SCN neuronal activity as observed in a rodent study, with firing rates increasing during REM and decreasing during NREM[108]. Furthermore, selective deprivation of slow-wave sleep during NREM increased SCN firing rates, while deprivation of REM reduced them[108]. Targeting REM sleep regulation may be particularly effective in modulation of the circadian system as it shows a significant relationship with circadian phase. Many clinical studies have observed a predictable organisation of REM sleep across nights[225,226], and REM sleep propensity, in particular, is significantly modulated by a circadian component, peaking shortly after the CBT minimum[18,227], coinciding with the circadian phase at which the density of the rapid eye movements is lowest[228]. Furthermore, irregular sleep timing in healthy adults has been associated with high fragmentation of REM sleep, concomitant with a reduced actigraphy rhythm amplitude[229], suggesting that consolidation of REM sleep may improve the amplitude of circadian outputs. This evidence shows a connection between REM sleep and the circadian system, and promise for REM sleep as a target. However, further investigation is needed to establish that modulation of REM sleep will, in fact, affect the circadian system in humans, and to clarify specifically what aspects of REM sleep (stability, timing, architecture) are most effective as modulation targets. Whatever the specific neuromodulation targets, these interventions of sleep-stage-driven stimulation would start at a specific time every

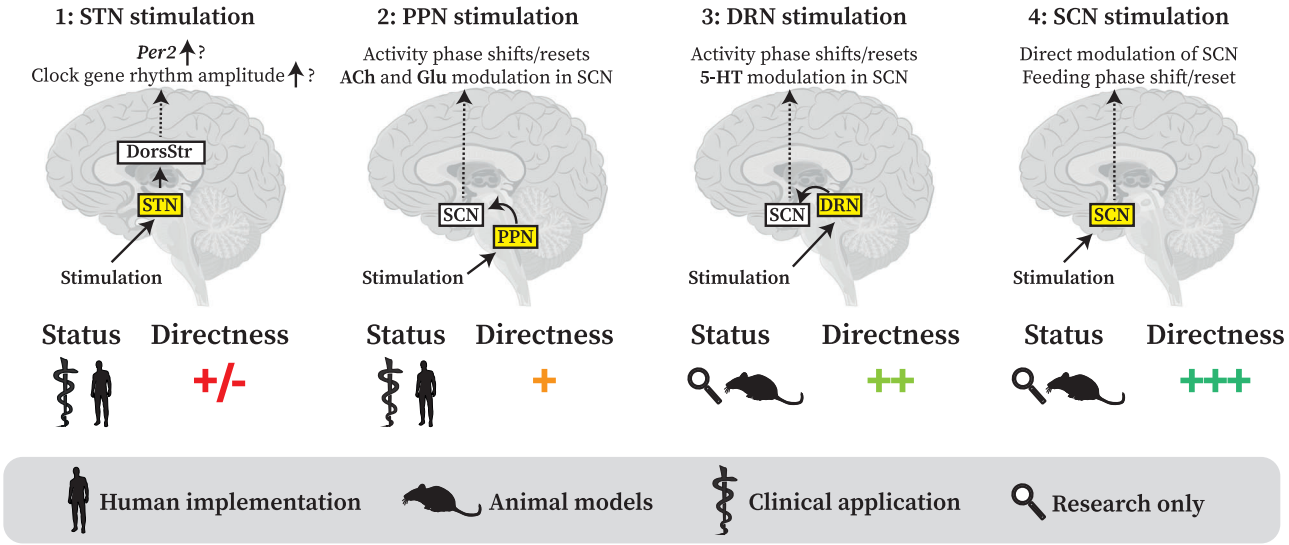


Fig. 3 | A figure outlining the different targets which may be stimulated for neuromodulation of the circadian system and the effects stimulation of each target is likely to have on the SCN. Effects of STN-DBS on the dorsal striatum have not yet been observed in experiment and are currently only hypothesised. Effects of DBS in all other targets have been observed in preclinical models. For each target we indicate the current translational status of the intervention (STN- and PPN-DBS are used clinically in human patients, DRN and SCN stimulation are limited to pre-clinical research only) as well as the potential directness of the intervention for influencing the circadian system (with direct modulation of the SCN representing the highest potential impact). The illustration of the brain is adapted from Injurymap at https://www.injurymap.com/free-human-anatomy-illustrations[258].

night, optimising sleep quality for a designated sleep period every day (Fig 2C). Compared to the time-of-day based stimulation, this approach adds a reactive component to therapy, using detected brain state to adjust therapy settings in real time.

3. Biomarker-based stimulation—DBS chronotherapy can also be implemented using LFP biomarkers as control signals, with time- or brain-state dependent thresholds and set points. In PD, pathological, elevated power and stability of beta-band (13–30 Hz) oscillations in STN-LFPs correlate with motor symptom severity and their suppression correlates with motor symptom alleviation, whether via L-dopa administration[230] or continuous DBS[201,231,232]. Thus, STN-LFP beta power is the main control signal used in aDBS for the adaptive alleviation of motor symptoms[201]. During sleep, STN-LFP beta power is also associated with a decreased propensity for sleep, increased frequency of awakenings, and REM sleep without atonia (a symptom of RBD)[56]. Thus, in a closed-loop aDBS system, adaptive stimulation parameters can be adjusted during the night with the goal of controlling beta power, ultimately to protect sleep. Since beta power is higher during daytime wakefulness than during night-time sleep[201], thresholds or set-points should be adjusted so that beta power is controlled appropriately depending on whether it's daytime or night-time[201]. This mode of operation could be activated upon detection of sleep, minimising sleep disruptions and thus maximising sleep quality during that period (previously implemented on investigational devices[184]), or could be enabled during a specific time frame every night to improve sleep using a scheduled approach[183] (Fig 2D). In an alternative approach, closed-loop control of beta power may also be applied so that the patient's 24-h beta power variation follows a -'healthy' pattern.

Experimentation is required to assess whether methods 1, 2, 3, or any combination of them provide an optimal synchronising pressure to the circadian system.

Direct neuromodulation of the circadian system. This approach involves the application of specific stimulation parameters (possibly at specific times) to elicit a desired response in the circadian system. Although clinical research in this field is currently very limited, there are four possible mechanisms/targets via which DBS could directly modulate the circadian system (Fig. 3). The following targets are listed in descending order of translational maturity (i.e. how established therapy in the area is):

1. STN Stimulation—Given that the STN has already been a common target in DBS for PD across decades, the ability to also use this target for circadian modulation would offer a highly practical solution. However, supporting evidence is currently limited. One human study observed no changes to peripheral blood clock gene expression rhythms following STN-DBS[72]. However, in rodent studies, STN-DBS was shown to increase DA metabolism in the striatum (a deep brain region near the STN)[233]. This finding suggests that more DA is being released and/or taken up in the striatum during STN-DBS. In a more recent study, human PD patients showed an increase in striatal DA transporters following STN-DBS[234]. Considering that DA is critical for modulating the expression of the clock gene *PER2*[235], and a lack of DA in the striatum can lead to blunted amplitudes in expression rhythms of clock genes[235], a mechanistic connection can be made that the increase in striatal DA metabolism/transporters from STN-DBS may help ameliorate blunted circadian amplitudes observed in PD. However, the link between STN-DBS and striatal clock gene activity may be more complex. Changes to clock gene activity will vary depending on which types of DA receptors are activated by STN-DBS (information which is currently lacking) - while greater activity of DA receptors belonging to type D_1 increase mRNA levels of all clock genes, greater activity of D_2 receptors decrease *CLOCK* and *PER1* mRNA levels, increase the protein expression of PER1 during night-time, and increase *PER2* mRNA and protein levels overall[235]. Some researchers also question the link between STN-DBS and DA-related striatal neurotransmission in humans, as studies have produced conflicting results[236]. This is especially the case for PD patients who have undergone DBS surgery - these patients are typically in a later stage of PD, meaning the DA pathways for the aforementioned mechanisms may already be significantly damaged and incapable of modulation[233].

Further research is required to clarify the connection between STN-DBS and striatal clock gene activity, and how changes resulting from this connection affect the wider circadian system (including the SCN), if at all.

2. PPN Stimulation—Although PPN-DBS is still rare in PD patients, a precedent for its implementation exists for PD patients experiencing freezing of gait (FoG) symptoms[237] and for patients with other movement disorders (e.g. MSA[238]). As a component of the reticular activating system that regulates arousal levels and transitions between sleep and wakefulness[239], it is a target of interest for DBS as a chronotherapy. In addition to the aforementioned frequency-dependent effects on sleep in human studies[58,70], there is some preliminary preclinical evidence that PPN-DBS may directly interact with the circadian system. One mouse study found that circadian phase and neurotransmitter levels in the SCN can be affected by electrical stimulation of nuclei in the brainstem, including the PPN and laterodorsal tegmental nucleus (LDTg)[73]. The study found that, in complete darkness, PPN stimulation could cause different magnitudes of phase delay in activity rhythms, depending on stimulation parameters and circadian phase/time of stimulation. LDTg stimulation could also advance activity rhythms but phase advances were not observed in PPN stimulation[73]. Additionally, depending on the stimulation parameters, the neurotransmitters acetylcholine (ACh) or glutamate (Glu), both important signalling agents in the SCN, were increased in the SCN following stimulation in both areas[73]. Further investigation is required on how stimulation parameters affect modulation of the circadian system.

   While these findings show promise, the evidence for PPN-DBS modulating the circadian system and sleep/vigilance is currently incomplete - the clinical and preclinical studies are still few and limited by small sample sizes, heterogeneous stimulation protocols, variable electrode placement, and inconsistent results. Further substantial research is still required before PPN-DBS can be translated to a circadian therapy.

3. Raphe Nuclei Stimulation—The raphe nuclei are a set of nuclei located in the midbrain (upper brainstem) and have a direct connection to the SCN via the neurotransmitter Serotonin (5-HT)[240]. As DBS in the area has no precedent in humans and has only been investigated in several rodent studies, there is a substantial barrier to investigation in humans. However, preliminary preclinical data shows promise in its ability to modulate the circadian system. In hamsters, similarly to PPN-DBS, stimulation of raphe nuclei has been shown to induce locomotor rhythm phase shifts[240–242], and 5-HT release in the SCN[240,241]. However, data are currently scant on how stimulation parameters affect neuromodulation. Significant, additional preclinical work is required before human implantation can be justified. Investigation of potential side-effects will be particularly important as the dorsal raphe nucleus plays an important role in regulating reward and aversion[243].
4. SCN Stimulation—Similarly to raphe nuclei stimulation, the SCN has no precedent for implantation in humans and thus, there is a greater barrier to investigation and implementation in humans. However, preclinical models have shown great promise. Direct electrical stimulation of the SCN has been shown to affect the phase and period of feeding rhythms in rats and hamsters, depending on circadian phase of stimulation[244]. Specifically, stimulation during the early subjective night led to phase delays while stimulation during the late subjective night led to phase advances[244]. This potential for electrical stimulation of the SCN merits further preclinical studies, which must occur before human implantation can be justified, particularly as side-effects could be significant.

In future, if any of these targets can show reliable neuromodulation of the circadian system, stimulation can be integrated with circadian monitoring to create a fully self-contained, closed-loop aDBS system for modulating the circadian system. Such an approach could be highly effective but currently requires substantial new research to lay the groundwork.

A translational roadmap for DBS as a circadian therapy

What, then, are the next steps required to enable investigations into the clinical benefit of DBS as a chronotherapy in PD? Here, we outline key technological requirements, consider how IPG-derived biomarkers of circadian function can be validated, sketch out an approach towards human clinical work, and consider risks of DBS as a chronotherapy.

Technological development

For the clinical implementation of DBS as a chronotherapy, a new generation of DBS systems is needed. Firstly, sensors are necessary to access several of the aforementioned measures of circadian state—LFPs, accelerometry, CBT, brain temperature, and/or impedance. While LFPs are already monitored on current closed-loop DBS systems, fewer systems have access to accelerometry[181] and no DBS implants record brain or body temperature. Impedance measurements are routinely carried out on DBS devices in-clinic but enabling regular measurements without interruption of therapy delivery requires a different approach.

Chronotherapy-enabled systems will also need to keep track of time-of-day using an internal clock, and potentially maintain a continuously-updating model of the patient's individual rhythmicity. The model should also incorporate an understanding of how we expect the circadian system to respond to changes in stimulation at the envisioned DBS target (phase and/or amplitude-response curves). This knowledge will be developed from future clinical investigations. Finally, systems will need to change stimulation parameters based on any of the biomarker measures above, time-of-day, and/or the model of the patient's circadian system. As DBS systems must be highly power-efficient, most devices are designed to carry out only the originally intended functions and are not capable of adding these features via firmware updates.

There are modern DBS systems, however, that have some of these features. The Picostim IPG with the DyNeuMo Mk-2 firmware is a skull-mounted, investigational device that has a 3-axis accelerometer on-board, LFP measurement at 625 Hz, impedance measurement, temperature sensor on-board, internal clock, and circadian scheduling capabilities where stimulation parameters can be changed based on time of day[181,183,194]. It is also capable of adapting stimulation based on measured motion and LFPs[181]. Another device is the investigational device Medtronic Summit RC+S[245]. It is capable of 4 channels of electrophysiological recordings at 250 or 500 Hz, or 2 channels at 1000 Hz, 3-axis accelerometry, and adaptive stimulation based on electrophysiological recordings[245]. This device was successfully able to differentiate sleep and wakeful states in a pilot study involving 4 patients[184]. However, the Summit RC+S uses continuous wireless connectivity and off-device processing to enable vigilance state estimation, which may not be clinically scalable[184,245].

Validation of circadian rhythmicity biomarkers

Although many of the implant-derived circadian biomarkers discussed in Section 4.1 show promise, they first require rigorous validation to ensure that any treatments informed by these biomarkers are safe and efficacious. For any physiological measurements to be considered a true circadian rhythm, their diurnal variations must persist when studied under constant environmental conditions[186]. However, for the purposes of practical chronotherapy, biomarkers used to infer the state of the circadian system do not need to be a true circadian rhythm, though they must satisfy two criteria. Firstly, it must correlate well with a gold standard measure of circadian rhythm such as melatonin, cortisol, or CBT rhythms[186]. Metrics used to assess the performance of biomarkers on this front will depend on assumptions about the statistical distribution of data, but could include error or absolute error and their standard deviations, median error and its range, the proportion of samples with error below a threshold, correlation between novel and gold standard markers, or circular regression analysis of the novel marker against the gold standard marker[186].

Secondly, the marker must be minimally affected by confounding environmental and behavioural changes, or it must be possible to remove their influence via a purification method. One purification method used for CBT rhythm measurements is known as purification by categories[246]. In this method, the data is split into 0.5-h bins and the data-points in each bin are split into a number of equally-spaced "categories" between the maximum and minimum values within the bin. Each of these categories represents a different level of activity. The category with the lowest values is assumed to correspond to sleep and the temperature value is increased to correct for the temperature-lowering effect of sleep. The category with the second lowest value is assumed to correspond to being awake but lying down, the activity that tends to have minimal masking effects on CBT, so measurements are kept unchanged. All other categories are assumed to correspond to different levels of activity and values are reduced separately. This process is repeated iteratively until the purified data approaches a sinusoid[246]. Another method is the use of large normative datasets which have studied how CBT varies under different conditions such as variations in postures. Average changes to CBT resulting from a particular posture can be noted (and whether this change depends on circadian phase) and used to correct CBT measurements accordingly[247]. This method requires knowledge of the patient's posture at any time, but this may be possible via a 3-axis accelerometer in the IPG. Both of these methods may be applied directly to CBT and brain temperature measures from the IPG, but they could also be adapted to account for other masking effects and to purify LFP, impedance, actigraphy, and BCG measurements. Purification can also involve other statistical filtering methods or multiple regression if many measurements are used at once[186].

To assess whether the proposed biomarkers meet these two criteria, clinical studies must be carried out under controlled conditions. Masking effects should be minimised, and any potential confounding factors should be measured or controlled. The ideal protocols for such experiments are constant routine or forced desynchrony. In a constant routine protocol, subjects are kept-awake, given evenly distributed nutritional intake, and placed under constant lighting, posture and other environmental conditions for over 24 h[248]. On the other hand, in forced desynchrony, sleep-wake, rest-activity, fasting-eating, and light-dark cycles are imposed on patients, with a period that is significantly shorter or longer than 24 h (e.g. 20 or 28 h, respectively). By applying this protocol over multiple days, measurements can be made for every time of the day under constant conditions[188]. Although slightly modified constant routine protocols have been used in PD[249], in general, it is impractical or even unethical to subject PD patients to such strict and disruptive protocols. Therefore, more practical approaches should be implemented to minimise masking effects in measurements. In particular, past clinical studies suggest light should be dimmed four hours before habitual bedtimes to avoid suppression of melatonin synthesis, blood samples should be collected at least two hours after insertion to avoid adrenergic responses and under constant posture for at least 10 minutes prior to blood sampling, physical activity outside of the patient's routine should be avoided at least 4 h before blood collection, and any dietary changes should be avoided at least a week before the study[250]. Additionally, the study may decide to control factors which can influence circadian rhythms and/or circadian biomarker measurements such as sleep-wake rhythms before the study, age, menstrual cycle phase, and substance consumption (e.g. caffeine, alcohol, nicotine, cannabis, non-steroidal anti-inflammatory drugs, drugs of abuse, etc)[250]. It is important to keep in mind that any protocols that are proposed should have an appropriate risk-benefit ratio for the PD patients involved. Satisfying that condition, the careful analysis of novel biomarker, gold-standard marker, and confounding factor data collected under these controlled conditions can enable assessment of the proposed, IPG-derived biomarkers.

Clinical investigations of DBS chronotherapy in PD

Ultimately, the true measure of chronotherapeutic DBS will be whether it achieves its clinical objectives of mitigating sleep and circadian disruption in PD patients better than existing approaches. A first step towards clinical validation is to demonstrate feasibility of the approach. This can be done in experimental medicine protocols involving patients who already have DBS implants, provided the implants have some ability to record relevant biomarkers and/or administer relevant stimulation programmes. There are now many PD patients with commercially-available implants in the STN or GP that are capable of monitoring some brain activity biomarkers (e.g. Medtronic Percept[251,252]). Some patients have clinical-grade, research devices (e.g. Medtronic Summit RC+S[253], DyNeuMo-2c[183]) implanted that provide additional functionality and flexibility in a research context. Moreover, an increasing number of patients have been implanted with DBS leads in the PPN for experimental treatment of PD[254]. Pragmatic recruitment of these populations will provide the fastest route to proving the concept of DBS chronotherapy, by making use of systems already implanted and imposing no additional surgical burden (or associated risks). Care should be taken to recruit PD patients with significant non-motor symptoms, including specific sleep and circadian disruptions.

Once patients are recruited, during an initial baseline phase, the circadian rhythms of patients would be tracked during standard therapy. Both the novel, implant-derived biomarker(s) and established measures of circadian rhythms will be tracked (e.g. melatonin and cortisol rhythms, CBT, sleep staging (polysomnography) and actigraphy). In addition, participants' self-reported sleep and circadian function should be collected. Confounding variables which have transient effects on these measures should be monitored concurrently, such as light exposure, physical activity schedules, drug intake (L-dopa, caffeine, etc), and meal schedules. Aforementioned experiments for validation of implant-derived biomarkers could also be carried out during this phase simultaneously. This phase will establish the baseline rhythmicity and can additionally confirm whether the implant-derived biomarkers for therapy correlate well with actual circadian status.

Next, there should be an intervention phase. The chronotherapeutic intervention would be implemented as a change in stimulation parameters according to clock-time, time relative to the habitual sleep-wake cycle, estimated circadian phase, detected sleep state, or a measured electrophysiological biomarker (as in Fig. 2). A simple starting point for time-based stimulation would be to change stimulation parameters for a participant based on habitual sleeping and waking times. This change could be in amplitude of stimulation to titrate the level of target engagement, or a change in other parameters such as stimulation frequency in order to change the nature of target engagement (e.g. suppression or enhancement of different neural oscillations). Where baseline DBS therapy is already used, it will be important to consider how sufficient alleviation of motor symptoms is maintained under the new stimulation programmes. A pragmatic control condition would be continuation of current therapy without chronotherapeutic modulation and unchanged medication schedule. During the intervention phase, circadian rhythms should be tracked with the same methods as during baseline, including patient self-reports. If the effects of stimulation show clear effects on phase and/or amplitude of the circadian system, it may be appropriate to map phase and/or amplitude response curves, which could enable a higher degree of optimisation and personalisation of therapy.

Efficacy trials

Once the feasibility of measuring and modulating circadian rhythms with DBS systems is established, the clinical benefit of the approach can be assessed. This will necessitate trials with more extensive control conditions, over longer (clinically relevant) timescales, and with careful blinding of participants and assessors to the intervention or control conditions.

To rule out that simply changing therapy for a part of the day has similar effects (i.e. that benefits are unrelated to adjustments of therapy at specific times), control conditions in trials seeking to establish efficacy should include the same temporal patterning of therapy but shifted each day such that no overall alignment with the diurnal rhythm occurs. A more targeted control condition could invert the therapy schedule such that day-optimised settings are delivered at night and vice versa - in anti-phase with endogenous rhythms. However, in each condition there should be clear monitoring of the patient experience and defined criteria for reverting to

conventional therapy if clear evidence of exacerbation of sleep and circadian disruption is observed.

In general, it should be noted that the extensive monitoring required for capturing gold-standard sleep and circadian information can constitute a high patient burden and can require the patient to spend multiple days in a clinical research facility. For efficacy trials where each condition needs to be experienced on a clinically relevant timescale, it will be essential to employ validated but lower-burden measures - e.g. monitoring sleep with wearable EEG rather than full polysomnography, or estimating CBT from wearable devices. This will also show whether the concept is able to translate from the clinical research facility setting to the patients' home environment and everyday routine.

Preparation for exploration of new DBS targets

While experimental medicine, and ultimately efficacy trials, may be able to use implants and DBS leads already implanted, investigating the modulation of new targets (dorsal raphe nucleus or SCN, Fig. 3) requires new surgical implantation of DBS leads in these locations. To ensure an acceptable risk/benefit profile for such trials, a solid evidence base would need to be built up before implantation. One avenue for building up such an evidence base is the use of preclinical models, which have been informative in the history of PD and DBS research. However, while these models often accurately display the motor symptoms of PD, care must be taken that chosen models replicate the relevant sleep and circadian symptoms[6].

In human (and possibly PD patient) cohorts, recent advances in non-invasive neuromodulation of deep brain targets using transcranial focused ultrasound (tFUS)[255] or electrical temporal interference (TI) stimulation[256] provide another promising avenue for investigation. These approaches could at least establish the feasibility of impacting circadian rhythms in the target population during shorter protocols, to evaluate the potential benefit of dedicated human DBS implantations.

Risks and challenges

DBS is already an approved therapy for PD, with well-defined risks including the usual surgical risks (e.g. stroke, bleeding, post-surgical infection) as well as use-case specific side-effects such as bradykinesia[61,62,257], dyskinesia[61,62], or dysarthria (affected speech)[61]. A review by Sarica et al[59] provides an in-depth look into infection rates and causes in PD-DBS studies, outlines other complications that could lead to replacement surgeries (e.g. Twiddler's Syndrome, broken electrodes), and battery life concerns, as well as how these risks have been mitigated. However, it should be noted that the risk and safety profile of DBS in current clinical practice is highly favourable.

Circadian DBS introduces additional risks. This paradigm could theoretically exacerbate insomnia, EDS, RBD, impulsivity, mood instability, motor symptoms, autonomic dysfunction, and/or cognitive fluctuations if stimulation timing is inappropriate or biomarkers are incorrectly interpreted (i.e. if the device clock/model and the human rhythm are misaligned). Misaligned therapy also has the potential to phase-shift symptoms and/or side-effects outside of expected time windows (e.g. the time at which tremor is worst is shifted to the night-time). Such a misalignment of therapy could occur whenever an error is introduced in the device clock, whether from device reset or slowing, daylight savings time, or a change in time zone. If using a rechargeable system, therapy alignment would also depend on users keeping their devices charged, as a battery depletion could trigger a device reset. Misalignment could also result from misinterpreted circadian biomarkers, which could arise from measurement artefacts. In the context of using non-circadian biomarkers to adapt stimulation (e.g. LFP beta-power is used to modulate sleep as in Fig 2D), measurement artefacts could lead to a mismatch between symptoms and therapy. This mismatch could become increasingly likely if, as treatment is administered, the pathological signal of interest decreases in amplitude. Finally, the volume of tissue activated by stimulation could include nearby structures and drive unexpected circadian system effects in unaccounted areas. Careful consideration of these risks throughout technological development, and investigations (clinical and preclinical) will be crucial.

Conclusion

In summary, circadian disruption forms a significant and debilitating part of PD for many patients, but is overlooked in conventional treatment. Several chronotherapies are currently being researched to address this issue including the scheduled timing of bright light exposure, physical activity, meals, sleep, L-dopa administration, and melatonin. DBS, an increasingly common treatment for PD, also carries potential for treating circadian disruption via integration with existing chronotherapies, the regulation and scheduling of sleep, or via direct neuromodulation of the circadian system. Further research into this field has the potential to unlock high-adherence, low-risk, and possibly high-reward treatment of circadian disruption in PD and beyond[258–263].

Data availability

No datasets were generated or analysed during the current study.

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M.M.K.—Conceptualization & design, writing (original draft preparation, synthesis, and editing), figures. J.J.v.R.—Writing (synthesis and editing), figures. V.S.M.—Writing (synthesis and editing). D.J.D.—Writing (synthesis and editing), figures, supervision. T.J.D.—Writing (synthesis and editing), supervision. T.G.C.—Conceptualization & design, writing (synthesis and editing), supervision. All authors have read and approved the manuscript.

Competing interests

M.M.K.—The author declares no competing financial or non-financial interests. JJvR - JJvR has received speaker fees from Medtronic in 2023 and was a paid consultant at Amber Therapeutics Ltd. in 2025. V.S.M.—V.S.M. was a paid intern for Medtronic, Inc. between 2019 and 2021 and a paid consultant at Amber Therapeutics Ltd. in 2025. D.J.D.—D.J.D. received equipment from Somnofy and is a consultant to KAMINO SYSTEMS, Boehringer-Ingelheim, AstronauTx Ltd, and Danisco Sweeteners OY. T.J.D.—T.J.D. is a founder and chief engineer of Amber Therapeutics Ltd., is the non-executive chairman of Mint Neurotechnologies Ltd, and a non-executive director at Onward Medical N.V. T.G.C.—T.G.C. is an employee, shareholder and director of Mint Neurotechnologies Ltd.

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