

Effect of stimulation of mRGCs on Alzheimer's and Parkinson's disease

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Abstract

Sleep problems are commonly seen in patients with Alzheimer's disease (AD) and Parkinson's disease (PD). They may contribute to morbidity and a poor quality of life. Reducing the sleep problems may improve the symptoms again and improve the quality of life. Sleep problems may be an effect of an disruption of the circadian rhythm. So, if melanopsin-containing retinal ganglion cells (mRGCs) are able to entrain the circadian rhythm, how does mRGC stimulation affect AD and PD patients with a disrupted circadian rhythm?

As light stimulates mRGCs, bright light therapy (BLT) is used in practice to stimulate the mRGCs. In AD, this hasn't been successful yet. Results have been very mixed and a meta-analysis even concluded that BLT on AD had no effect on cognition, sleep, challenging behavior and psychiatric symptoms. However, due to the lack of a precise protocol on BLT, there is still a chance significant results will be seen in the future. Also, BLT might lead to a good circadian rhythm, but since many factors contributes to good sleep, this doesn't necessarily translates to good sleep.

In PD, BLT has been more successful. Studies found that BLT significantly improves symptoms, including motor dysfunctions and sleep behavior problems. It is suggested that this could be due to the effect of mRGCs on dopaminergic signaling. Also, BLT is able to decrease the amount of dopaminergic replacement drug a patient needs. As dopaminergic replacement drugs cause dyskinesia in PD patients, the reduction also leads to better sleep. However, the number of studies of BLT on PD patients is limited, and the studies differ in timing, dosage and treatment duration. So in the future more research must done to determine the optimal parameters.

1. Introduction

1.1. *Introducing problem*

Cerebral neurodegenerative disorders are a high burden in Europe. It is estimated that the prevalence of Alzheimer's disease (AD) in Europe is at 5,05% (Niu, Álvarez-Álvarez, Guillén-Grima, & Aguinaga-Ontoso, 2017), which makes it the most common neurodegenerative disorder. The second most frequent neurodegenerative disorder, Parkinson's disease (PD), was estimated back in 2000 to have a prevalence of around 1,8% in Europe (de Rijk et al., 2000). These are only two of the many neurodegenerative disorders, which includes Huntington's disease, motor neuron diseases (including amyotrophic lateral sclerosis (ALS)), Creutzfeldt-Jakob disease and multiple sclerosis. Many of these disorders are more prevalent in the elderly. As the number of elderly in Europe continues to grow, estimated to reach 25% of the total population in 2030, the number of neurodegenerative patients will also increase rapidly.

Neurodegenerative disorders are characterized by the process of neurodegeneration, which is the progressive loss of structure or function of neurons. In many neurodegenerative disorders, neurodegeneration will lead to problems in sleep behavior, affecting for instance 60% of the Parkinson patients (Tandberg, Larsen, & Karlsen, 1998). This contributes to morbidity and the poor overall quality of life. And in some diseases, it could even be involved in driving the disease process itself, which may be a possibility in AD (Ju, Lucey, & Holtzman, 2014). Thus it is important that sleep disorders in neurodegenerative disorders are treated, as treatment may improve symptoms of the neurodegenerative condition and improve the quality of life, and in some cases, could possibly even slow down the disease process.

1.2. *Circadian rhythm*

Sleep in humans follows a circadian rhythm. The endogenous human circadian rhythm is however not precisely 24 hours. But through external and internal time cues, it will be synchronized to a 24 hour rhythm. These stimuli are known by the German word 'Zeitgeber'. Out of the several Zeitgebers, light is the most important one. In synchrony with the solar time, the suprachiasmatic nucleus (SCN), which lies in the hypothalamus, dictates a 24 hour rhythmicity in many biological processes of the organism and thus entrains the circadian rhythm (Berson, 2003). The main afferent pathways come from the melanopsin-containing retinal ganglion cells (mRGC), which are also known as intrinsically photosensitive retinal ganglion cells (ipRGCs). They reach the SCN either directly through the retinohypothalamic tract or indirectly through retinogeniculate pathways (Dardente & Cermakian, 2007). The main efferent pathways project to the subparaventricular zone and paraventricular nucleus of the hypothalamus. The SCN can also communicate through humoral signals via melatonin, which is a hormone that is produced in the pineal gland (Tosini & Menaker, 1998). It is only secreted during the dark phase of the light/dark cycle, hence it is sometimes called the 'hormone of darkness'. During the light phase of the light/dark cycle, the melatonin secretion is inhibited through mRGC regulation via the retinohypothalamic tract (Claustrat, Brun, & Chazot, 2005). This mechanism causes melatonin to be involved in signaling the 'time of day' and 'time of year'.

The circadian rhythm is regulated by a core set of clock genes (Moore, 2013). They control a substantial proportion of the genome. It is estimated that they regulate approximately 10% of all expressed genes. The circadian clocks are present in almost all peripheral tissues. While the peripheral circadian clocks are influenced by their own synchronizers, they are probably synchronized by either direct input from the SCN or through SCN-mediated messages (Bernard, Gonze, Čajavec, Herzel, & Kramer, 2007).

1.3. Desynchronization of the circadian clock

What happens when the circadian clock desynchronizes? Wulff, Gatti, Wettstein, & Foster (2010) proposes a complex relationship between neuropathology and circadian rhythm. At the core of this relationship is the psychiatric or neurodegenerative disorder. This disorder causes an abnormal neurotransmitter release. As neurotransmitters have an effect on sleep and circadian rhythm, an abnormal neurotransmitter release can cause circadian rhythm disruption, for instance through a disrupted timing of melatonin or core body temperature (Reghunandanan & Reghunandanan, 2006). Circadian disruption can cause an reduced sleep efficiency, leading to an increased tendency to fall asleep during the daytime, together with an increased wakefulness during the night. Subsequently, this will lead to an abnormal light exposure and social behavior. These abnormalities cause the activation of the stress axis, which will affect hormone production and other physiological responses. Together with medication or perhaps substance abuse, the net result will be a serious disruption of multiple neural and neuroendocrine pathways. Because of the many variables, this can lead to many possible effects. Effects include impaired cognition, impaired emotions, metabolic abnormalities, reduced immunity and elevated risks of cancer and coronary heart disease (Wulff et al., 2010).

1.4. Melanopsin-containing RGCs

To keep the body from desynchronizing, stimuli from the most important Zeitgeber, light, may be needed. Light is being absorbed by the retina through photoreceptors. While rhodopsin and photopsin are the pigments of respectfully scotopic and photopic vision, melanopsin is the pigment that controls pupil size and the sleep/wake cycle. In humans, it is expressed in the eye, exclusively by a small percentage of the retinal ganglion cells (RGCs), the melanopsin-containing RGCs (mRGCs) (Hattar, Liao, Takao, Berson, & Yau, 2002). As indicated earlier, mRGCs project directly through the retinohypothalamic tract to the SCN (Dardente & Cermakian, 2007), which causes entrainment of the circadian rhythm (Berson, 2003).

Less active mRGCs are able to cause a disruption in the circadian rhythm. This was shown in Glaucoma patients. Glaucoma is a group of optic neuropathies, which are characterized by the progressive degeneration of RGCs. Gracitelli et al. (2015) showed that this is associated with the dysregulation of the circadian rhythm and a high incidence of sleep disorders. This is further confirmed by an abnormal melatonin secretion and light-induced melatonin suppression that was found in glaucoma patients (Pérez-Rico, de la Villa, Arribas-Gómez, & Blanco, 2010).

1.5. Alzheimer's disease and Parkinson's disease

As AD and PD are the most common and researched neurodegenerative disorders. Therefore, they will be further discussed. AD is clinically characterized by a slowly progressive cognitive decline, with predominant dysfunction in anterograde memory, along with aphasia, apraxia and executive dysfunction. The disease causes neuronal death. It spreads from the entorhinal cortex to the hippocampus and surroundings to eventually the neocortex (Braak & Braak, 1991). Sleep disorders are very common in patients with AD. Many patients with AD have a high prevalence of day-time sleeping (Tractenberg, Singer, & Kaye, 2006). Together with fragmented sleep at night, this ultimately could result in internal desynchronization (Wulff et al., 2010), which has a major impact on the quality of life. In fact, sleep disturbances are one of the main factors for AD patients to be institutionalized (Pollak & Perlick, 1991).

PD is the result of degeneration of dopaminergic neurons within the substantia nigra. Characteristic to PD patients are the Lewy bodies, which are intraneuronal α -synuclein inclusions. PD patients develop

several motor problems such as tremor, bradykinesia, rigidity, and gait impairment. They also develop several non-motor manifestations caused by PD affected neurotransmitter systems. An example of a non-motor manifestation is an impaired circadian rhythm. Dopamine is a neurotransmitter that influences the circadian rhythm, but the dopamine signaling activity is also influenced by the circadian rhythm (Videnovic & Golombek, 2013). So impaired circadian rhythm could not only alter the sleep-wake cycle, but also negatively affect the dopamine signaling, therefore aggravating autonomic, cognitive, psychiatric and motor manifestations of the disease.

mRGCs stimulate entrainment to solar time, but it is yet unknown if an disrupted circadian rhythm that is affected by a neurodegenerative disease, is able to entrain to solar time again through mRGC stimulation. Since AD and PD are the discussed diseases, how does mRGC stimulation affect AD and PD patients with a disrupted circadian rhythm? This question will be answered by first finding out how both diseases and the sleep cycle are exactly linked. Then, the effect of bright light therapy on AD and PD will be discussed.

2. How are AD and PD linked to the sleep cycle?

2.1. Alzheimer's disease

AD patients tend to have an increased wakefulness during the night in advanced but also mild to moderate AD patients (Bonanni et al., 2005). Research estimates that because AD patients sleep highly fragmented, they spend approximately 40% of their night awake and a large portion of the solar day asleep (Ancoli-Israel, Parker, Sinaee, Fell, & Kripke, 1989). AD patients also have decreased REM sleep (Bliwise, 1993). Furthermore, a typical indicator of circadian rhythm change in AD is a phase delay, which increases with the disease duration and progression (Harper et al., 2004).

Research has been done on individuals in the first stage of preclinical AD who are still cognitively normal, but have evidence of amyloid plaque. It was found that they have a worse quality of sleep than individuals without evidence of amyloid plaque (Ju et al., 2013). Ju et al. also found that this is a bidirectional relationship, as problems in the sleep-wake cycle have been found to increase the A β levels of the brain (Ju et al., 2014). Chronic sleep deprivation will even result in chronic accumulation of A β . Once A β accumulates, increased wakefulness and altered sleep patterns continue to develop (Kang et al., 2009). Kang et al. also found that sleep extension through treatment with an orexin receptor antagonist decreased A β plaque deposition.

Histological and optical coherence tomography (OCT) studies in AD have shown a loss of RGCs and consequently axonal depletion in the optic nerve (Hinton, Sadun, Blanks, & Miller, 1986). The optic nerve consists of four quadrants. The inferior quadrant gets information from the superior visual field, the superior quadrant from the inferior field. The temporal quadrant gets the information from the nasal field, the nasal quadrant from the temporal visual field. Recent OCT studies point out that the axonal depletion is more pronounced in the superior quadrant of the optic nerve in AD patients (Kirbas, Turkyilmaz, Anlar, Tufekci, & Durmus, 2013).

La Morgia et al. (2016) found that the mRGCs are especially affected by AD. It was found that A β deposits were present within and around the mRGCs. These were also more evident in the superior quadrant of the retina (Alexandrov, Pogue, Bhattacharjee, & Lukiw, 2011). Furthermore, La Morgia et al. found that even when the RGC count was normal, there was still a loss of mRGCs, suggesting that a specific AD pathology targets mRGCs. As less active mRGCs cause a disruption in circadian rhythm in glaucoma patients, it can be argued that when mRGCs are affected in AD patients, it too may contribute to circadian dysfunction. This has recently been affirmed by La Morgia et al. (2016), who found a correlation between loss of mRGCs in AD retinas and circadian dysfunction in mild to moderate AD patients.

Environmental factors also play a role in sleep disorders in AD patients. Elderly tend to spend more time indoors (Shochat, Martin, Marler, & Ancoli-Israel, 2000), where the artificial light is usually too low to entrain rhythms (Ancoli-Israel et al., 1997). This is especially true in nursing homes, where patients hardly receive any bright light. Demented patients have been found by Ancoli-Israel et al. to receive bright light for only one minute. Furthermore, nursing homes can generate noise that can disrupt the patients sleep. 35-50% of the awakenings of patients in nursing homes can be attributed to ambient noise, which can be largely attributed to nursing staff (Schnelle, Ouslander, Simmons, Alessi, & Gravel, 1993). Another important environmental factor is physical activity. A study by Namazi, Zadorozny, & Gwinnup (1995) found a 25% increase in observed 'sound sleep' in AD patients that live on a special care unit following a four-week program of 40 minutes of daily exercise.

Brain damage in areas that affect sleep also play a role in sleep disorders in AD patients. Brain nuclei in the anterior hypothalamus (e.g. ventrolateral preoptic nucleus (VLPO) and the SCN), lateral and posterior hypothalamus and the basal forebrain contain key regulatory circuits for the control of sleep and vigilance (Wulff et al., 2010). AD patients show a higher level of neuropathology in the SCN, compared to healthy individuals (Hofman & Swaab, 1994). Furthermore, a degeneration of the cholinergic neurons in the basal forebrain will cause a disruption of the REM sleep. If the VLPO is weakened too, it will lead to a reduction in slow-wave sleep (Wulff et al., 2010).

2.2. Parkinson's disease

Markers of circadian rhythms provide some insight into the circadian timekeeping in PD. The amplitude of melatonin rhythm is decreased, and the phase of the melatonin rhythm was advanced compared to newly diagnosed patients (Bordet et al., 2003), while newly diagnosed patients were found to have a preserved melatonin rhythm compared to healthy controls (Fertl, Auff, Doppelbauer, & Waldhauser, 1993). The core body temperature has however a similar 24-hour rhythm compared to healthy controls (Pierangeli et al., 2001), but research studies nevertheless seem to suggest the presence of modifications of circadian rhythmicity in PD (Videnovic & Golombek, 2013).

A dysregulated circadian rhythm in PD could be a consequence of disrupted sleep. Sleep disorders are present in almost all PD patients (Tandberg et al., 1998). The most common ones are insomnia, periodic limb movement disorder, sleep-disordered breathing and sleep behavior disorder. The disorders are partly due to the motor and non-motor symptoms of the PD patients, which continue overnight and are part of the reason PD patients suffers from fragmented sleep (Malhotra, 2018). This is also caused by long-term dopaminergic medications, as it can cause dyskinesia in PD patients, which is found to be positively associated with poor nighttime sleep in PD patients (Mao et al., 2018).

In addition, sleep problems are also affected by sleep-controlling centers that are affected by the disease. These sleep-controlling center are involved in REM and slow wave sleep disorders. In animal models, they have been found to also be involved in PD (Takakusaki, Saitoh, Harada, Okumura, & Sakamoto, 2004), and they could be the reason PD patients have a reduced slow wave sleep and REM sleep (Malhotra, 2018).

Also excessive daytime sleepiness is a symptom that is common in PD patients. Abbott et al. (2005) even suggested that hypersomnia could be preceding the development of other motor symptoms in PD, demonstrating that sleepy adults had three times higher risk of developing PD than non-sleepy adults. Hypersomnia could also be a side effect of the dopamine agonists that are used on PD patients, as hypersomnia is a known side effect of dopamine therapy.

Inversely, the circadian rhythm also has an influence in PD. PD patients have more intense motor symptoms in the afternoon and evening (Bonuccelli et al., 2000). As Bonuccelli et al. point out, this does not relate to the pharmacokinetics of dopaminergic medication. Videnovic, Lazar, Barker, & Overeem (2014) argue that rather it is likely related to circadian regulation of dopaminergic systems.

A disrupted circadian rhythm might be the consequence of affected mRGCs. This further could be suggested due to visual problems which occur frequently in PD. Some of the visual problems are a result of a reduction in dopamine levels in the retina. (Bodis-Wollner, 1990). However, evidence for RGC loss in PD is also observed (Yu et al., 2014), which unlike AD, affects the temporal sector of the optic nerve (Yu et al., 2014). Recent studies suggest a α -synuclein deposition in the retina of PD patients, suggesting that PD pathology also affects the eye (Bodis-Wollner, Kozlowski, Glazman, & Miri, 2014). Also, an α -synuclein has been found in a potential, unconfirmed mRGC cell (Beach et al. 2014). The presence of α -synuclein in mRGCs could mean that this contributes to the circadian disruption that is found in PD. This however, remains to be tested.

3. Effects of Bright light therapy on neurodegenerative disorders?

3.1. Bright light therapy

So it appears there is the link between AD and PD, and the disruption of the circadian rhythm is partly due to mRGC dysfunction. Now it is interesting to see when the mRGCs are stimulated, if that would improve the circadian rhythm? One of the ways the mRGCs are stimulated in practice is through the use of a bright light. In bright light therapy (BLT), patients are exposed for a certain time to white, UV-filtered, diffuse illumination that generally has a illuminance of around 10.000 lux. It seems that BLT has an antidepressant response and a normalization of a hypersomnic and fractionated sleep pattern while it is possible to phase-shift the sleep (Terman et al., 1990). Generally, protocols follow a 24-hour lighting scheme, where sessions start either every morning or in the evening.

BLT has already been successfully implied in patients with seasonal affective disorder (SAD). SAD patients show depressive episodes during winter. It is hypothesized that they have abnormal responses to diminishing day length in fall (Dallassezia & Benedetti, 2011). Patients are given morning light exposure which should signal the spring dawn. This has been proven rather successful and is now the primary choice to treat winter depression (M. Terman & Terman, 2005). In treating SAD, the protocol includes a dose of 10.000 lux for 30 minutes or 2500 lux for 2 hours. Furthermore, it has been found that morning light is superior to evening light (M. Terman & Terman, 2005).

BLT has also been implied in treating mood disorders, cognitive disabilities, circadian misalignment, and alterations of sleep-wake behavior (Dallassezia & Benedetti, 2011). On this experience, it is interesting to research how BLT affects Alzheimer's disease and Parkinson's disease.

3.2. Alzheimer's disease

A precise protocol for BLT with AD patients hasn't been developed yet. The light intensities that were used in studies range from 2500-10.000 (McCurry et al., 2011) (Burns, Allen, Tomenson, Duignan, & Byrne, 2009), they were used either in the morning or evening, and the experiments lasted from 1 week (Satlin, Volicer, Ross, Herz, & Campbell, 1992) to several months (Dowling et al., 2008).

Results regarding the effect of bright light have been very mixed. For instance, Sloane et al. (2007) showed a statistically significant improvement in nighttime sleep with morning or all-day light, with greater improvement among persons with severe dementia. Furthermore, while testing the effects of morning versus evening light, Dowling, Mastick, Hubbard, Luxenberg, & Burr (2005) found that both groups evidenced a significantly more stable rest-activity rhythm acrophase over the 10-week treatment period compared with the controls. They however, found no difference between the groups, while they hypothesized that based on the fact that a lot of AD patients are phase delayed, morning light should have had the most improvement.

Contrary to these findings, Dowling et al. found in 2008 no effect of light treatment alone on nighttime sleep, daytime wake or rest-activity rhythms. In addition, a meta-analysis by Forbes et al. (2014) on BLT in AD patients puts doubt on the methods used of a lot of studies. Forbes et al. argues that over a quarter of the studies show a high risk of bias towards performance bias, detection bias and reporting bias. Furthermore, the study analyzed the results on improvements in cognition, sleep, challenging behavior and psychiatric symptoms. In all the cases, pooled data revealed no significant improvements on AD due to bright light therapy.

Figueiro (2017) addresses the study from Forbes et al. by stating that the mixed results are due to the fact that a precise protocol hasn't been developed, which may lead to the weakening of the therapeutic effects of light. Many studies also use different light delivery methods. In fact, many studies mentioned by Forbes et al. also didn't have any control over how much light subjects were actually exposed to during the intervention. According to Figueiro, studies that actually did carefully deliver controlled light, found a positive impact of light on sleep quality of those with AD (Figueiro et al., 2014; Hanford & Figueiro, 2013). Unfortunately, Figueiro can only cite own papers, so it should be interpreted with caution. Figueiro further states that even if bright light therapy causes a good circadian rhythm, that doesn't necessarily lead to good sleep, as other factors also affect sleeping behavior.

Thus BLT in AD hasn't had enough convincing results to be used in practice for sleep problems. Based on research from Figueiro (2017) that might be due to bad protocols where studies didn't put enough effort into controlling the amount of light that reaches the cornea. It is also possible that improving the circadian rhythm does not lead to an improvement in sleep. Sleep has many important brain areas throughout the brain as summed up nicely by Brown, Basheer, McKenna, Strecker, & McCarley (2012). If brain damage in those areas caused by AD results in a non-circadian sleep disorder, light therapy might not be effective.

3.3. Parkinson's disease

Also in Parkinson's disease a precise protocol for BLT hasn't been developed. Bright light intensities in studies range from 1000 to 10.000 lux, durations last from 30 min to 1,5 hours, and they were used in the morning, evening or twice a day (Aleksandar Videnovic et al., 2017) (Willis, Moore, & Armstrong, 2012a) (Paus et al., 2007) (Willis & Turner, 2007).

While the amount of studies revolving around PD and BLT are scarce, the results are more positive compared to AD patients. In the studies, BLT significantly improves motor dysfunction including bradykinesia, rigidity, tremor, nocturnal movements, dyskinesia, and postural imbalance. It also improved sleep behavior problems like, insomnia, excessive daytime sleepiness, and overall fragmentation of the sleep-wake cycle. Also an antidepressant and antianxiety effect has been found in PD patients. These effects were similar to the effects that were found by using BLT on depression.

A recent article by Martino, Freelance, & Willis (2018) looked at the long-term results from BLT on PD patients. It was found that 1 hour exposure to light significantly improved insomnia and reduced REM Sleep Behavior Disorder after one month after commencing BLT. This improvement was maintained for as long as the BLT treatment was continued, which was a period of four to six years.

Another positive effect of BLT is that PD patients are able to decrease the amount of L-DOPA medication by 50% while still maintaining therapeutic efficacy (Willis et al., 2012a). L-DOPA is dopaminergic replacement drug and it has been known that these can lead to poor nighttime sleep (Mao et al., 2018). So a reduced intake of L-DOPA could have a positive effect on nighttime sleep. Yet PD patients already see improvement in nighttime sleep using BLT in the presence of high dosing with dopaminergic replacement drugs (Willis, Moore, & Armstrong, 2012b).

There is a possibility that BLT mediates its effects through the stimulation of the dopaminergic signaling. This hypothesis is supported by an electrophysiological study in rodents that showed that dopaminergic neurons respond to light (Dommett et al., 2005). In addition, it has been shown that a decrease in dopamine has negative effects on the retina (Bodis-Wollner, 1990). Therefore, the hypothesis is certainly not far-fetched, yet additional research on how light influences dopaminergic signaling is needed.

While studies show that BLT can have a positive effect on the sleep behavior of PD patients, it is still not clear what the precise protocol should be in PD patients. Since many PD patients show a phase-advanced behavior, it can be argued that the light intervention should take place in the evening at least for some time, as it has been shown that this causes a phase-delay (Duffy, Scheuermaier, Münch, & Ronda, 2013). However, both the studies with morning interventions (Paus et al., 2007) as the studies with evening interventions (Martino et al., 2018) yield positive outcomes. Because the sources are scarce and the studies themselves differ in timing, dosage, and treatment duration, it is not possible to define the optimal parameters as of yet and thus that requires more research.

4. Discussion & Conclusions

BLT is now being used for therapy in several disorders. As a result, research is expanding and trying to find if it may help in neurodegenerative disorders, like AD and PD.

In AD, the effect remains unclear. The results in research aren't convincing and a meta-analysis in 2014 by Forbes et al. therefore concluded that BLT has no effect on cognitive function, sleep, challenging behavior, or psychiatric symptoms associated with dementia. The results by Forbes can still be disputed by stating that there aren't many significant results because a precise correct protocol for BLT in AD is still lacking. Figueiro for instance, did find significant results in several of her studies.

Fragmented sleep-wake patterns might not improve with BLT because mRGCs might be damaged themselves. La Morgia et al. (2016) found A β deposits in mRGCs. Also a loss of mRGCs was observed during a normal RGC count, suggesting that a specific AD pathology targets mRGCs. To further strengthen this hypothesis, A axonal depletion has been observed in the optic nerve, most pronounced in the superior quadrant.

Fragmented sleep-wake patterns might also not improve because the stimulation of mRGCs doesn't affect the brain areas that are affected by AD. This might be due to the fact that mRGCs don't project to the area that is affected. This is probably the case for non-circadian disorders. The area might also not respond to the stimulation. For instance, AD patients show a higher level of neuropathology in the SCN, which if bad enough, could hypothetically inhibit any response to stimulation. Environmental factors of nursing homes can also contribute to fragmented sleep-wake disorders, as patients can be awakened by roommates, ambient noise, or bed-checks.

At the moment, bad protocols can still be blamed for bad results. So to find out if BLT might have an effect on AD, it is important to determine what the best lighting protocol is to follow. Furthermore, it may be helpful to look into the mRGC signaling during BLT and the brain damage of the test patients, as patients with damaged mRGCs and patients with brain damage in certain areas may not be fit for BLT stimulation anymore.

The effect of BLT in PD is considerably more positive than in AD. While the number of studies are limited, BLT did significantly improve motor dysfunction, sleep behavior problem and overall fragmentation of the sleep-wake cycle. Also an antidepressant and anti-anxiety effect has been found in PD patients.

Direct mRGC damage in PD patients hasn't been observed yet. However, RGC loss and a α -synuclein deposition can be seen in the retina. Furthermore, a reduction of dopamine in the retina of PD patients has been observed, which is the cause for contrast sensitivity problems.

The positive outcomes of BLT can have several causes. First, mRGCs might be able to positively affect the circadian rhythm by stimulation of the retinohypothalamic tract. An effect of the circadian rhythm on the dopaminergic system could explain the reduction in motor dysfunction. Second, light may have a more direct effect on the stimulation of dopaminergic signaling. Third, dopaminergic replacement drugs are known to be able to cause dyskinesia which leads to poor nighttime sleep. BLT causes PD patients to be able to reduce the L-DOPA intake by 50% while still maintaining therapeutic efficacy. Thus, this may lead to less dyskinesia in PD patients. This is however not the primary cause, as Willis, Moore & Armstrong (2012b) observed that patients also had improvement in nighttime sleep in the presence of high dosing with dopaminergic replacement drugs.

While PD patients that used BLT showed improvements, a lot is still not known. A precise protocol for BLT with PD patients to follow hasn't been made yet, and with the limited amount of studies it is not possible to determine what the protocol with the best outcome is. So, future studies should be comparing different settings for BLT so this can be determined. Further, the mechanism is still not known. Future studies should aim to determine the mechanism so this can be included in a design for a protocol.

Compared with AD, PD shows better outcomes using BLT. This might be due to the different progression or different origins of the disorders. BLT has been observed as having an effect in dopaminergic systems, so it might be more useful for PD patients than to AD patients. The better outcomes also could be the result of research on BLT in PD patients being restricted to a small select group of researchers. The variety of authors is larger in AD and that causes the variety in protocols and methods to be larger, causing more different results. In addition, an meta-analysis about BLT with PD patients is still missing, so the positive outcomes could still be the result of a bias or faulty methods. Therefore, it is important that more research groups will be involved and that articles will be written that evaluate the now-written articles about BLT with PD patients.

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