Photobiomodulation, Photomedicine, and Laser Surgery
Volume XX, Number XX, 2021

Pp. 1–11
DOI: 10.1089/photob.2021.0056

Remote Photobiomodulation Treatment for the Clinical Signs of Parkinson's Disease: A Case Series Conducted During COVID-19

Ann Liebert, PhD,[1,2] Brian Bicknell, PhD,[3] E-Liisa Laakso, PhD,[4,5] Parastoo Jalilitabaei, MBBS,[1] Sharon Tilley, BAppSci(Physiotherapy),[6] Hosen Kiat, MBBS, DMedSc,[7,8,i] and John Mitrofanis, PhD[1]

Abstract

Objective: To assess whether remote application of photobiomodulation (PBM) is effective in reducing clinical signs of Parkinson's disease (PD).
Background: PD is a progressive neurodegenerative disease for which there is no cure and few treatment options. There is a strong link between the microbiome–gut–brain axis and PD. PBM in animal models can reduce the signs of PD and protect the neurons from damage when applied directly to the head or to remote parts of the body. In a clinical study, PBM has been shown to improve clinical signs of PD for up to 1 year.
Methods: Seven participants were treated with PBM to the abdomen and neck three times per week for 12 weeks. Participants were assessed for mobility, balance, cognition, fine motor skill, and sense of smell on enrolment, after 12 weeks of treatment in a clinic and after 33 weeks of home treatment.
Results: A number of clinical signs of PD were shown to be improved by remote PBM treatment, including mobility, cognition, dynamic balance, spiral test, and sense of smell. Improvements were individual to the participant. Some improvements were lost for certain participants during at-home treatment, which coincided with a number of enforced coronavirus disease 2019 (COVID-19) pandemic lockdown periods.
Conclusions: Remote application of PBM was shown to be an effective treatment for a number of clinical signs of PD, with some being maintained for 45 weeks, despite lockdown restrictions. Improvements in clinical signs were similar to those seen with the application of remote plus transcranial PBM treatment in a previous study. Clinical Trial Registration number: U1111-1205-2035.

Keywords: photobiomodulation, Parkinson's disease, remote treatment, mobility, cognition

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, affecting more than 10 million people worldwide, with growing numbers due to increasing incidence with age in an aging population, longer duration of the disease,[1] and possible neurological sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[2,3] The disease incurs a substantial economic burden.[4] To date, there is no curative treatment or effective strategy to halt or even slow symptom progression.

There is an increasing acknowledgement of the gut–brain axis, which can influence such diverse diseases and symptoms as behavior, anxiety, autism spectrum disorder, depression, schizophrenia, addictive and compulsive behaviors,

[1]Faculty of Medicine and Health Sciences, Sydney University, Camperdown, Australia.
[2]Office of Research and Governance, Adventist Hospital, Wahroonga, Australia.
[3]Faculty of Health Sciences, Australian Catholic University, North Sydney, Australia.
[4]Mater Research Institute, University of Queensland, South Brisbane, Australia.
[5]Menzies Health Institute, Griffith University, Gold Coast, Australia.
[6]Lymphoedema and Laser Therapy, Stepney, Australia.
[7]Cardiac Health Institute, Epping, Australia.
[8]Department of Clinical Medicine, Macquarie University, Macquarie Park, Australia.
[i]ORCID ID (https://orcid.org/0000-0002-2899-118X).

and neurodegenerative diseases.[5] The link is particularly strong in PD, with gastrointestinal signs being common and often preceding neurological signs and symptoms by years.[6] Individuals with PD have also been shown to have increased gut permeability leading to increased inflammatory processes.[7] This relationship suggests the possibility of the gut as a therapeutic target for PD therapies,[8] and studies are beginning to emerge investigating this possibility by fecal microbial transplantation (FMT),[9,10] diet,[11] and probiotic[12] interventions.

Photobiomodulation (PBM) therapy is the use of narrow-wavelength bands of nonthermal light (either light-emitting diode [LED] or laser) to modulate cellular responses, including mitochondrial function, downstream cellular signaling, and the modification of transcription factors.[13,14] One of the primary effects of PBM is anti-inflammatory, which has profound effects on many body processes.[15] PBM has been known for many years to be safe and free of side effects.[16,17] In addition to the direct effect on the target cells, PBM also has a systemic[15,18–20] and a delayed effect, likely due to the activation of DNA transcription factors.[13,14] Treatment of areas remote from the site of injury can be an effective strategy in animal models,[20] including models of PD and Alzheimer's disease[18,21–24] even when the head of the animal is shielded from irradiation.[25] The mechanism of this systemic effect may be stimulation of stem cells,[20,26] immunomodulation,[27] stimulation of circulating cell-free mitochondria,[28] modulating circulating chemical messengers,[21] or a combination of these. Another potential mechanism of action is via the microbiome.[29]

To begin to understand the role that different remote treatment protocols play in the effectiveness of PBM to potentially stabilize the signs and symptoms of PD, a proof-of-concept study was performed using an abdominal and neck PBM treatment protocol without any transcranial component. The abdomen was irradiated to target the enteric nervous system and the microbiome, and the neck was irradiated to target the vagus nerve connection of the gut–brain axis. This study complements a previous study[30] that used a combination of transcranial, intranasal, neck, and abdominal treatment to treat PD.[30]

Methods

The study had human research ethics approval by Griffith University Human Research Ethics Committee (2018/16) and Adventist HealthCare Limited Human Research Ethics Committee (2019/32) and was registered with the Australian New Zealand Clinical Trials Registry. All participants gave written informed consent before taking part.

Participants

Participants were recruited in August 2019 from a database of individuals clinically diagnosed with idiopathic PD by a neurologist, who had contacted the researchers at the completion of a previous proof-of-concept study.[30] All participants were examined by a physician to ensure suitability for enrolment. Inclusion and exclusion criteria are given in Table 1.

PBM treatment protocol

Seven participants were treated with PBM for 12 weeks in a clinical setting by a trained therapist from September 30, 2019, three times per week at the same time each day, during their ''on'' period after medication (if taken). The protocol (Table 2) consisted of a laser device with four class-1 diodes (904 nm 30 mW) targeting nine abdominal points (1 min each), and the posterior C1/C2 region of the neck (1 min), to give a total abdominal dose of 64.8 J and a neck dose of 7.2 J (Fig. 1). At the completion of the clinical treatment period, participants were supplied a home treatment laser device, and participants and carers were given a 20-min training session in its use, which was essentially identical to the clinical treatment protocol. Participants continued PBM treatment at home for an additional 33 weeks. Participants were not monitored during this home treatment, although carer feedback was sought regarding treatment compliance at the completion of the study.

Table 1. Inclusion and Exclusion Criteria for Study Participants

Inclusion criteria
Males or females
Between 60 and 80 years
Diagnosed idiopathic PD
Hoehn and Yahr stage I to III
Stable (unchanged for 6 months) anti-PD medications (if taken)
Exclusion criteria
Not capable of self-care
Cognitive impairment defined as <24 on the MoCA
History of significant psychotic episode(s) within the previous 12 months
History of suicidal ideation or attempted suicide within previous 12 months
Taken potentially photosensitizing medication, especially imipramine, hypericum, phenothiazine, lithium, chloroquine, hydrochlorothiazide, or tetracycline
History of structural brain disease, active epilepsy, stroke or acute illness, factors affecting gait performance and stance such as severe joint disease, orthopedic injuries, weakness, peripheral neuropathy with proprioceptive deficits, severe peripheral vascular occlusive disease, severe musculoskeletal disorders, uncorrected vision, vestibular problems, or other severe conditions that would preclude the use of PBM therapy, place the patient at risk during evaluation of their PD, or interfere with the evaluation of their PD
Unstable or uncontrolled cardiac disease or cardiovascular problems
Currently participating in other clinical trials of PD treatment, such as advanced therapies (Duodopa, apomorphine, deep brain stimulation)

MoCA, Montreal Cognitive Assessment; PBM, photobiomodulation; PD, Parkinson's disease.

Participant assessment

Participants were informed that a minority of people receiving PBM therapy might experience minor temporary effects (dizziness and/or mild nausea). Participants were monitored by therapists for these effects during the clinical treatment period and participants and carers were instructed to address any concerns or perceived adverse reactions from the PBM treatment to the researchers or therapists. Participants were assessed for outcome measures on enrolment, after the clinical treatment period and after the home treatment period.

Table 2. Photobiomodulation Parameters

Parameter	*Treatment in clinic*	*At-home treatment*
Manufacturer	Spectro Analytic Irradia AB (Sweden)	Spectro Analytic Irradia AB (Sweden)
Model	Prototype class 1, 4 diode probe	MIDCARE laser
Produced	2019	2019
Laser diodes	4×904 nm (GaAs)	2×904 nm (GaAs)
Wavelength	904 ± 10 nm	904 ± 10 nm
Laser class	1	1
Output power per diode	30 mW	30 mW
Peak power	25,000 mW	25,000 mW
Pulse frequency	50 Hz	50 Hz
Beam spot size	0.636 cm^2	0.636 cm^2
Power density per diode	47 mW/cm^2	47 mW/cm^2
Total output power	120 mW	60 mW
Irradiation time per point	60 sec	120 sec
Total irradiation time	600 sec	1200 sec
Total energy per point	7.2 J	7.2 J
Energy density	11.3 J/cm^2	11.3 J/cm^2
Number of points	10 (9 abdomen, 1 neck)	10 (9 abdomen, 1 neck)
Total energy dose per treatment	72 J	72 J
Treatment frequency	Three times per week for 12 weeks	Three times per week for 33 weeks
Application mode	Probe stationary in skin contact with firm pressure and perpendicular to target area	
Cumulative dose	2592 J	7128 J

Outcome measures

The primary outcome measure (Table 3) was timed up-and-go (TUG) as measure of functional mobility (balance plus gait). Secondary outcome measures included a range of motor signs, including additional tests of mobility (walking speed, stride length, TUG motor, and TUG cognition), fine motor skills, dynamic balance, static balance, micrographia, cognition and sense of smell.

Analysis

For micrographia, analysis of variance (ANOVA) was carried out to analyze changes between assessments. Due to small numbers and heterogeneity of the participants, no statistical analysis for other outcome measures was attempted. Individual changes in outcome measures were assessed using minimal clinically important difference (MCID), defined as the smallest benefit that has value to individuals. Change in outcomes measures was compared with baseline (mean of 19 participants: 7 from the current study and 12 from the previous study). An MCID occurred if there was an improvement of greater than ½ standard deviation (SD) from this baseline.[31] Larger changes were registered as 1 SD and 2 SD above baseline.

Results

Participants

Participants enrolled in August 2019 and consisted of seven males (average age 64.4 years), of whom six were right-handed and four had right-side onset of PD (Table 4). Two participants had previously received transcranial PBM treatment for PD with a VieLight Gamma™.

Safety and compliance

No adverse side effects were reported from the treatment by therapist, participants, or carers, and there were no safety concerns for PBM at this dose. All participants and carers reported that the home treatment regimen was followed for 33 weeks.

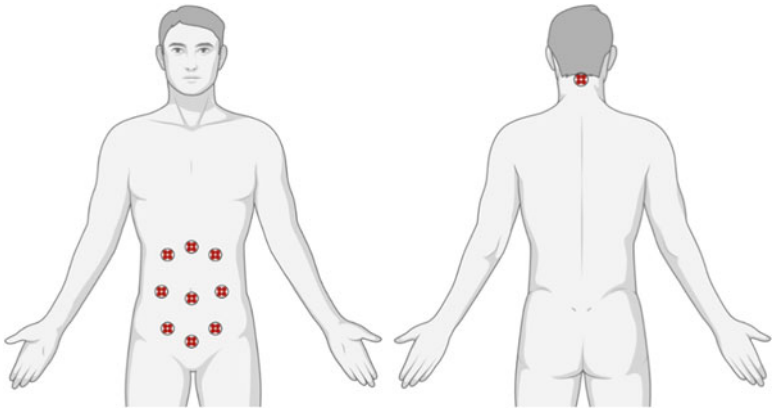


FIG. 1. PBM treatment sites. PBM, photobiomodulation.

Table 3. Outcome Measures Assessed Before Photobiomodulation Treatment and After 12 and 45 Weeks of Photobiomodulation Treatment to the Abdomen and Neck

Outcome measure	*Test*	*Description*	*Reference*
Primary outcome measure			
Functional mobility	TUG test	Assessors measured the time taken for a participant to stand from a chair, walk 3 m, turn around a marker, return and sit down.	71
Secondary outcome measures			
Mobility	TUG motor	As for TUG except that the participant was carrying a cup of water.	71
	TUG cognitive	As for TUG except that the participant was asked to count backward from 40 in twos.	71
	10 MWT speed	Participants walked a 10 m track. After walking 2 m, assessors measured the time taken to walk a further 6 m.	72
	10 MWT stride length	During the 10 MWT, assessors also counted the number of strides taken to walk 6 m.	72
Dynamic balance	Step test	Participants stood with feet together, 10 cm from a 10 cm high step. Assessors counted the number of times that a participant placed their foot repeatedly on the step in 15 sec. Both legs were tested.	73
Cognition	MoCA	Participant completed the MoCA test version 8.1 (www.mocatest.org), which was scored by an assessor.	74
Fine motor skill	Spiral test	Assessors recorded the time taken to draw between the lines of a printed Archimedean spiral. A time penalty of 3 sec was given for touching a line and 5 sec for crossing a line. Dominant hand was tested.	75
	NHPT	Assessors recorded the time taken to place nine pegs in holes and then return the pegs to the reservoir. Both hands were tested.	76
	Micrographia	Participants were asked to write the same sentence at each assessment. The area and perimeter of selected words were measured using the ImageJ software.	
Static balance	TS	Assessors recorded the time a participant could stand with one foot in front of the other (heel to toe) eyes closed until eyes were opened, a step taken, or a hand was used to steady themselves. The assessment was terminated at 30 sec. Both legs tested.	77
	SLS	Assessors recorded the time that a participant could stand with one leg raised with eyes closed until eyes were opened, a step taken, or a hand was used to steady themselves. The assessment was terminated at 30 sec. Both legs tested.	77
Olfactory loss	SIT	Five participants who had indicated that they suffered some olfactory loss completed a scratch and sniff test consisting of 40 odorants. Scores were converted to an olfactory diagnosis, as described in the SIT Administration Manual.	78

MWT, meter walk test; NHPT, nine-hole peg test; SIT, Smell Identification Test™; SLS, single leg stance; TS, tandem stance; TUG, timed up-and-go.

Grouped outcomes

Participants showed a number of improvements in outcome measures after the clinical treatment period (Table 5; full data in Supplementary Table S1). The median value for the primary outcome (TUG) improved over 12 weeks. There was also improvement in other measures of mobility (TUG, walk speed), dynamic balance (step test), fine motor control (spiral test), and also cognition (Montreal Cognitive Assessment [MoCA]). In contrast, single leg stance (SLS) declined for the affected leg and stride length decreased.

After 33 weeks of home treatment, there was some further improvement in median TUG, as well as TUG motor, TUG cognitive, and the step test with the affected leg. The

Table 4. Demographic Characteristics of Participants in the Study

Participant	*Sex*	*Years of diagnosis*	*Dominant hand*	*Affected hand*	*Comments*
S1	M	4	R	L	Previous transcranial PBM
S2	M	7	R	R	
S3	M	8	R	L	Previous transcranial PBM
S4	M	4	R	R	
S5	M	2	L	N	Family history of PD
S6	M	1.5	R	R	Lung infection and antibiotic use in weeks 2 and 3 of clinical treatment period
S7	M	5	R	R	

L, left; M, male; N, both hands equally affected; R, right.

Table 5. Medians and InterQuartile Ranges of Outcome Measures for the Photobiomodulation Parkinson's Disease Studies, Determined on Enrolment, After 12 Weeks of Clinical Treatment, and After a Further 33 Weeks of Self-Administered Home Treatment

	Enrolment (n = 7)	*12 Weeks of treatment* (n = 7)	*45 Weeks of treatment* (n = 6)
Primary outcome measure			
Functional mobility			
TUG (sec)	7.6 (2.8)	6.1 (2.10)	5.85 (1.7)
Secondary outcome measures			
Mobility tests			
TUG motor (sec)	7.9 (1.6)	7.0 (2.4)	6.6 (2.0)
TUG cognitive (sec)	7.6 (3.3)	7.5 (3.4)	6.6 (2.6)
Walk speed (m/sec)	1.76 (0.6)	2.14 (0.6)	1.13 (0.7)
Stride length (m)	1.00 (0.15)	0.86 (0.18)	0.53 (0.25)
Dynamic balance test			
Step test—affected leg (*n*)	16.0 (5.0)	17.0 (5.0)	19.0 (8.0)**
Step test—unaffected leg (*n*)	16.0 (7.5)	17.0 (4.0)	16.0 (7.0)**
Cognitive test			
MoCA score	26.5 (4.0)*	30.0 (2.3)*	29.0 (3.0)**
Fine motor control tests			
NHPT—affected hand (sec)	27.6 (11.5)*	26.4 (7.8)	32.6 (19.7)
NHPT—unaffected hand (sec)	27.1 (8.4)*	27.6 (8.0)	27.0 (9.7)
Spiral test—dominant hand (sec)	27.5 (9.6)*	21.8 (7.7)	27.3 (15.4)
Static balance tests			
TS affected foot behind (sec)	11.2 (17.3)	9.3 (26.0)	10.5 (20.6)
TS unaffected foot behind (sec)	7.4 (13.6)	8.8 (16.5)	9.3 (26.0)
SLS affected leg raised (sec)	3.3 (3.9)	2.9 (2.7)	2.6 (2.2)
SLS unaffected leg raised (sec)	2.6 (2.2)	3.6 (8.8)	4.0 (6.3)

*$n = 6$, **$n = 5$.

remainder of the outcome measures showed a deterioration, although the median MoCA score remained above the pretreatment median.

Individual outcomes

Individual improvements in outcome measures are depicted as a heat map (Table 6) representing MCID change compared with baseline. There was overall improvement for most participants during clinical treatment in many outcome measures. Participants showed improvements in cognition, walking speed, and dynamic balance with fewer improvements in fine motor skill reaching MCID. Measures of static balance (tandem stance [TS] and SLS) showed the least improvement, although two participants (S2 and S4) improved in TS to the maximum measurement (30 sec) and one participant (S1) did not show improvement since he was at maximum before treatment began.

While many participants showed an observable improvement in writing (Fig. 2), there was not a significant change in area or perimeter of words (Fig. 3). Participant S5 showed a nonsignificant decrease in letter size over the home treatment period.

A number of the improvements in individual outcome measures attained during clinical treatment were lost in some participants after home treatment (Table 6), particularly evident for walking speed, stride length, and the step test, most noticeably for participants S7 and S2.

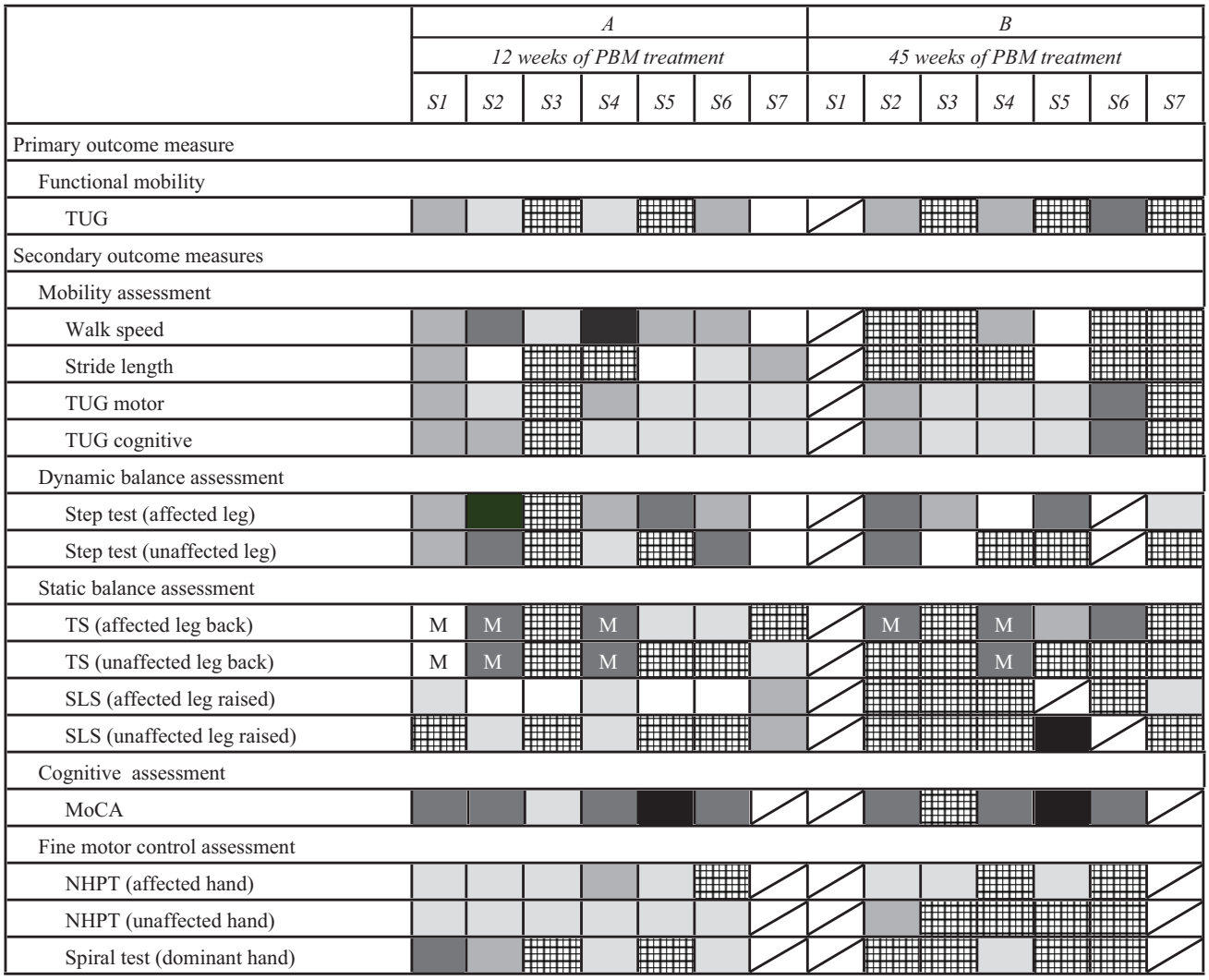
Two participants improved from ''total anosmia'' to ''severe microsmia'' after clinical treatment (Table 7), two participants showed no change from ''severe microsmia,'' and one participant showed no change from the lower 33% of ''normal.'' These results remained unchanged after home treatment.

Discussion

We have demonstrated that a number of clinical signs of PD can be improved by PBM targeting the abdomen and neck with no transcranial treatment over a 12-week period. Improvements were comparable to our previous study,[30] which used a combination of remote and transcranial PBM treatment, although it should be recognized that in the previous study the PBM dose was down-titrated over 12 weeks. Despite some of the improvements that were gained during the clinical treatment being lost in certain participants during the home treatment, many of the improvements were maintained. This is despite the complications to the study that occurred as a result of the coronavirus disease 2019 (COVID-19) pandemic and the related shutdowns. While transcranial PBM has received attention as a nonpharmacological noninvasive treatment for brain-related conditions, such as traumatic brain injuries and neurodegenerative diseases,[32–35] and has been used to treat PD in a series of case studies,[36,37] this study is the first to report that remote PBM treatment may be effective for clinical signs of PD. Importantly, no adverse reactions to the PBM treatment were reported.

The primary outcome of the study was functional mobility as measured by TUG. This improved after clinical treatment for four of the seven participants and was maintained in three of these for 45 weeks (the fourth did not attend this assessment). Many secondary outcome measures

Table 6. Heat Map Depicting Changes in Outcome Measures, Compared with Baseline of (A) 12 Weeks of Photobiomodulation in the Clinical Treatment Period and (B) Additional 33 Weeks of Photobiomodulation in the Home Treatment Period



The columns are individual participants. The rows are assessed outcome measures.

- Decline in outcome measure
- No change in outcome measure
- Small improvement in outcome measure (< ½ SD)
- MCID improvement in outcome measure (> ½ SD)
- Large improvement in outcome measure (> 1 SD)
- Large improvement in outcome measure (> 2 SD)
- Not determined

MCID, minimal clinically important difference; SD, standard deviation.

of mobility also improved over the clinical treatment period, suggesting an improvement of dynamic balance and mobility that is normally progressive in a degenerative disease. Postural instability is a major debility in PD, leading to incapacitation and increased falls risk. It occurs as a result of increasing damage to the basal ganglia and a progressive reduction in dopamine production. The improvement of mobility and balance seen here suggests that remote PBM treatment may have the capacity to modulate the neural pathways involved in postural stability, acting to compensate for the damage. While there was a deterioration in some assessments of mobility after 45 weeks, TUG improvements were for the most part maintained and, in some cases, continued to improve (S2, S6).

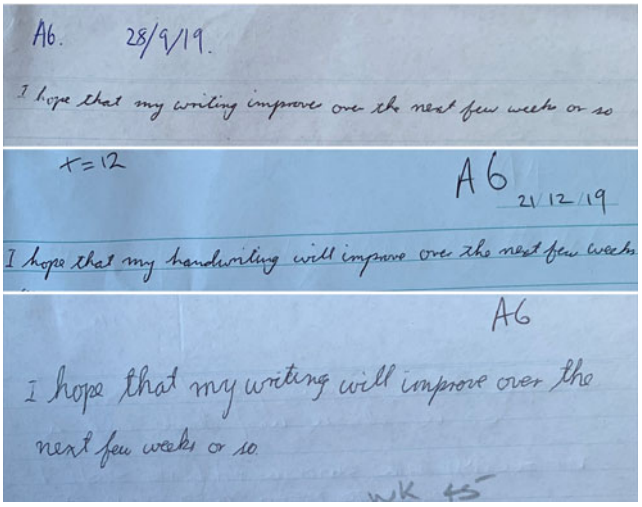


FIG. 2. An example of change in micrographia after 12 and 45 weeks of PBM treatment.

Although the improvements in static balance and fine motor skill seen at 12 weeks were mostly lost by 45 weeks, there was no worsening in micrographia, with some participants' handwriting continuing to improve during the home treatment period. Micrographia is a common early symptom of PD, related to basal ganglia dysfunction.[38] It is noteworthy that a case series with transcranial PBM also showed a stabilization of micrographia in some participants.[36] Results from our study suggest that remote PBM intervention can also stabilize micrographia.

Improvement in cognitive function over the clinical treatment period was a notable result, which concurred with our previous study. Cognitive improvement was also consistently maintained over the full treatment period, with only one participant showing a decline. Progressive loss of cognition is a major concern in PD, with the majority of people with PD progressing to dementia.[39] A recent review of treatment options for non-motor signs of PD[40] concluded that ''there were no clinically useful interventions identified to treat non-dementia-level cognitive impairment.'' The improvement in cognition using PBM is not unique to our studies, with others reporting improved cognition in participants with different forms of dementia by transcranial PBM.[32,35,41] As far as is known, this is the first report of improved cognition using a remote PBM treatment with no transcranial component.

Olfactory loss is common in neurodegenerative and neurological diseases[42] correlated with cognitive loss,[43] with up to 95% of PD sufferers having some degree of loss[44] and the symptoms of hyposmia appearing up to 10 years before diagnosis.[45] A potential cause of this loss may be an early involvement of the olfactory bulb in PD.[46] In our previous study,[30] 6 of 12 participants reported an improvement in sense of smell, with 2 reporting a profound change from complete anosmia. In the current study, five participants reported a loss of olfactory ability when enrolling in the study and were then tested using a validated instrument.[47] The improvement of two participants from complete anosmia, despite being a small objective change, is important for participants living for many years with the complete lack of a sense of smell. To our best knowledge, reversal of anosmia does not occur with any standard intervention for

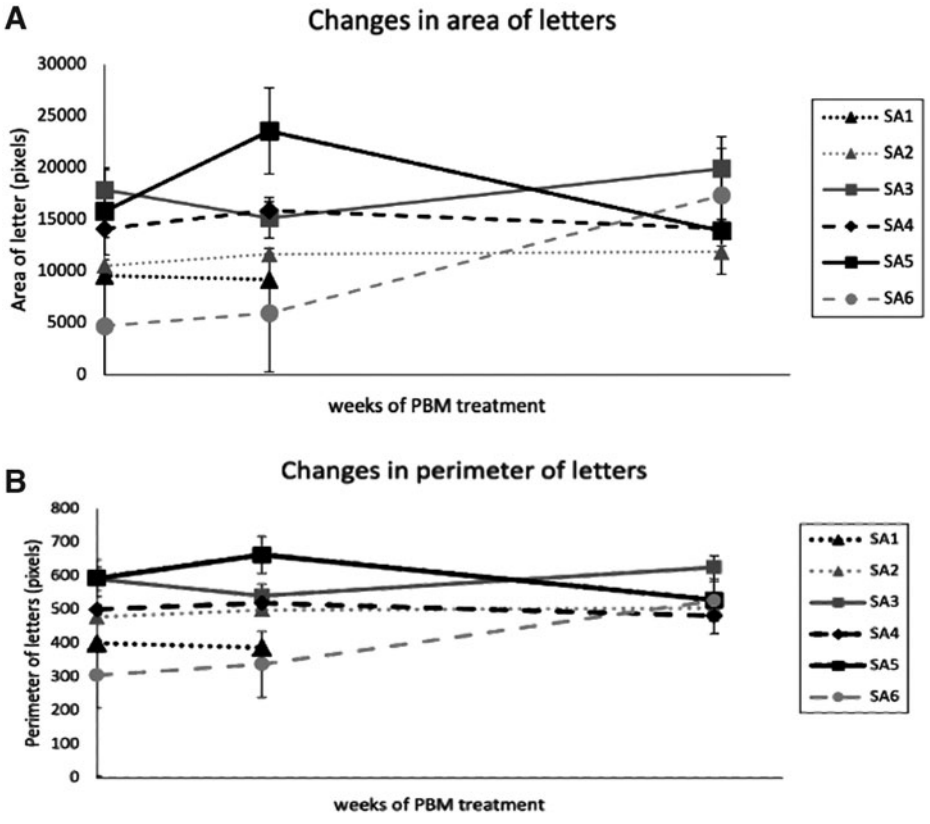


FIG. 3. Changes in micrographia of participants over the PBM treatment period. **(A)** Area of words; **(B)** perimeter of words.

Table 7. Results of Participants' Smell Identification Test

	Enrolment		*12 Weeks of treatment*		*45 Weeks of treatment*	
Participant	*Score*	*Interpretation*	*Score*	*Interpretation*	*Score*	*Interpretation*
S1	15	Total anosmia <5%[a]	ND		ND	
S2	12	Total anosmia <5%	19	Severe microsmia 14%	19	Severe microsmia 14%
S3	16	Total anosmia <5%	19	Severe microsmia 14%	19	Severe microsmia 14%
S4	ND		ND		ND	
S5	25	Severe microsomia 30%	24	Severe microsmia 25%	ND	
S6	34	Normal 33%	31	Normal 23%	34	Normal 33%
S7	22	Severe microsomia 11%	19	Severe microsmia 11%	20	Severe microsmia 11%

[a]Percentage for the gender and age who fall at or below the score attained by the participant.
ND, not determined.

treatment of PD. It has, however, been reported in a case study of transcranial PBM intervention in cognitive decline.[48] While the mechanism of reversal of anosmia with transcranial and nasal PBM[30] could be linked with a direct PBM effect on the olfactory bulb, the mechanism using abdominal and neck treatment alone is a matter of conjecture but may be due to a blood transmissible signal. The reversal of anosmia using remote PBM treatment is worthy of further study.

The use of ½ SD as an estimate of MCID is not an ideal measure. The small number of participants ($n = 19$) used to calculate the baseline for each outcome measure results in a higher SD than would be expected with a larger cohort, leading to MCID being more difficult to achieve and is consequently a conservative estimate of improvement. The response of participants to PBM treatment was individual, both in the clinical signs that improved and in the magnitude of that improvement. This agrees with our previous study. Four of the participants showed a strong response to PBM in a range of outcome measures over 12 weeks (S1, S2, S4, and S6), whereas S3 and S7 showed a weaker response. This was also seen after 45 weeks of treatment. PD is remarkably diverse in the symptoms expressed by different individuals[49] and individuals' response to light in general, and PBM in particular can also vary.[50] A larger study with a more homogeneous cohort of participants is necessary to determine the most appropriate treatment protocols and target of PBM treatment for individual differences.

During the study, outcome measure assessments were very likely influenced by individual participant circumstances (Table 4), including S5 who had a family history of PD and S6 who developed a severe lung infection and underwent prolonged antibiotic therapy. Two of the participants (S1 and S3) had used transcranial LED for some months before our study. Thus, their baseline values represented the previous effect of transcranial therapy and any improvements seen in our study would be additional benefit of the abdominal and neck treatment. Participant S3 showed the least improvement of all participants, with small improvements in the nine-hole peg test and the MoCA and decreases in many other outcome measures, possibly due to the discontinuation of transcranial PBM. However, participant S1 showed improvements in many outcome measures including cognition, tests of mobility, dynamic balance, and the spiral test, although not in TS, since he was already at maximum (30 sec). These results from these two participants suggest that a combination of PBM targets may provide the greatest benefit and that treatment may need to be personalized for individual with PD.

The improvements in mobility, balance, cognition, fine motor control, and sense of smell, which were seen at 12 weeks and maintained by some participants to 45 weeks, occurred despite two major confounding factors that affected our study. Wildfires in the greater Sydney region blanketed Sydney with a smoke haze for weeks during the clinical treatment period, increasing air pollution to hazardous levels. This was most severe in the week of assessment in December 2019 (https://www.abc.net.au/news/2019-12-10/sydney-smoke-returns-to-worst-ever-levels/11782892). This adversely affected participants' well-being and their ability to carry on daily activities, including exercise and almost certainly affected their performance on motor assessments at week 12. The second confounding factor was the COVID-19 pandemic and the measures introduced to combat the virus spread, included a number of lockdowns and travel restrictions, which were particularly enforced for vulnerable and elderly individuals, such as our study participants. While PBM treatment continued, normal daily activity, socializing, and exercise were severely curtailed. All seven participants reported adverse psychological and physical consequences of the restrictions imposed. The week-45 assessment (August 2020) took place after the first full lockdown period in Sydney but while travel restrictions were still in place (https://www.health.nsw.gov.au/Infectious/covid-19/Pages/public-health-orders.aspx).

Our results using remote PBM agree with animal models of remote therapy for PD.[18,21,24,51] The mechanism of action underlying the effects of abdominal and neck treatment is likely to be pathways involving the gut–brain axis and beyond those proposed for transcranial PBM.[52,53] PBM may stimulate the rich network of neurons comprising the enteric nervous system and directly influence the brain via the vagus nerve to compensate for losses of dopamine, in a mechanism similar to that proposed for transcranial PBM.[52] PBM may also downregulate the systemic inflammation that is a hallmark of many diseases of aging,[54] including PD,[55] via immune cells in abdominal adipose tissue. PBM may directly influence the gut microbiome, as has been recently shown in animal models.[56,57]

There is compelling evidence that PD can begin in the gut. The gut microbiome in PD is altered compared with the healthy population,[58] and this can cause bacterial metabolites to leak from the lumen into the surrounding tissues and circulation,[59] contributing to chronic inflammation.

Inflammation has been postulated to cause α-synuclein aggregation in the gastrointestinal immune system in susceptible individuals, which can then transported to the brain via the vagus nerve.[60] This hypothesis is supported by the increased risk of PD in individuals with inflammatory bowel disease[61] and irritable bowel syndrome,[62] the observation that truncal vagotomy is somewhat protective against PD development,[63] by brain imaging,[64] as well as epidemiological evidence linking antibiotics with PD incidence.[65,66] The gut microbiome has been suggested as a therapeutic target for PD,[8] using diet, probiotics, prebiotics, or FMT.[67,68] Modifying the microbiome with PBM would positively influence the brain[29] by the direct vagus nerve connection,[69] by the release of microbial metabolic products including neurotransmitters [dopamine, norepinephrine, gamma aminobutyric acid (GABA)] and hormones (serotonin, catecholamines),[5] and by reducing gut permeability and leakage of inflammatory bacterial products into the tissues. The precise mechanism of the remote treatment of PD by PBM warrants further investigation.

Conclusions

This study demonstrated for the first time the effectiveness of a remote treatment option on the clinical signs of PD. The signs most improved were cognition, mobility and balance, although the improvement in the sense of smell for two participants is noteworthy. These results paralleled those found in our previous study, which used a combination of PBM targets including transcranial application. The study also highlighted the difficulties of conducting clinical studies during adverse environmental conditions, including lockdown and travel restrictions introduced to control a pandemic. Despite this, some clinical signs of PD remained improved or did not deteriorate over a 45-week period for a number of participants. While the potential for PBM to stabilize the signs and symptoms of PD, especially over longer times would need to be scrutinized in a larger, prospective, randomized placebo-controlled trial with a long-term follow-up, the use of remote PBM treatment shows great promise for a disease that has limited treatment options beyond dopamine replacement therapies, which are associated with clinically troubling, dose-dependent side effects.[70] Remote PBM treatment for PD symptoms extends available therapeutic options and may improve patient comfort and compliance and warrants a fuller assessment in future larger, randomized placebo-controlled studies.

Authors' Contributions

A.L., H.K., and J.M. conceived and organized the study. E.L.L., A.L., and B.B. contributed to the study design. A.L. coordinated the study. A.L., S.T., and B.B. carried out treatments and assessments in the study. A.L., B.B., and P.J. analyzed the data. A.L., B.B., and H.K. prepared the draft article. All authors contributed to, reviewed, and approved the article.

Acknowledgments

The authors would like to thank Dr. Joanne Bullock-Saxton for assistance with study design; Dr. Roberta Chow and Dr. Greg Bennett for clinical assessments; Ms. Angela Torresi for assistance in conducting participant assessments; Prof. Jonathan Stone for ongoing support and advice; Dr. Dan Johnstone for many useful discussions; the participants in the study; Spectro Analytic Irradia AB for supply of photobiomodulation devices used in this study.

Author Disclosure Statement

Since February 2020, A.L. and B.B. are founders and current employees of SYMBYX Pty Ltd., a med-tech device company that is developing devices for the treatment of neurological conditions. B.B. is an agent for Spectro Analytic Irradia AB, a laser manufacturer. The other authors declare that they have no competing interests.

Funding Information

The study was funded by donations from the San Foundation, the Cardiac Health Institute, and anonymous donors. Laser devices used in the study were supplied by SUMOLITE Pty Ltd. and Spectro Analytic Irradia AB.

Supplementary Material

Supplementary Table S1

References

1. Rocca WA. The burden of Parkinson's disease: a worldwide perspective. Lancet Neurol 2018;17:928–929.
2. Victorino DB, Guimarães-Marques M, Nejm M, Scorza FA, Scorza CA. COVID-19 and Parkinson's disease: are we dealing with short-term impacts or something worse? J Parkinsons Dis 2020;10:899.
3. Beauchamp LC, Finkelstein DI, Bush AI, Evans AH, Barnham KJ. Parkinsonism as a third wave of the COVID-19 pandemic? Journal of Parkinson's Disease J Parkinsons Dis 2020;10:1343–1353.
4. Yang W, Hamilton JL, Kopil C, et al. Current and projected future economic burden of Parkinson's disease in the U.S. NPJ Parkinsons Dis 2020;6:15.
5. Cryan JF, O'Riordan KJ, Cowan CS, et al. The microbiota-gut-brain axis. Physiol Rev 2019;99:1877–2013.
6. Scheperjans F, Derkinderen P, Borghammer P. The gut and Parkinson's disease: hype or hope? J Parkinsons Dis 2018; 8:S31–S39.
7. Forsyth CB, Shannon KM, Kordower JH, et al. Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson's disease. PLoS One 2011;6:e28032.
8. Lubomski M, Davis RL, Sue CM. The gut microbiota: a novel therapeutic target in Parkinson's disease? Parkinsonism Relat Disord 2019;66:265–266.
9. Xue L-J, Yang X-Z, Tong Q, et al. Fecal microbiota transplantation therapy for Parkinson's disease: a preliminary study. Medicine 2020;99:e22035.
10. DuPont HL, Suescun J, Jiang Z-D, et al. Microbiome characterization and reversal of dysbiosis in Parkinson's disease by fecal microbiota transplantation (1825). Neurology 2020;94:1825.
11. Hegelmaier T, Lebbing M, Duscha A, et al. Interventional influence of the intestinal microbiome through dietary intervention and bowel cleansing might improve motor symptoms in Parkinson's disease. Cells 2020;9:376.
12. Tamtaji OR, Taghizadeh M, Daneshvar Kakhaki R, et al. Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Clin Nutr 2019;38:1031–1035.

13. Benson P, Kim JY, Riveros C, Camp A, Johnstone DM. Elucidating the time course of the transcriptomic response to photobiomodulation through gene co-expression analysis. J Photochem Photobiol B 2020;208:111916.
14. Hamblin MR. Mechanisms and mitochondrial redox signaling in photobiomodulation. Photochem Photobiol B 2018;94:199–212.
15. Hamblin MR. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. AIMS Biophys 2017;4:337–361.
16. Khan I, Tang E, Arany P. Molecular pathway of near-infrared laser phototoxicity involves ATF-4 orchestrated ER stress. Sci Rep 2015;5:10581.
17. Moro C, Torres N, Arvanitakis K, et al. No evidence for toxicity after long-term photobiomodulation in normal non-human primates. Exp Brain Res 2017;235:3081–3092.
18. Johnstone DM, Mitrofanis J, Stone J. Targeting the body to protect the brain: inducing neuroprotection with remotely-applied near infrared light. Neural Regen Res 2015;10:349–351.
19. Liebert A, Bicknell B, Adams R. Protein conformational modulation by photons: a mechanism for laser treatment effects. Med Hypotheses 2014;82:275–281.
20. Blatt A, Elbaz-Greener GA, Tuby H, et al. Low-level laser therapy to the bone marrow reduces scarring and improves heart function post-acute myocardial infarction in the pig. Photomed Laser Surg 2016;34:516–524.
21. Kim B, Brandli A, Mitrofanis J, Stone J, Purushothuman S, Johnstone DM. Remote tissue conditioning—an emerging approach for inducing body-wide protection against diseases of ageing. Ageing Res Rev 2017;37:69–78.
22. Moro C, Massri NE, Torres N, et al. Photobiomodulation inside the brain: a novel method of applying near-infrared light intracranially and its impact on dopaminergic cell survival in MPTP-treated mice. J Neurosurg 2014;120:670–683.
23. Johnstone D, Coleman K, Moro C, et al. The potential of light therapy in Parkinson's disease. ChronoPhysiol Ther 2014;4:1–14.
24. Gordon LC, Johnstone DM. Remote photobiomodulation: an emerging strategy for neuroprotection. Neural Regen Res 2019;14:2086.
25. Stone J, Johnstone D, Mitrofanis J. The helmet experiment in Parkinson's disease: an observation of the mechanism of neuroprotection by near infra-red light. In: 9th WALT Congress. E-L Laakso, C Young, (eds.). Medimond, Bologna, Italy 2013, pp. 17–20.
26. Ganeshan V, Skladnev NV, Kim JY, Mitrofanis J, Stone J, Johnstone DM. Pre-conditioning with remote photobiomodulation modulates the brain transcriptome and protects against MPTP insult in mice. Neuroscience 2019;400:85–97.
27. Lima AAM, Spínola LG, Baccan G, et al. Evaluation of corticosterone and IL-1β, IL-6, IL-10 and TNF-α expression after 670-nm laser photobiomodulation in rats. Lasers Med Sci 2014;29:709–715.
28. Al Amir Dache Z, Otandault A, Tanos R, et al. Blood contains circulating cell-free respiratory competent mitochondria. FASEB J 2020;34:3616–3630.
29. Liebert A, Bicknell B, Johnstone D, Gordon L, Kiat H, Hamblin M. ''Photobiomics'': can photobiomodulation alter the microbiome? Photobiomodul Photomed Laser Surg 2019;37:681–693.
30. Liebert A, Bicknell B, Laakso E-L, et al. Improvements in clinical signs of Parkinson's disease using photobiomodulation: a prospective proof-of-concept study. BMC Neurol 2021;21:256.
31. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003; 41:582–592.
32. Naeser MA, Zafonte R, Krengel MH, et al. Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: open-protocol study. J Neurotrauma 2014;31:1008–1017.
33. Lamartiniere R, Bergeron R, Aung-Din R, Bennett M, Stephan W, Banas L. Chapter 42—Photobiomodulation treatment for brain disorders: posttraumatic stress disorder (PTSD) and dementia. In: Photobiomodulation in the Brain. MR Hamblin, Y-Y Huang (eds.). Cambridge, MA: Academic Press, 2019; pp. 589–597.
34. Schiffer F, Johnston AL, Ravichandran CT, et al. Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety. Behav Brain Funct 2009;5:46.
35. Saltmarche AE, Naeser MA, Ho KF, Hamblin MR, Lim L. Significant improvement in cognition in mild to moderately severe dementia cases treated with transcranial plus intranasal photobiomodulation: case series report. Photomed Laser Surg 2017;35:432–441.
36. Hamilton CL, El Khoury H, Hamilton D, Nicklason F, Mitrofanis J. ''Buckets'': early observations on the use of red and infrared light helmets in Parkinson's disease patients. Photobiomodul Photomed Laser Surg 2019;37:615–622.
37. Hamilton C, Hamilton D, Nicklason F, Mitrofanis J. Transcranial photobiomodulation therapy: observations from four movement disorder patients. In: Photobiomodulation in the Brain. M Caldieraro, P Cassano (eds.). Cambridge, MA: Elsevier, 2019; pp. 463–472.
38. Wu T, Zhang J, Hallett M, Feng T, Hou Y, Chan P. Neural correlates underlying micrographia in Parkinson's disease. Brain 2016;139:144–160.
39. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. Brain Pathol 2010;20: 633–639.
40. Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. Mov Disord 2019;34:180–198.
41. Berman MH, Halper JP, Nichols TW, Jarrett H, Lundy A, Huang JH. Photobiomodulation with near infrared light helmet in a pilot, placebo controlled clinical trial in dementia patients testing memory and cognition. J Neurol Neurosci 2017;8:176.
42. Klopfenstein T, Toko L, Royer P-Y, Lepiller Q, Gendrin V, Zayet S. Features of anosmia in COVID-19. Méd Mal Infect 2020;50:436–439.
43. Camargo CHF, Jobbins VA, Serpa RA, Berbetz FA, Sabatini JS, Teive HAG. Association between olfactory loss and cognitive deficits in Parkinson's disease. Clin Neurol Neurosurg 2018;173:120–123.
44. Haehner A, Boesveldt S, Berendse H, et al. Prevalence of smell loss in Parkinson's disease–a multicenter study. Parkinsonism Relat Disord 2009;15:490–494.
45. Fullard ME, Morley JF, Duda JE. Olfactory dysfunction as an early biomarker in Parkinson's disease. Neurosci Bull 2017;33:515–525.
46. Rees RN, Noyce AJ, Schrag A. The prodromes of Parkinson's disease. Eur J Neurosci 2019;49:320–327.

47. Morley JF, Cohen A, Silveira-Moriyama L, et al. Optimizing olfactory testing for the diagnosis of Parkinson's disease: item analysis of the university of Pennsylvania smell identification test. NPJ Parkinsons Dis 2018;4:2.
48. Salehpour F, Hamblin MR, DiDuro JO. Rapid reversal of cognitive decline, olfactory dysfunction, and quality of life using multi-modality photobiomodulation therapy: case report. Photobiomodul Photomed Laser Surg 2019;37:159–167.
49. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79:368–376.
50. Liebert A. Emerging applications of photobiomodulation therapy: the interaction between metabolomics and the microbiome. Photomed Laser Surg 2018;36:515–517.
51. Johnstone D, El Massri N, Moro C, et al. Indirect application of near infrared light induces neuroprotection in a mouse model of parkinsonism–an abscopal neuroprotective effect. Neuroscience 2014;274:93–101.
52. Cassano P, Petrie S, Hamblin M, Henderson T, Iosifescu D. Review of transcranial photobiomodulation for major depressive disorder: targeting brain metabolism, inflammation, oxidative stress, and neurogenesis. Neurophotonics 2016;3:031404.
53. Zomorrodi R, Loheswaran G, Pushparaj A, Lim L. Pulsed near infrared transcranial and intranasal photobiomodulation significantly modulates neural oscillations: a pilot exploratory study. Sci Rep 2019;9:1–11.
54. Tchkonia T, Morbeck DE, Von Zglinicki T, et al. Fat tissue, aging, and cellular senescence. Aging Cell 2010;9:667–684.
55. Houser MC, Tansey MG. The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? NPJ Parkinsons Dis 2017;3:3.
56. Bicknell B, Liebert A, Johnstone D, Kiat H. Photobiomodulation of the microbiome: implications for metabolic and inflammatory diseases. Lasers Med Sci 2018;34:317–327.
57. Chen Q, Jinpeng WU, Dong X, et al. Gut flora-targeted photobiomodulation therapy improves senile dementia in an Aß-induced Alzheimer's disease animal model. J Photochem Photobiol B 2021;216:112152.
58. Lubomski M, Tan AH, Lim S-Y, Holmes AJ, Davis RL, Sue CM. Parkinson's disease and the gastrointestinal microbiome. J Neurol 2020;267:2507–2523.
59. van IJzendoorn SC, Derkinderen P. The intestinal barrier in Parkinson's disease: current state of knowledge. J Parkinsons Dis 2019;9:S323–S329.
60. Barbut D, Stolzenberg E, Zasloff M. Gastrointestinal immunity and alpha-synuclein. J Parkinsons Dis 2019;9:S313–S322.
61. Brudek T. Inflammatory bowel diseases and Parkinson's disease. J Parkinsons Dis 2019;9:S331–S344.
62. Fu P, Gao M, Yung KKL. Association of intestinal disorders with Parkinson's disease and Alzheimer's disease: a systematic review and meta-analysis. ACS Chem Neurosci 2019;11:395–405.
63. Liu B, Fang F, Pedersen NL, et al. Vagotomy and Parkinson disease: A Swedish register–based matched-cohort study. Neurology 2017;88:1996–2002.
64. Horsager J, Andersen KB, Knudsen K, et al. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. Brain 2020;143:3077–3088.
65. Ternák G, Kuti D, Kovács KJ. Dysbiosis in Parkinson's disease might be triggered by certain antibiotics. Med Hypotheses 2020;137:109564.
66. Mertsalmi TH, Pekkonen E, Scheperjans F. Antibiotic exposure and risk of Parkinson's disease in Finland: a nationwide case-control study. Mov Disord 2020;35:431–442.
67. Dutta SK, Verma S, Jain V, et al. Parkinson's disease: the emerging role of gut dysbiosis, antibiotics, probiotics, and fecal microbiota transplantation. J Neurogastroenterol Motil 2019;25:363.
68. Uyar GÖ, Yildiran H. A nutritional approach to microbiota in Parkinson's disease. Biosci Microbiota Food Health 2019;38:115–127.
69. Kaelberer MM, Buchanan KL, Klein ME, et al. A gut-brain neural circuit for nutrient sensory transduction. Science 2018;361:eaat5236.
70. You H, Mariani L-L, Mangone G, Le Febvre de Nailly D, Charbonnier-Beaupel F, Corvol J-C. Molecular basis of dopamine replacement therapy and its side effects in Parkinson's disease. Cell Tissue Res 2018;373:111–135.
71. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up Go Test. Physical Therapy 2000;80:896–903.
72. Lang JT, Kassan TO, Devaney LL, Colon-Semenza C, Joseph MF. Test-retest reliability and minimal detectable change for the 10-meter walk test in older adults with Parkinson's disease. J Geriatric Physical Therapy 2016;39.
73. Hill K, Bernhardt J, McGann A, Maltese D, Berkovits D. A new test of dynamic standing balance for stroke patients: reliability, validity, and quantitative clinical tests. Physiotherapy Canada 1996;47:257–262.
74. Gill DJ, Freshman A, Blender JA, Ravina B. The Montreal cognitive assessment as a screening tool for cognitive impairment in Parkinson's disease. Movement Disorders 2008;23:1043–1046.
75. Pullman SL. Spiral analysis: a new technique for measuring tremor with a digitizing tablet. Movement Disorders 1998;13:85–89.
76. Earhart GM, Cavanaugh JT, Ellis T, Ford MP, Foreman KB, Dibble L. The 9-hole PEG test of upper extremity function: average values, test-retest reliability, and factors contributing to performance in people with Parkinson disease. J Neurol Phys Ther 2011;35:157–163.
77. Smithson F, Morris ME, Iansek R. Performance on clinical tests of balance in Parkinson's disease. Phys Ther 1998;78:577–592.
78. Doty RL. The Smell Identification Test administration manual, 2013. Haddon Heights, NJ: Sensonics.

Address correspondence to:
Ann Liebert, PhD
Faculty of Medicine and Health Sciences
Sydney University
Camperdown
New South Wales 2050
Australia

E-mail: ann.liebert@sydney.edu.au

Received: April 26, 2021.
Accepted after revision: July 28, 2021.
Published online: December 15, 2021.