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RESEARCH ARTICLE

Improvements in the clinical signs of Parkinson's disease using photobiomodulation: a 3-year follow-up case series

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Abstract

Parkinson's disease is a progressive neurodegenerative disease with clinical signs and symptoms that deteriorate over time. We have previously demonstrated that a combination of transcranial and remote photobiomodulation treatment has the potential to improve some clinical signs of Parkinson's disease for up to one-year. The objective of the current study was to assess the effectiveness of continued home photobiomodulation treatment over a three-year period. Eight of the original twelve participants returned for reassessment at 2 years and six at 3 years. Participants were assessed for mobility, fine motor control, balance, and cognition. Median values for mobility and cognition continued to improve to 2 years and slightly declined to 3-years although not to pre-treatment levels. Individual participants typically improved in some outcome measures to 2-years and some participants continued to improve to 3-years. Cognition was the most sustained outcome improvement and static balance the least. Two participants who discontinued treatment after 1 year showed a decline in outcome measures. No negative side-effects of the treatment were reported. In conclusion, results suggested that at-home photobiomodulation treatment was effective to maintain improvements in clinical signs and symptoms of Parkinson's disease for as long as treatment continued. The results of this study warrant a larger prospective randomized trial.

Keywords: Parkinson's disease, photobiomodulation, motor symptoms, cognition, balance

Introduction:

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and its prevalence is increasing throughout the world. The symptoms of idiopathic PD occur as a result of build-up of α-synuclein, reduced mitochondrial function, damage to neurons in the substantia nigra compacta and the subsequent decrease in the production of the neurotransmitter dopamine. The cardinal clinical signs and symptoms of PD are relentlessly progressive, leading to increased debilitation and reduced health related quality of life. The motor signs and symptoms include bradykinesia, rigidity, resting tremor, and postural instability, while the non-motor counterparts include autonomic disturbances involving gastrointestinal, genitourinary, and cardiovascular systems, sleep disturbances, cognition deficit, visual disturbances, loss of sense of smell and mood disorders.

Individual symptoms, especially non-motor symptoms, are variable in their progression but can increase significantly in the early stages of PD[1]. Both motor signs and non-motor symptoms, as determined by the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores, have shown significant increases in scores over a four-year[2], and an eight-year period[3]. A recent study[4] with up to a five year follow-up, showed an annual average rise in MDS-UPDRS scores of 4.7 points, with the MDS-UPDRS part III (motor) being responsible for just over half of this effect. Cognitive ability has also been shown to significantly decline with time. A large cohort study followed PD patients for 4 years and showed a decline of 46%[2]. This observation was recently confirmed in a longitudinal study of 423 treatment naïve PD patients, with significant progression of motor and non-motor symptoms (including cognition) being seen at 5 years, with males faring worse than females and requiring more medication[5].

Despite recent advances in interventional and pharmacotherapeutic approaches for PD patients, no single treatment measure has been able to claim long-term effectiveness in reversing or retarding symptoms and signs of PD[6-8]. The mainstay treatment of dopamine replacement therapy (DRT) with levodopa combined with carbidopa, can improve some of the motor symptoms but suffers from the triple problem of significant 'on-off' periods, a reduced effect over time leading to the need for dose escalation and increased frequency of dosing, and is frequently accompanied by an array of debilitating drug adverse effects such as dyskinesia and nausea.

The evidence for the treatment of Parkinson's disease symptoms using photobiomodulation (PBM) has recently been reviewed in animal models[9] and in human trials[10].It has been previously demonstrated[11] that PBM using laser light to the abdomen and neck, and light emitting diode (LED) light to the head reduced a number of the clinical signs and symptoms of PD for participants. Despite being a small proof-of-concept study, the participants showed significant improvement using validated tests in the objectively assessed motor functions of walk speed, stride length, timed up-and-go (TUG) tests,

fine motor control, balance, as well as evidence of cognitive improvement. Importantly it has been shown that these improvements were maintained for up to one year[11]. Here the results of reassessments of up to 3 years for the study participants is reported.

Methods

The study was conducted in Adelaide, Australia. The original study received human research ethics approval by the Griffith University Human Research Ethics Committee (2018/16) and was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR - a primary registry in the WHO International Clinical Trial Registry Platform), registration number: ACTRN12618000038291p, registered on 12/01/2018. The current follow-up study was conducted under two extensions of the ethics approval (March 2021 and January 2022). The study method was executed in accordance with the ethics approved protocols.

Participants in the current study were a subset of participants from the original study[11] (Table S1). Group A participants (A1 to A6) had begun PBM treatment soon after enrolment in the study and Group B participants (B1 to B6) had been Waitlisted and began treatment 14 weeks after enrolment. All participants were invited to return for follow-up assessments, which occurred on 29th March 2021 for the 2-year reassessment and 11th April 2022 (participants A4, A5, B1, B2, B5) and 26th July 2022 (participant B4) for the 3-year reassessment. Seven participants attended in 2021 and six in 2022 (Table 1). Of the participants who did not attend, the partner/caregiver of one participant (A3) was deceased and the participant could not continue the treatment; one participant (A6) had a diagnosis of Multi System Atrophy (MSA) and did not continue the treatment; one participant (A2) continued the treatment but had other health issues (multiple respiratory infections) that precluded attending follow-up assessment days; and one participant (A1) did not continue the treatment and did not return for reassessment.

Table 1: Assessments for participants

Participant	Baseline	12-Week	1-Year	2-Year	3-Year	Comments
A1	√	√	√	discontinued		discontinued PBM after year 1; did not respond to follow-up invitations
A2	√	√				continued PBM but not reassessed due to repeated respiratory infections
A3	√	√	discontinued			partner/caregiver passed away; participant moved to aged care facility
A4	√	√	√	√	√	diagnosed with multi system atrophy between 2-year and 3-year assessments; continued PBM
A5	√	√	√	√	√	partner/caregiver left the domestic relationship with the participant. Used transcranial device only (no abdominal treatment)
A6	√	√	√	discontinued		diagnosed with multi system atrophy after 1-year assessment; discontinued PBM
B1	√	√	√	√	√	
B2	√	√	√	√	√	
B3	√	√	√	√		breast cancer therapy b/n 12-week & 1-year; discontinued PBM after 1-year assessment; agreed to be reassessed at 2-year follow-up
B4	√	√	√		√	Missed 3 months of abdominal treatment
B5	√	√	√	√	√	
B6	√	√	√	√		discontinued PBM after year 1 assessment; agreed to be reassessed at 2-year follow-up

PBM treatment protocol.

Participants continued with the treatment protocol as previously described[11]. Following the original study in 2019, participants were supplied with a "PDCare" laser device (SYMBYX Pty Ltd), which was equivalent to the previously used "MIDCARE" laser device (Spectro Analytic Irradia AB) and a "Coronet" LED transcranial helmet (Well Red Pty Ltd) in place of the "VieLight Gamma" LED device. Full PBM parameters are provided in Table S2. All treatments were self-applied at home by the participants with the assistance of their caregiver as required. Participants and caregivers had previously undertaken a 20-minute training session in the use and care of the PBM devices. The PDCare laser device was used 3 times per week (Monday, Wednesday, and Friday) and as a class 1 laser device registered for home use, had no requirement for safety glasses. The Coronet helmet was used between 3 and 6 days per week as advised by trial therapists. Participants were able to contact investigators via telephone or email if any problems arose with the equipment or if they had any concerns regarding the treatment and its effects, including safety concerns or adverse events.

Outcome measures

The outcome measures assessed included those showing responses to treatment at the 1-year assessment (Table S3) as previously described[11], and consisted of timed up-and-go (TUG) tests, walk speed and stride length (10 m walk test – 10MWT), dynamic balance (step test), static balance (tandem stance (TS) and single leg stance (SLS) tests), fine motor control (spiral test) and cognition (Montreal Cognitive Assessment (MoCA)). Outcome measures were assessed during the 'on' stage of medication and were reassessed by the same investigators as previous assessments[11].

Because of the small sample size, the analysis is descriptive only. Medians and interquartile ranges are reported for all outcomes, at each time point, and trajectory plots for changes in outcome measures from baseline, for individual participants, are given.

Results

Seven participants attended the 2-year and 6 attended the 3-year reassessments (Table 1). No participants reported device related safety issues or suffered any adverse effects attributed to the devices. All participants reported using both PBM devices consistently since the 1-year assessment, with the exception of participant A5 who acknowledged that he did not use the PBM treatment consistently, sometimes forgetting to deliver the treatment for a number of weeks. Participants B3 and B6 discontinued using PBM treatment after the 1-year assessment but agreed to be assessed at the 2-year reassessment. Participant A4 was diagnosed with MSA after the 2-year reassessment. Participants A5 had only used the transcranial LED device (no laser device on the abdomen and neck) since the 1-year assessment. B4 had not used the abdominal laser device for over 3 months prior to the 3-year reassessment due to technical issues; the device was replaced, and the participant was reassessed after a further 3 months of using both devices.

Grouped outcomes for participants continuing treatment

Six participants continued PBM treatment for 3 years and the median results of the outcome measures are shown in Table 2, except that participant A4 was excluded (MSA diagnosis). Median scores for each outcome measure were improved, apart from static balance tests, above the median baseline before PBM treatment more than three years previously. Median scores showed a decline in performance between the 2-year and 3-year reassessments for walk speed, stride length, TUG motor, step tests (affected leg and unaffected leg), and spiral writing test but the decline did not bring the scores below the baseline medians. TUG, TUG cognitive, and MoCA tests showed improvements in median scores from the 2-year to 3-year reassessments.

Table 2: Median scores (interquartile ranges) for outcome measures at assessment times. Participants B3 and B6 excluded from 2 year (discontinued treatment); participant A4 excluded from 2 and 3 year (diagnosis of multi system atrophy)

	baseline (n=12)	1-year (n=9)	2-year (n=5)	3-year (n=5)
Cognition test				
MoCA	26.0 (2.5)	29.7 (1.0)	29.7 (0.3)	30.0 (1.0)
Gait tests				
10MWT walk speed (m/s)	1.50 (0.72)	1.75 (0.31)	2.05 (0.09)	1.9 (0.05)
10MWT stride length (m)	0.60 (0.12)	0.75 (0.00)	0.88 (0.06)	0.75 (0)
TUG (s)	7.50 (1.90)	6.55 (1.88)	6.05 (0.55)	5.81 (1.08)
TUG motor (s)	8.20 (1.55)	6.81 (2.26)	6.08 (0.48)	6.28 (0.78)
TUG cognitive (s)	7.60 (2.32)	6.60 (2.41)	6.44 (0.37)	6.09 (0.86)
Dynamic Balance test				
step test - affected leg (n)	13.0 (3.00)	17.0 (6.00)	19.0 (2.75)	15.0 (7.00)
step test - unaffected leg (n)	12.0 (3.00)	19.0 (7.00)	16.5 (3.25)	15.0 (5.00)
Fine Motor Skill tests				
Spiral test - dominant hand (s)	28.7 (10.76)	24.4 (14.33)	24.6 (12.80)	28.9 (14.95)
Static Balance tests				
TS affected leg behind (s)	6.0 (9.00)	4.0 (26.20)	15.0 (30.00)	8.25 (6.60)
TS unaffected leg behind (s)	4.0 (5.25)	2.5 (7.48)	2.4 (11.07)	3.9 (5.00)
SLS affected leg raised (s)	1.6 (0.98)	5.4 (9.10)	0 (9.8)	2.8 (1.60)
SLS unaffected leg raised (s)	2.1 (1.75)	30 (12.5)	0 (0)	0 (0)

Individual outcomes for participants who continued treatment

Individual outcome measures are shown in Figure 1 as changes from the participants' individual baseline measurements (determined before PBM treatment began). Full results are presented in Table S4. Participants showed an improvement above baseline for most outcome measures at both 2-year and 3-year reassessments.

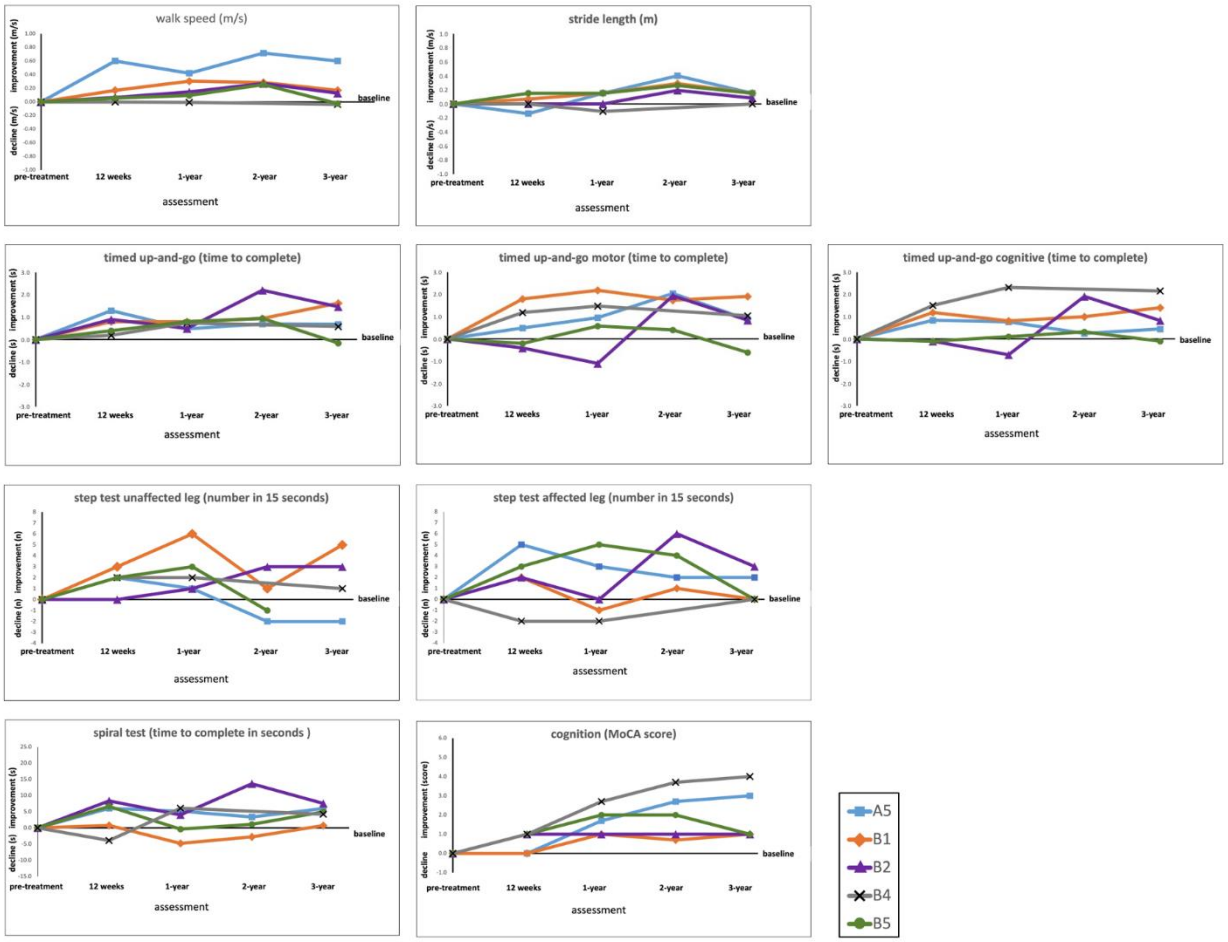

Figure 1: Changes in participant outcomes compared to individual baseline assessments (prior to photobiomodulation treatment) for participants who continued treatment for 3 years

Four participants (A5, B1, B2, B5) showed improved walk speed and stride length from the 1-year to the 2-year reassessment, and declined by the 3-year reassessment, but were still above their baseline. B4 showed a slight decline in stride length at the 1-year assessment but this was improved by the 3-year reassessment. The three TUG outcome measures showed improvements above baseline to the 2-year reassessment for most participants, followed by a decline at the 3-year reassessment for participants B2 and B5, while participant B1 showed continued improvement from the 2-year to the 3-year reassessment.

The test of fine motor control (spiral test) showed improvements for participants A5, B1, and B5 from the 1-year assessment to the

2-year and 3-year reassessments, although for participant B1 this was from below baseline at 12 weeks. Participant B4 had a largely unchanged score and participant B2 improved to the 2-year reassessment and then declined by the 3-year reassessment.

Dynamic balance (step test) showed considerable variability between participants but was generally above individual baseline measures (Figure 1). Static balance also showed considerable variability (Figure 2). Participant B1 began with good static balance at baseline, with 3 of 4 tests with eyes open scoring 30 seconds (indicating a 'pass' time for the test). This improved with treatment to the 3-year reassessment, with 3 of 4 balance tests now being passed (30 seconds) with eyes closed. Participant B2 began with poor static balance at baseline and low scores for all tests with eyes open. Static balance gradually improved in tests with both eyes open and eyes closed at each assessment. Participants A5, B4 and B5 showed variability over time with their measures of static balance with outcome measures generally below their baseline assessment for participants A5 and B5 at the 3-year reassessment.

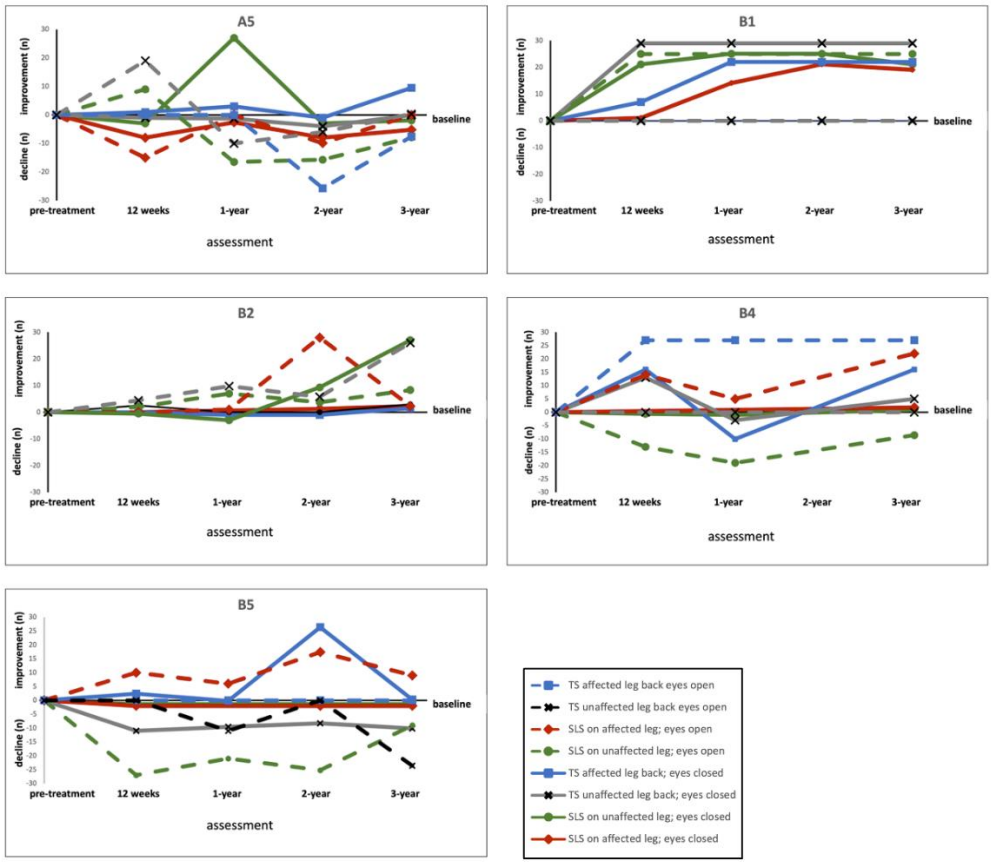

Figure 2: Changes in participant static balance outcomes compared to individual baseline assessments (prior to photobiomodulation treatment) for participants who continued treatment for 3 years. SLS = single leg stance; TS = tandem stance.

Cognition as measured by MoCA improved for all participants from baseline scores to maximum (30) or near maximum (29.7) for 1-year and 2-year assessments (Figure 1). MoCA scores remaining at or close to the maximum score of 30 for the 3-year reassessment, with the exception of participant B5 who declined from 30 to 29 and participant A4 who declined from 29 to 28 (Table S4).

Individual outcomes for participants discontinuing PBM treatment or having a subsequent diagnosis.

Three participants (A4, B3 and B6) did not share the generally positive outcomes at 2-year and/or 3-year reassessments (Figure 3, Figure 4 and Table S4). Participant A4 (MSA diagnosis) showed an initial improvement in most outcome measures at 12 weeks but the improvements were lost at subsequent assessments. Participants B3 and B6 discontinued treatment and lost many improvements seen at the 1-year assessment by the 2-year reassessment. An exception was the MoCA, which was not reduced at the 2-year reassessment, remaining at 30 (B3) and 29.7 (B6).

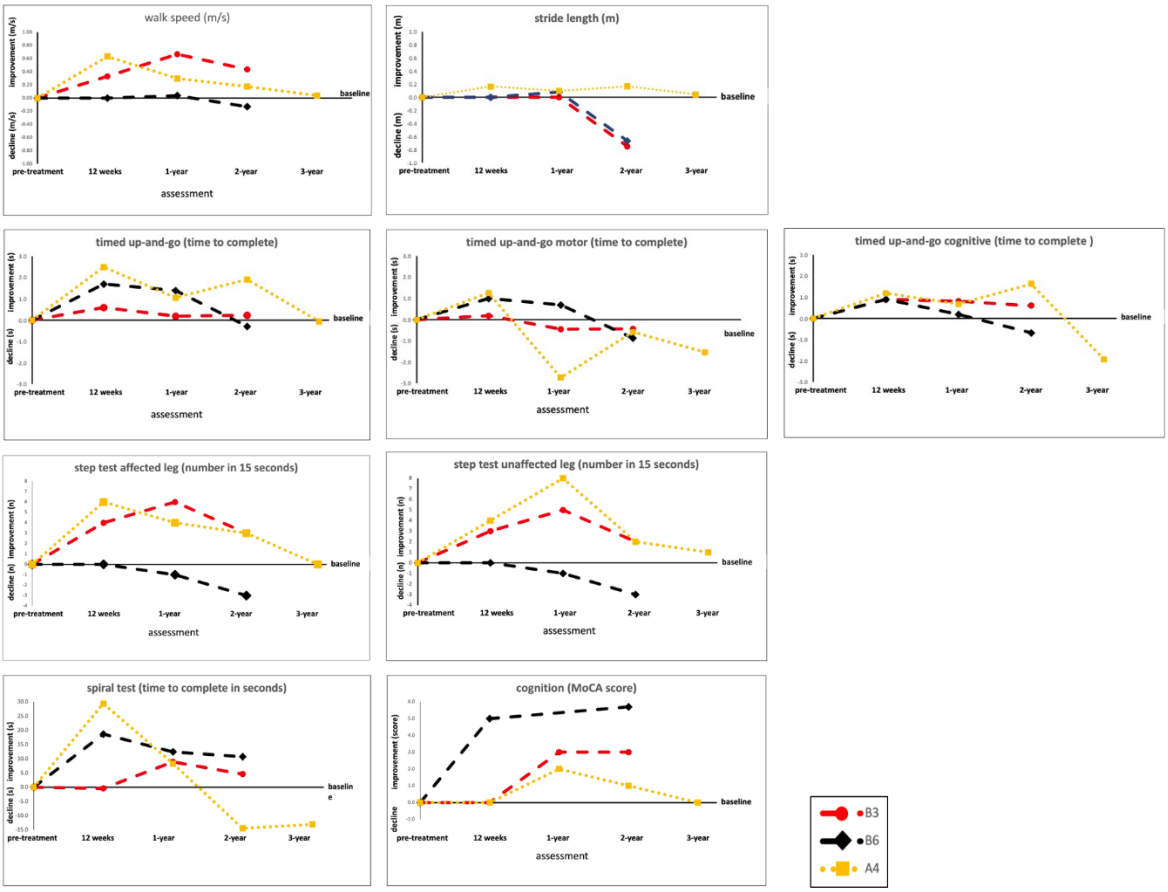

Figure 3: Changes in participant outcomes compared to individual baseline assessments (prior to photobiomodulation treatment) for participants who discontinued treatment after 1 year or were diagnosed with multi system atrophy

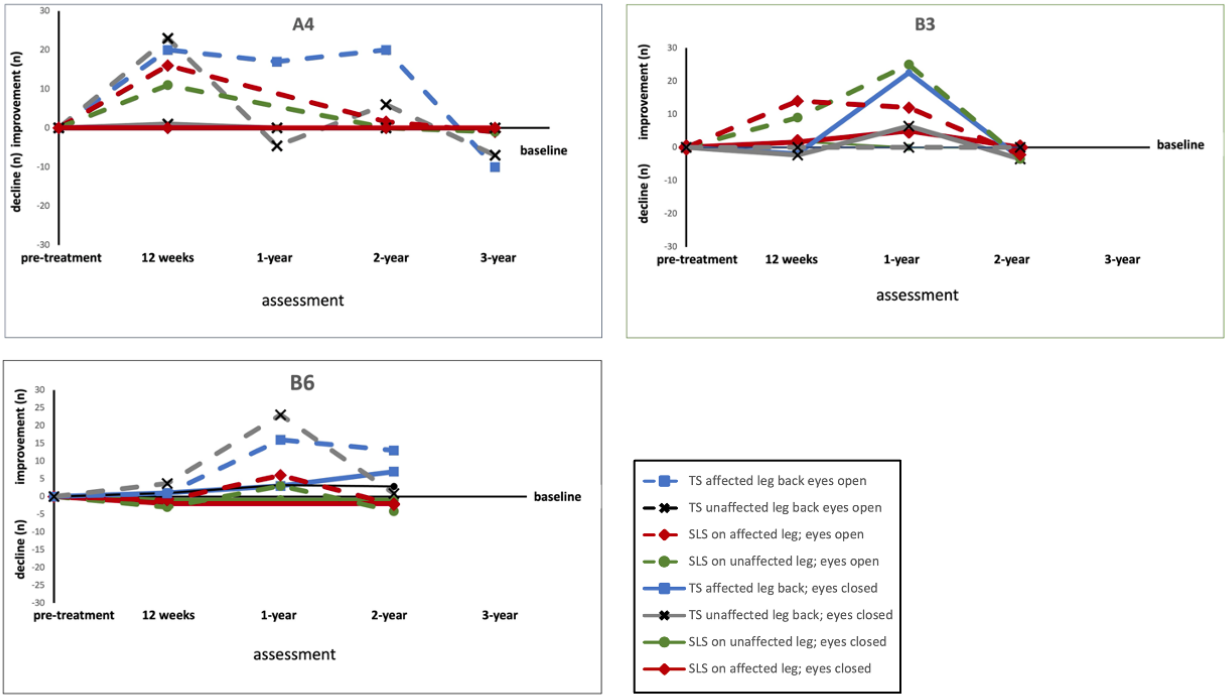

Figure 4: Changes in participant static balance outcomes compared to individual baseline assessments (prior to photobiomodulation treatment) for participants who discontinued treatment after 1 year or were diagnosed with multi system atrophy

Discussion

In the original study[11] it was shown that PBM therapy applied as a combination of LED treatment to the head and laser treatment to the abdomen and neck, resulted in improvement of some of the clinical signs and symptoms of Parkinson's disease for up to one year. Here it has been shown that these improvements can last for up to three years for some participants. Most of the study outcomes (including walk speed, stride length, TUG tests, spiral test, step test, and MoCA scores) measured at 2-year and 3-year reassessments remained above the participants' individual PBM treatment naïve baseline measures. Some outcome measures (such as TUG tests, MoCA scores and static balance), continued to improve from the 2-year to the 3-year reassessment for some participants. Gradual deterioration in motor signs and non-motor symptoms would normally be expected over a three-year period in this neurodegenerative disease. The improvement in some clinical motor signs and non-motor symptoms, and the maintenance this improvement, might be clinically important for treatment of PD with PBM.

As a progressive neurodegenerative disease, the symptoms associated with PD would be predicted and anticipated to increase in severity with time. In clinical studies this is most often assessed using the UPDRS or MDS-UPDRS and often using the motor section (UPDRS-III) as the primary outcome

measure. This is despite the UPDRS's relative insensitivity for detecting clinical changes, especially in early PD[12], and it's failure to estimate or predict PD progression[13,14]. None-the-less, annual increases in UPDRS-III have been found to range from 0.2 to 8.8 in various studies[3], with annual increases of 2.2 points in a 8 year study[3], 1.8 points in a 4 year study[15] and between 2.4% and 7.4% in UPDRS-III in a 4-year study[16]. One recent, single year study conducted during the COVID-19 pandemic, found much higher rates of progression, with an average annual increase of 11.83 points[17]. Most studies have also reported considerable variation within the cohorts.

In contrast to the MDS-UPDRS-III, the TUG test is often considered a more sensitive measure of subtle changes in motor signs. Following a nation-wide reassessment program in South Korea, a relationship was observed between slowing TUG and the development of PD, suggesting that this test could be used as a marker for prodromal PD[18]. Using values from the literature, it has been estimated that an increased time of between 2 and 5 seconds to complete the TUG might be a clinically meaningful measure of PD progression[19]. Similarly, a decrease in walking speed and stride length may also be good indicators of PD progression. The minimum detectable change for walking speed was calculated to be between 0.11m/s and 0.25m/s[19] and between 0.5m/s and 0.22m/s[20]. The implication is that a decrease in walk speed more than these values represents a clinically relevant decline in PD.

It is noteworthy that most of the motor outcomes (TUG, TUG motor, TUG cognitive, walk speed, stride length) assessed for the 5 participants who completed the 3 years of treatment remained above their individual baseline measures, indicating that participants experienced an improvement rather than a decline in motor signs where a decline would normally be expected in this progressive neurological disease.

It is known that there is a strong placebo effect in PD. Up to a 59% improvement in symptoms has been observed with placebo medication[21]. The placebo effect can influence changes in subjective symptoms, in objective measures and also in neurochemical changes, including an increase in the release of dopamine in the ventral and dorsal striatum[22,23]. Placebo effects, however, are usually sustained for weeks or months only[24]. Movement disorder improvements due to placebo (improvements in bradykinesis, rigidity, tremor, gait) have been shown to be maintained for up to 6 months[25], with 17% of participants showing placebo associated improvements (10.3% at 4 weeks, 7.1% at 13 weeks, 6.7% at 26 weeks), but only 1.6% of participants showing the placebo associated improvements at all 3 assessments[24]. In a systematic review the placebo response was calculated as 16% (range: 0–55%)[26]. In the original study[11] a strong Hawthorne effect was reported for the study participants during the clinic phase of the trial. It would be expected that any placebo effect would be diminished by the 1-year, 2-year and 3-year assessments, especially since the treatment was self-administered in the home environment with no physical contact with study therapists or investigators.

While the symptoms of PD are many and varied, the motor symptoms of postural instability and gait disturbances have a major effect on quality of life and are associated with decreased independence and a significantly increased risk of falls, with estimates of up to 60% of PD patients falling per year[27]. Falls result in hospitalisation, reduced quality of life and increased mortality. Reduced balance and impaired gait (as well as previous falls history) are major risk factors for falls[28], with reduced walk speed and stride length also contributing to the risk[29]. Problems with walking, balance and falls become increasingly important to patients with PD as the disease progresses[30]. The TUG is a validated test for PD[31,32] and is also a valid measure of falls risk for PD, with the dual task TUG, and specifically the TUG cognitive test, significantly correlated with falls risk[33,34]. Four of the five participants in the current study maintained the initial improvements in TUG, TUG motor, TUG cognitive, as well as the step test throughout the three years of treatment, with two participants showing improvements in balance for up to 3 years. PBM treatment appears to have the potential to deliver sustained improvements in gait, mobility, and balance, which could translate to a reduced risk of falls and improved quality of life among PD sufferers.

Non-motor symptoms are present from the earliest stages of PD and progressive, possibly partly due to DRT side effects[35]. Non-motor symptoms of PD also worsen with time but follow different trajectories to motor symptoms, are symptom specific, and are variable between patients[36]. Longitudinal non-motor symptom changes, as measured by the MDS-UPDRS-I significantly worsened over 3 years, and was correlated with a significant decline in quality of life, despite the ongoing administration of PD medications[2]. Cognitive dysfunction is arguably the most clinically important non-motor symptom, having a profound impact on independence and quality of life. Most PD patients experience cognitive dysfunction and dementia with disease progression which suggests that it might be used as a marker of other non-motor symptoms progression[37]. In a cohort of 125 early PD patients with stable UPDRS-III parameters, other measures such as olfactory changes and cognition changes (MoCA) were shown to be good predictive markers of PD progression[8]. Cognition was found to significantly decrease by 44%, from year 2 to year 4 in a 4 year study[35], to decrease by 0.2 mini-mental state examination (MMSE) points per year in a cohort of 135 early PD patients over 4 years[15], and a recent study of patients with early PD showed significantly worsened MoCA scores over a 3 year period[5]. An important outcome of the current study was the improvement in MoCA score and its maintenance for all participants for up to 3 years. Interestingly, the 2 participants who had discontinued PBM treatment (B3, B6) did not show a reversal of their improvements in the MoCA score when treatment was suspended.

Despite the overall maintenance of improvements in PD symptoms with PBM treatment, there was a great deal of heterogeneity among participants, with some participants who completed the 3 years of

treatment showing good improvement in many outcome measures (participants B1, B2) and others less so (participants A5, B4, B5). This is to be expected due to the variability in PD symptoms among patients, the variability in individual responses to PBM[38] and the small size of the participant group in this study. It should also be remembered that the home PBM treatment and the 2-year and 3-year reassessments were conducted during the COVID-19 pandemic. Although the response to the pandemic were less severe in Adelaide compared to many parts of Australia, the COVID-19 response resulted in two short lockdowns (November 2020 and July 2021) and a number of periods of restrictions on indoor venues, public transport, and outdoor gatherings (November 2020, June 2021, July 2021, December 2021). While contracting COVID-19 is known to worsen PD symptoms, people with PD who have not caught COVID-19 can also exhibit exacerbated existing symptoms as well as presenting with new symptoms[39], including motor symptoms, mood, and cognition.

An inclusion criterion of the original trial was that participants exercised regularly for at least 6 hours spread over each week, using any PD specific or general exercise program. The ability to continue with regular exercise from 1 to 3 years of PBM treatment was adversely affected by the COVID-19 restrictions over this time and was commented on by most returning participants, but who, none-the-less, continued with their own exercise programs to the best of their ability and the prevailing COVID-19 restrictions (including for gyms). Participant B5, in particular, indicated that the periods of isolation necessitated by her own diagnosis of COVID-19 and the measures to limit COVID-19 spread, had a major effect on her ability to exercise, her gain in weight, her mood, and the ability to socialise. She showed a decline in motor sign outcome measures from the 2-year to the 3-year assessment.

Static balance as tested by tandem stance and single leg stance showed the greatest variability of all outcome measures. Two participants demonstrated increased balance over time (B1, B2), while the 3 other participants who completed 3 years of treatment showed great variability in static balance over the period of assessment.

Participants A5 and B4 showed a great deal of variability in outcome measures. Participant A5 used only the transcranial PBM treatment in the 2 years since the 1-year assessment and participant B4 had used only the transcranial PBM treatment for three months before recommencing the abdominal treatment. Abdominal treatment may be an important component of the PBM treatment of PD. A study using abdominal treatment alone on a small cohort of participants showed improvements in motor, cognitive and olfactory symptoms in a 1-year study[40]. Participants B3 and B6 demonstrated the importance of continued PBM treatment. In almost all assessments, there was improvement at the 12-week and 1-year assessments followed by a decline after treatment was discontinued. This is most apparent in static and dynamic balance and stride length. Interestingly, cognition as measured by the MoCA did not decline at the 2-year assessment.

Participant A4 was originally diagnosed with PD by a neurologist before enrolment into the study but was subsequently diagnosed with MSA between the 2-year and the 3-year assessments. Most of the outcome measures showed a decline, after an initial improvement at 12 weeks. This suggests that the PBM treatment may be less effective for this disease or that different PBM dosage may be needed.

It has been estimated that over 90% of PD patients exhibit olfactory loss to some extent[23], and the University of Pennsylvania Smell Identification Test (UPSIT) score has been suggested as a marker for PD progression[8]. Although not objectively measured in the current study, anecdotal observations from participants B2 and B4 suggested reversal of an 8-year and a 3-year (respectively) history of profound loss of olfaction (total anosmia) by the 12-week assessment, first noticed after 4 weeks of PBM treatment with continued improvement for at least 2 years in the case of participant B2. Reversal of anosmia and/or increased sense of smell was also documented using the UPSIT in a small study using only abdominal PBM treatment[40].

Conclusion

There is no cure for PD at present. The current approach to treating PD is to slow progression of symptoms and improve the quality-of-life[41]. Although the number of participants in the current study was small and participants showed variability in the measured outcomes, the early clinical evidence suggests that PBM treatment can improve the clinical signs of PD, including cognition and potentially improve quality of life. In some of the cases presented, there was sustained improvement above baseline in clinical signs and symptoms for up to 3 years, which is beyond any placebo effect. There is, therefore, value in undertaking further studies to investigate the full potential of PBM treatment for Parkinson's disease, in a larger, prospective, randomized placebo-controlled trial with sufficient power and a longer follow-up period. Our ongoing research will examine whether PBM treatment may slow some of the expected decline in the clinical signs and symptoms of PD and may complement, but not replace, the current treatment options (including medication) in the management of the clinical signs of PD, with a treatment that is safe and easily administered in the home environment.

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Supplementary Material:

Table S1 - Summary of participants' demographic characteristics at the beginning of the clinical trial, January 2019

Table S2 - Parameters of PBM devices

Table S3 - Outcome measures

Table S4 - Individual data for participant assessments at baseline (treatment naïve) and at 12-week, 1-year, 2-year and 3-year assessments

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Authors' contributions:

Conceptualization, AL, HK, JM; Methodology and study design E-LL, AL, BB; study Administration AL; Treatments and assessments AL, ST, VP, BB; Analysis AL, BB, GiH, & GeH; Original draft preparation AL, BB; Writing, Review and Editing all authors; Funding Acquisition AL.

Conflicts of interests:

AL and BB are co-founders of, and scientific consultants to Symbyx Pty Ltd, a med-tech company developing treatments for neurological disorders. AL was a director of Symbyx Pty Ltd at the time of the study. VP was employed by Symbyx Pty Ltd at the time of the study. The other authors declare no conflict of interest. The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest, in the design, execution, interpretation, writing or choice of publication of the study.

Ethics approval:

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Research Ethics Committee of Griffith University (2018/16; approved February 3rd, 2018, with extensions approved March 2021 and January 2022). All protocols were approved by the Griffith University Human Research Ethics Committee and were conducted in accordance with their regulations and guidelines.

Informed consent:

Informed consent was obtained from all subjects involved in the study, as per ethics approval.

Clinical Trial Registration:

The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), a Primary Registry in the WHO Registry Platform; registration number: ACTRN12618000038291p, registered on 12/01/2018.

Data Availability:

All data generated and analysed during this study for this report are included in this published article and its supplementary information files. Additional study data can be requested from the corresponding author.

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SUPPLEMENTARY MATERIAL:

Table S1: Summary of participants' demographic characteristics at the beginning of the trial, January 2019

	Sex	Hoehn & Yahr stage	MDS UPDRS score	MDS UPDRS motor score	Dominant hand	Affected side	PBM treatment begun
A1	M	2	89	31	R	L	immediately
A2	F	2	31	13	R	L	immediately
A3	F	3	57	37	R	L	immediately
A4	M	2	52	23	R	L	immediately
A5	M	2	53	15	R	L	immediately
A6	M	1	36	15	L	L	immediately
B1	F	2	53	23	R	L	14 weeks after enrolment
B2	F	2	70	49	R	L	14 weeks after enrolment
B3	F	2	42	19	R	R	14 weeks after enrolment
B4	M	1	29	18	R	L	14 weeks after enrolment
B5	F	2	36	20	L	R	14 weeks after enrolment
B6	F	2	67	17	R	R	14 weeks after enrolment

Table S2: Parameters of the photobiomodulation devices and treatments used

A - Laser

PARAMETER	Irradia prototype Laser	Irradia MIDCARE Laser	SymByx PDCARE Laser
Manufacturer	Spectra Analytic Irradia AB	Spectra Analytic Irradia AB	Spectra Analytic Irradia AB
Diodes	904nm laser diodes (GaAs)	904nm laser diodes (GaAs)	904nm laser diodes (GaAs)
Wavelength	904nm	904nm	904nm
Laser class	1	1	1
Number of diodes	4	2	2
Output power /diode	30 mW	30 mW	30 mW
Peak power / diode	25,000 mW	25,000 mW	25,000 mW
Pulse frequency	50 Hz	50 Hz	50 Hz
Beam spot size	0.635 cm^2	0.635 cm^2	0.635 cm^2
Power density / diode	47 mW/cm^2	47 mW/cm^2	47 mW/cm^2
Total output power	60mW	60 mW	60 mW
Irradiation time / point	30 s	60 s	60 s
Total irradiation time	330 s	660 s	660 s
Total energy per point	1.8 J	3.6 J	3.6 J
Number of sites	11 (9 abdomen, 2 neck)	11 (9 abdomen, 2 neck)	11 (9 abdomen, 2 neck)
Total energy / treatment	39.6 J	39.6 J	39.6 J
Treatment frequency	3 x weekly (Mon, Wed, Fri)	3 x weekly (Mon, Wed, Fri)	3 x weekly (Mon, Wed, Fri)

B – Transcranial LED Helmet

PARAMETER	Coronet Duo	
Manufacturer	Well Red Pty Ltd	
Wavelength and bandwidth [nm]	670 nm +/- 10 nm	810 nm +/- 10 nm
Number of LEDs	40	40
Peak current each LED (mA DC @ 100% duty cycle)	350	350
Power each LED (W)	0.742	0.574
Optical power per LED at 100% duty cycle (W)	0.345	0.267
Total optical power at 100% duty cycle (W)	13.8	10.7
Peak optical power per LED (mW)	345	267
Pulse frequency (Hz)	40	40
Actual duty cycle (%)	12	20
Average whole head irradiance (W)	1.656	2.136
Assumed irradiated head area [cm2]	350	350
Whole head average radiant intensity [mW/cm2]	4.7	6.1
Exposure duration (minutes)	12	12
Average radiant exposure [mJ/cm2/s]	19.7	6.1
Peak radiant exposure [mJ/cm2/s]	39.3	20.3
Radiant energy per session [J]	1192.32	1538
Treatment frequency	6 times per week	

Table S3: Outcome measures

Outcome measure	test	description	Reference
Functional mobility	Timed up-and-go (TUG)	Assessors measured the time taken for a participant to stand from a chair, walk 3 m, turn around a marker, return and sit down	(Shumway-Cook et al., 2000)
	TUG-motor	As for TUG except that the participant was carrying a cup of water	
	TUG-cognitive	As for TUG except that the participant was asked to count backwards from 40 in twos	
Gait	10-meter walk test (10MWT) speed	Participants walked a 10 m track. After walking 2 m, assessors measured the time taken to walk a further 6m.	(Lang et al., 2016)
	10MWT Stride length	During the 10MWT, assessors also counted the number of strides taken to walk 6m	
Dynamic Balance	Step test	Participants stood with feet together, 10 cm from a 10cm high step. Assessors counted the number of times that a participant placed their foot repeatedly on the step in 15 seconds. Both legs were tested	(Hill et al., 1996)
Cognition	Montreal Cognitive Assessment (MoCA)	Participant completed the MoCA test version 8.1 (www.mocatest.org), which was scored by an assessor	(Gill et al., 2008)
Fine motor skills	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 secs for crossing a line. Dominant hand was tested	(Pullman, 1998)
Static Balance	Tandem stance (TS)	Assessors recorded the time that a participant could stand with one foot in front of the other (heel to toe) until a step was taken, or the participant used a hand to steady themselves. The assessment was terminated at 30 sec. Both legs were tested with eyes open and closed.	(Smithson et al., 1998)
	Single leg stance (SLS)	Assessors recorded the time that a participant could stand with one foot raised in the air until a step was taken, or the participant used a hand to steady themselves. The assessment was terminated at 30 sec. Both legs were tested with eyes open and closed.	

Table S4: Individual data for participant assessments at baseline (treatment naïve) and at 12-week, 1-year, 2-year and 3-year re-assessments (percent improvement or decline compared to baseline). TUG=timed up-and-go; MoCA=Montreal Cognitive Assessment; TS=tandem stance; SLS=single leg stance; nd=not determined

	WALK SPEED (metres/second)					STRIDE LENGTH (metres)				
	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year
A4	1.03	1.67 (61%)	1.33 (29%)	1.21 (17%)	1.07 (3%)	0.50	0.67 (34%)	0.60 (20%)	0.67 (34%)	0.55 (10%)
A5	1.33	1.94 (45%)	1.75 (32%)	2.05 (54%)	1.94 (46%)	0.60	0.46 -(23%)	0.75 (25%)	1.00 (67%)	0.75 (25%)
B1	1.76	1.94 (10%)	2.07 (17%)	2.05 (16%)	1.94 (10%)	0.60	0.67 (11%)	0.75 (25%)	0.89 (48%)	0.75 (25%)
B2	1.54	1.60 (4%)	1.69 (10%)	1.81 (18%)	1.67 (9%)	0.67	0.67 (0%)	0.67 (0%)	0.86 (29%)	0.75 (13%)
B3	1.88	2.21 (18%)	2.54 (36%)	2.31 (23%)	nd	0.75	0.75 (0%)	0.75 (0%)	0.75 (0%)	nd
B4	1.94	1.94 (0%)	1.93 (0%)	nd	1.90 -(2%)	0.86	0.86 (0%)	0.75 -(13%)	nd	0.86 (0%)
B5	1.90	1.96 (3%)	2.00 (5%)	2.16 (13%)	1.88 -(1%)	0.60	0.75 (25%)	0.75 (25%)	0.86 (43%)	0.75 (25%)
B6	1.50	1.50 (0%)	1.54 (3%)	1.37 -(9%)	nd	0.67	0.67 (0%)	0.75 (13%)	0.75 (13%)	nd

	TUG (seconds)					TUG MOTOR (seconds)					TUG COGNITIVE (seconds)				
	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year
A4	11.0	8.5 (23%)	9.9 (10%)	9.1 (17%)	11.1 -(1%)	10.6	9.3 (12%)	13.3 -(26%)	11.2 -(6%)	12.1 -(14%)	10.5	9.3 (11%)	9.8 (6%)	8.9 (15%)	12.4 -(18%)
A5	6.5	5.2 (20%)	6.0 (7%)	5.8 (11%)	5.8 (11%)	7.1	6.6 (7%)	6.1 (14%)	5.1 (28%)	6.2 (13%)	6.0	5.2 (14%)	5.2 (13%)	5.8 (3%)	5.6 (7%)
B1	7.4	6.6 (11%)	6.6 (11%)	6.5 (12%)	5.8 (22%)	8.2	6.4 (22%)	6.0 (27%)	6.5 (21%)	6.3 (23%)	7.5	6.3 (16%)	6.7 (11%)	6.5 (13%)	6.1 (19%)
B2	8.5	7.6 (11%)	8.0 (6%)	6.3 (26%)	7.0 (18%)	8.1	8.5 -(5%)	9.2 -(14%)	6.2 (23%)	7.3 (10%)	8.8	8.9 -(1%)	9.5 -(8%)	6.9 (22%)	8.0 (9%)
B3	6.5	5.9 (9%)	6.3 (3%)	6.3 (3%)	nd	6.5	6.3 (3%)	7.0 -(7%)	6.9 -(6%)	nd	7.3	6.4 (12%)	6.5 (11%)	6.7 (8%)	nd
B4	7.3	7.1 (3%)	6.6 (10%)	nd	6.7 (8%)	8.3	7.1 (14%)	6.8 (18%)	nd	7.3 (12%)	7.5	6.8 (9%)	6.4 (15%)	nd	6.7 (11%)
B5	6.7	6.3 (6%)	5.9 (12%)	5.8 (13%)	6.8 -(1%)	6.4	6.6 -(3%)	5.8 (9%)	6.0 (6%)	7.0 -(9%)	6.7	6.8 -(1%)	6.6 (1%)	6.4 (4%)	6.8 -(1%)
B6	9.3	7.6 (18%)	7.9 (15%)	9.6 -(3%)	nd	9.1	8.1 (11%)	8.4 (8%)	10.0 -(10%)	nd	9.0	8.1 (10%)	8.8 (2%)	9.7 -(8%)	nd

	STEP TEST (number of steps) affected leg					STEP TEST (number of steps) inaffected leg				
	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year
A4	14	20 (43%)	18 (29%)	17 (21%)	14 (0%)	12	16 (33%)	20 (67%)	14 (17%)	13 (8%)
A5	18	23 (28%)	21 (17%)	20 (11%)	20 (11%)	20	22 (10%)	21 (5%)	18 -(10%)	18 -(10%)
B1	21	23 (10%)	20 -(5%)	22 (5%)	21 (0%)	18	21 (17%)	24 (33%)	19 (6%)	23 (28%)
B2	12	14 (17%)	12 (0%)	18 (50%)	15 (25%)	12	12 (0%)	13 (8%)	15 (25%)	15 (25%)
B3	15	19 (27%)	21 (40%)	18 (20%)	nd	15	19 (27%)	21 (40%)	18 (20%)	nd
B4	13	11 -(15%)	11 -(15%)	nd	13 (0%)	11	13 (18%)	13 (18%)	nd	13 (18%)
B5	13	16 (23%)	18 (38%)	17 (31%)	13 (0%)	12	17 (42%)	19 (58%)	15 (25%)	13 (8%)
B6	15	15 (0%)	14 -(7%)	12 -(20%)	nd	15	15 (0%)	14 -(7%)	12 -(20%)	nd

	SPIRAL TEST (seconds) dominant hand					MoCA score				
	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year
A4	52.5	23.2 (56%)	44.2 (16%)	67.0 -(28%)	65.6 -(25%)	28	28 (0%)	30 (7%)	29 (4%)	28 (0%)
A5	22.6	16.5 (27%)	17.4 (23%)	19.2 (15%)	16.6 (26%)	27	27 (0%)	28.7 (6%)	29.7 (10%)	30 (11%)
B1	29.6	28.9 (3%)	34.4 -(16%)	32.4 -(9%)	28.9 (2%)	29	29 (0%)	30 (3%)	29.7 (2%)	30 (3%)
B2	38.2	29.9 (22%)	34.2 (11%)	24.6 (36%)	30.7 (20%)	29	30 (3%)	30 (3%)	30 (3%)	30 (3%)
B3	28.7	29.1 -(1%)	19.8 (31%)	24.1 (16%)	nd	27	27 (0%)	30 (11%)	30 (11%)	nd
B4	42.0	45.9 -(9%)	35.9 (14%)	36.9 (12%)	37.8 (10%)	26	27 (4%)	28.7 (10%)	29.7 (14%)	30 (15%)
B5	20.7	14.1 (32%)	21.1 -(2%)	19.6 (5%)	15.7 (24%)	28	29 (4%)	30 (7%)	30 (7%)	29 (4%)
B6	40.3	21.7 (46%)	27.9 (31%)	29.6 (27%)	nd	24	29 (21%)	nd	29.7 (24%)	nd

	TS eyes open (seconds) affected foot behind					TS eyes open (seconds) unaffected foot behind					TS eyes closed (seconds) affected foot behind					TS eyes closed (seconds) unaffected foot behind				
	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year
A4	10.0	30.0	27.0	30.0	0.0	7.0	30.0	2.4	13.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0
A5	30.0	30.0	30.0	4.3	22.4	11.0	30.0	1.0	5.0	11.3	1.0	2.0	4.0	0.0	10.5	4.0	3.0	2.7	0.0	3.9
B1	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	8.0	15.0	30.0	30.0	8.3	9.2	30.0	30.0	30.0	30.0
B2	3.0	2.5	0.0	12.3	30.0	4.0	8.4	13.8	9.8	30.0	1.0	1.0	nd	0.0	2.5	0.0	2.5	nd	0.0	3.0
B3	30.0	30.0	30.0	30.0	nd	30.0	30.0	30.0	30.0	nd	7.5	5.6	30.0	4.4	nd	4.3	2.0	10.7	0.8	nd
B4	3.0	30.0	30.0	nd	30.0	30.0	30.0	30.0	nd	30.0	14.0	30.0	3.9	nd	30.0	3.0	16.0	nd	nd	8.0
B5	30.0	30.0	30.0	30.0	30.0	30.0	30.0	19.0	30.0	6.4	3.6	6.0	3.4	30.0	3.9	13.0	2.0	3.4	4.8	2.9
B6	4.0	4.9	20.0	17.0	nd	2.0	5.7	25.0	2.9	nd	0.0	1.0	3.0	17.0	nd	0.0	1.0	3.2	2.9	nd

	SLS eyes open (seconds) affected foot raised					SLS eyes open (seconds) unaffected foot raised					SLS eyes closed (seconds) affected foot raised					SLS eyes closed (seconds) unaffected foot raised				
	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year	baseline	12-weeks	1-year	2-year	3-year
A4	1.0	12.0	nd	1.0	0.0	1.0	17.0	nd	2.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	nd	0.0	0.0
A5	21.0	30.0	4.5	5.3	13.1	30.0	15.0	30.0	20.1	30.0	3.0	0.0	30.0	0.0	1.1	8.0	0.0	5.4	0.0	2.8
B1	5.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	4.9	26.0	30.0	30.0	26.0	8.9	10.0	23.0	30.0	28.0
B2	3.0	5.0	10.0	6.7	11.3	2.0	2.0	3.0	30.0	4.3	0.0	0.0	nd	0.0	2.1	0.0	0.0	nd	1.3	2.3
B3	5.0	14.0	30.0	1.6	nd	3.0	17.0	15.0	0.8	nd	0.0	1.7	nd	0.0	nd	1.0	1.6	5.0	0.0	nd
B4	30.0	17.0	11.0	nd	21.1	6.0	20.0	11.0	nd	28.0	3.0	2.4	2.0	nd	3.9	1.0	5.0	2.0	nd	2.8
B5	30.0	3.0	9.0	4.8	21.0	5.0	15.0	11.0	22.4	14.0	1.0	0.0	nd	0.0	0.0	2.0	0.0	nd	0.0	0.0
B6	5.0	2.0	8.0	0.9	nd	3.0	2.0	9.0	0.7	nd	1.0	0.0	nd	0.0	nd	2.0	0.0	nd	0.0	nd