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Effects of Low-Level Laser Therapy in Autism Spectrum Disorder

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Abstract

The study examined the efficacy of low-level laser therapy, a form of photobiomodulation, for the treatment of irritability associated with autistic spectrum disorder in children and adolescents aged 5–17 years. Twenty-one of the 40 participants received eight 5-min procedures administered to the base of the skull and temporal areas across a 4-week period (test, i.e., active treatment participants). All the participants were evaluated with the Aberrant Behavior Checklist (ABC), with the global scale and five subscales (irritability/agitation, lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech), and the Clinical Global Impressions (CGI) Scale including a severity-of-illness scale (CGI-S) and a global improvement/change scale (CGI-C). The evaluation took place at baseline, week 2 (interim), week 4 (endpoint), and week 8 (post-procedure) of the study. The adjusted mean difference in the baseline to study endpoint change in the ABC irritability subscale score between test and placebo participants was −15.17 in favor of the test procedure group. ANCOVA analysis found this difference to be statistically significant ($F = 99.34$, $p < 0.0001$) compared to the baseline ABC irritability subscale score. The study found that low-level laser therapy could be an effective tool for reducing irritability and other symptoms and behaviors associated with the autistic spectrum disorder in children and adolescents, with positive changes maintained and augmented over time.

Keywords

Autism spectrum disorder · Brain · Clinical trial · Low-level laser therapy · Neuronal networks · Photobiomodulation

1 Introduction

Autism spectrum disorder (ASD) is a complicated syndrome characterized clinically by language impairment, dysfunction in social engagement, stereotypical movements and behaviors, and various cognitive deficits (McPartland and Volkmar 2012; South et al. 2012; Zappella 2012; Melillo and Leisman 2010). In earlier work, we have also noted an excess of high-frequency EEG, suggesting an imbalance in the excitation-

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inhibition homeostasis in the neocortex (Machado et al. 2015).

Recent theories have proposed that deficits in the integration of transient activity patterns in diverse brain regions suggest a possible temporal binding deficit in ASD (Leisman et al. 2012; Testa–Silva et al. 2012; Vissers et al. 2012; Melillo and Leisman 2009). Binding denotes the effective incorporation of dissimilar neural information in shaping an individual's unified experience of the world and self, reportedly impaired in ASD (Machado et al. 2015; McPartland and Volkmar 2012; South et al. 2012; Zappella 2012; Melillo and Leisman 2010). We have suggested that synchronous activity in the neocortex may be critical for sensory integration and is associated with integrated perceptual experiences (Ding et al. 2017), selective attention (Salo et al. 2017), and working memory (Griffiths and Kumar 2017), all of which are part of the myriad deficits reported in ASD. The evidence from both animal and human studies demonstrates that changes in neuronal synchrony occur during all of these processes.

Augmented coherence values, reflecting inefficiencies in brain networking noted in ASD, likely reflect rigid neuronal networks that could explain the typical manifestation of repetitive behaviors, deficiencies in social interaction, and communication and imagination, characteristics of ASD (Machado et al. 2015; Gadow and Drabick 2012; Zappella 2012).

Brain specialization does not fully explain most aspects of brain function. Confirmatory studies indicate that integrative functions over multiple distributed systems and areas support diverse cognitive processes such as visual recognition (Behrmann and Plaut 2013), language (Friederici and Gierhan 2013), cognitive control (Power and Petersen 2013), emotion (Pessoa 2012), and social cognition (Barrett and Satpute 2013). The neural substrate enabling integration of distributed neural information and the emergence of a coherent cognitive state depends partly on neural communication among specialized brain regions existing within a network of interregional projections (Fuster 1997; Goldman-Rakic 1988). The result is associated with large-scale patterns of synchronization and information flow (Brovelli et al. 2004) between connected elements.

A significant literature exists on the ability of low-level light therapy (LLLT) to penetrate the skull. Low-energy light passes the skull and a therapeutic effect likely exists. LLLT systems employ the so-called quantum optically induced transparency effect (Scherman et al. 2012; Weis et al. 2010). This effect controls optical properties of dense media enhancing transparency contrast by a factor of five. Therefore, the skull, spine, or joints can be penetrated even with moderate intensity light reaching deep layers in muscles, connective tissue, and even bone, enabling transcranial effects of LLLT (Hamblin 2018; Hiwaki and Miyaguchi 2018; Grover Jr et al. 2017; deTaboada et al. 2006).

LLLT achieves a therapeutic effect by employing non-ionizing light, including lasers, light-emitting diodes, or broadband light in the visible red (600–700 nm) and near-infrared (780–1100 nm) spectra (Shanks and Leisman 2018; deFreitas and Hamblin 2016). LLLT is a nonthermal process occurring when a chromophore is exposed to a suitable wavelength of light. Chromophores are responsible for the color associated with biological compounds such as hemoglobin and cytochromes (Cotler et al. 2015). With chromophore absorption of a photon of light, an electron transits to an excited state, with a physiologic effect occurring when photons dissociate the inhibitory signaling molecule nitric oxide (NO) from cytochrome-C-oxidase, increasing the electron transport, mitochondrial membrane potentials, and production of mitochondrial products such as ATP and NADH (deFreitas and Hamblin 2016; Wang et al. 2016, 2015). Other effects include the production of reactive oxygen species (ROS) which activate transcription factors, leading to the cellular proliferation and migration (Farivar et al. 2014).

Based on these complex characteristics, LLLT possesses physiologically modifying properties associated with light characteristics such as wavelength and irradiance, varied by exposure parameters, such as energy density, irradiation duration, and treatment frequency. On the basis

of the above, we investigated behavioral and cognitive changes in ASD as a consequence of the delivery of red LLLT.

2 Methods

2.1 Participants

The study received an approval from the Helsinki Committee of the Institute for Neurology and Neurosurgery in Havana, Cuba, and was registered with the FDA (Identifier: NCT03379662). Informed written consent was obtained from the parent or guardian of each participant after a full explanation of the procedures to be undertaken. The informed consent forms, research protocol, and approvals are available for inspection in the Office of Research Integrity at the Institute of Neurology and Neurosurgery in Havana, Cuba.

The participants consisted of 40 individuals distributed at baseline in the fashion described in Tables 1, 2, and 3. Participants in both groups spanned 5–16 years, with the mean participant age of approx. 8 years. A *t*-test for independent samples revealed no statistically significant difference in age between test and placebo group participants (μa-$\mu b = -0.13$; $t = -0.13$; $df = 38$; p(two-tailed) = 0.90 ($p > 0.05$)).

All study participants were recruited from among the investigator's normal pool of new and existing patients who voluntarily came with their parents seeking treatment for the symptoms of ASD and from among the individuals who responded to recruitment flyers and print ads. Participants did not receive any financial compensation for participation.

Table 1 Age of study participants by the procedure group

Age (years)	Test[a] (n = 21)	Placebo (n = 19)
Mean	8.2	8.4
Standard deviation	3.0	3.2
Range	5–16	5–16

[a]Test group was the active treatment group

Table 2 Participant gender breakdown for the test and placebo group participants

Gender	Test[a] (n = 21)	Placebo (n = 19)
Male	16	14
Female	5	5

[a]Test group was the active treatment group

2.2 Inclusion and Exclusion Criteria

Each eligible participant satisfied each of the following inclusion criteria and none of the exclusion criteria. Males or females aged 5–17 years meeting the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, for ASD, are diagnosed by a qualified medical professional. Diagnosis was confirmed by the Autism Diagnostic Interview (ADI-R) (Constantino et al. 2003). Each participant demonstrated "irritable" behaviors such as tantrums, aggression, self-injurious behavior, or a combination of thereof. The participant's Aberrant Behavior Checklist (ABC) irritability subscale (Rojahn et al. 2003) score was >18; the Clinical Global Impressions Severity Scale (CGI-S) (Berk et al. 2008) score was ≥ 4 (4 = moderately ill). The participants' therapeutic/intervention plan had been consistent/stable for 3 months. They abstained from undertaking new treatments during the study time.

Exclusion criteria were the following: history of a primary or concurrent diagnosis of another disorder, including neurological, use of a psychotropic drug, or any participation in a research study within 30 days prior to the commencement of the current study.

2.3 Baseline Concomitant Medications and Low-Level Light Therapy (LLLT)

Table 4 presents the OTC and prescription medications reported by participants at the baseline evaluation used in the past by both test and placebo group participants. No participant took any OTC medication during the study time.

Table 5 lists the non-drug therapies routinely used by both test and placebo group participants

Table 3 Participant ethnicity by the procedure group

Ethnicity	Test[a] (n = 21)	Placebo (n = 19)
Caucasian	3	4
Hispanic	9	1
African	8	13
Hispanic and African	1	0
Asian	0	1

[a]Test group was the active treatment group

Table 4 Prior medication used to treat the symptoms of autistic disorder by the procedure group

Medication[a]	Test[b] (n = 21)	Placebo (n = 19)
Carbamazepine	10	7
Risperdal	9	8
Valproate	2	3
Methylphenidate	3	1
Haloperidol	1	3
Chlorpromazine	1	2
Risperidone	1	1
Conductosa	1	1
Thioridazine	0	2
Levomepromazine	0	1

[a]Some participants previously used several medications; therefore, medication use by participant group adds up to greater than the participant sample size *per* group; [b]test group was the active treatment group

to treat the symptoms of ASD at the time of entry to the study. Therapy used to treat symptoms of ASD was minimal and equal between test and placebo group participants.

Medications routinely used by both test and placebo group participants at the time of study enrollment for indications other than to treat the symptoms of autistic disorder are listed in Table 6.

2.4 Procedure

All the 40 participants completed the course according to the protocol. Twenty-one of them were randomized to the test (active treatment) procedure group, and 19 were randomized to the placebo procedure group.

Participants received eight 5-min laser light applications to the base of the skull and temporal areas with the Erchonia® EAL Laser (active or sham) across a 4-week period: two applications *per* week, 3–4 days apart at the investigator's test site. A pulsed laser of 635 nm with a power output of 15 mW and a red 635 nm LED were used as treatment and placebo, respectively.

Participants were required to maintain their regular medication schedule and treatment regimens, as reported at the baseline evaluation, to treat symptoms related to autistic disorder throughout the study time. All of them complied with this requirement.

2.5 Outcome Measures

Pre-post treatment outcome measures included the Aberrant Behavior Checklist (ABC). The global score and the five subscale scores consisted of (a) irritability and agitation, (b) lethargy and social withdrawal, (c) stereotypic behavior, (d) hyperactivity and noncompliance, and (e) inappropriate speech. The ABC is an informant rating instrument empirically derived by principal component analysis. The global score for the ABC has not been psychometrically derived and is not statistically valid (Farmer and Aman 2012).

The second outcome measure consisted of the Clinical Global Impressions (CGI) scale including a severity-of-illness scale (CGI-S) and a global improvement/change scale (CGI-C). Leucht and Engel (2006) have noted that both the CGI and the Brief Psychiatric Rating Scale (BPRS) are often employed in drug trials. Those authors have found that by calculating the effect size and its 95% confidence interval for both continuous (standardized mean differences) and dichotomous (odds ratio) outcomes, there was no significant differences between tests, which indicates a good inter-test reliability.

Table 5 Therapies used to treat the symptoms of autistic disorder by the procedure group

Therapy	Test[a] (n = 21)	Placebo (n = 19)
Logopedic therapy for language	2	2
Hydrotherapy for hyperactivity	1	0

[a]Test group was the active treatment group

Table 6 Baseline non-autism-related concomitant medication use by the procedure group

Medication (Indication)	Test[a] (n = 21)	Placebo (n = 19)
Ketotifen (*allergies*)	3	1
Benadryl (*allergies*)	0	1
Meclizine (*allergies*)	0	1
Fluticasone (*Asthma*)	1	0
Vitamins A, B6, and C	0	1

[a]Test group was the active treatment group

The ABC and CGI-S and CGI-C were administered prior to treatment and then 2 (midpoint) and 4 weeks (endpoint) of treatment and finally 8 weeks after treatment (post-procedure evaluation).

3 Results

3.1 Pre-procedure Measures

Aberrant Behavior Checklist (ABC) Mean and standard deviation baseline (pre-procedure) of the ABC global and subscale scores for test and placebo group participants are provided in Table 7.

T-tests for independent samples revealed no statistically significant differences in the baseline ABC global score or in any of the five ABC subscale scores between test and placebo group participants ($p > 0.05$) as shown in Table 8.

Clinical Global Impressions Severity (CGI-S) Score Table 9 shows the CGI-S baseline score for the test and placebo group participants. The majority of participants in both groups had a baseline CGI-S score of 6, corresponding to "severely ill".

3.2 Primary Efficacy Outcome Analysis

The evaluation time point at which study success was analyzed (study endpoint) was predetermined as 4 weeks following baseline (pretreatment) evaluation. The study was predetermined to be considered successful if, using the intent-to-treat (ITT) last observation carried forward (LOCF) analysis, the primary endpoint was statistically significant at the 0.05 level. The primary efficacy outcome measure was predefined as the mean change from baseline to endpoint (end of the 4-week treatment period) in the ABC irritability and agitation subscale score, with a minimum mean difference of −8.5 points between the test and placebo groups.

The primary outcome measure was evaluated for the following two populations:

1. *Intent-to-Treat (ITT).* ITT analysis included all participants with valid measurements at baseline, randomized to a procedure group. Dropouts and terminated participants were handled by carrying forward the last observation for all time points following the dropout (LOCF). If a participant was not a dropout but had no data in a relative day range, the last observation prior to the time point being analyzed was employed.
2. *Per-Protocol Population.* Per-protocol analysis of results intended to corroborate

Table 7 ABC global and subscale scores by the procedure group

	Test[a] (n = 21)	Placebo (n = 19)
	Mean ± SD	Mean ± SD
Global score	30.5 ± 6.7	29.6 ± 6.8
Irritability and agitation	23.1 ± 9.3	24.7 ± 5.1
Lethargy and social withdrawal	13.7 ± 4.1	12.3 ± 5.6
Stereotypic behavior	32.8 ± 7.8	36.9 ± 7.9
Hyperactivity and noncompliance	7.2 ± 3.1	6.4 ± 4.0
Inappropriate speech	107.3 ± 20.3	104.7 ± 28.7

[a]Test group was the active treatment group

Table 8 *T*-test results for differences in ABC global and subscale scores between the two procedure group (test vs. placebo)

	μa-μb	t	df	p
Global score	0.95	+0.44	38	0.66
Irritability and agitation	−1.64	−0.68	38	0.50
Lethargy and social withdrawal	1.40	+0.91	38	0.37
Stereotypic behavior	−4.09	−1.64	38	0.11
Hyperactivity and noncompliance	0.77	+0.69	38	0.49
Inappropriate speech	2.60	+0.33	38	0.74

Table 9 CGI-S baseline scores by the procedure group

CGI-S Score	Test[a] (n = 21)	Placebo (n = 19)
7: Among the most extremely ill patients	3	0
6: Severely ill	14	15
5: Markedly ill	4	4

[a]Test group was the active treatment group

conclusions drawn from the ITT analysis. This analysis excluded the participants with major protocol deviations and incompletes (dropouts, non-compliant participants, disqualified participants, etc.). All participants in this study completed all study visits and procedures and had all study measurements recorded through to the study endpoint evaluation. Therefore LOCF was not applied.

3.3 General Statistical Evaluation

For the ABC irritability subscale score, changes were evaluated by analysis of covariance (ANCOVA), with baseline measures as a covariate and a procedure group (active or placebo) as the main effect. Table 10 shows the observed and adjusted means for the absolute change in ABC irritability subscale score from baseline to endpoint, adjusting for the covariate of baseline ABC irritability subscale scores.

The adjusted mean difference in the baseline to endpoint change in the ABC between the test and placebo groups was −15.2, almost double the pre-established study success criteria of −8.5 points between the procedure groups, in favor of the test group ($F = 99.3$; $p < 0.0001$). Table 11 shows the observed mean and standard deviation at baseline and endpoint for the ABC score and change between the evaluations by the procedure group.

The ABC score decreased 14.8 points for participants in the test group, while it increased by 0.32 points for participants in the placebo group, resulting in an observed difference between the two groups in the ABC irritability

Table 10 Change in ABC irritability subscale score from baseline to endpoint, adjusting for baseline ABC irritability subscale score

ABC irritability subscale score	Test[a] (n = 21)	Placebo (n = 19)
Observed mean	−14.81	0.32
Adjusted mean	−14.83	0.34

[a]Test group was the active treatment group

Table 11 ABC irritability subscale score from baseline to endpoint by the procedure group

	Test[a] (n = 21)	Placebo (n = 19)
ABC irritability subscale score	Mean ± SD	Mean ± SD
Baseline	30.5 ± 6.7	29.6 ± 6.8
Endpoint	15.7 ± 9.9	29.9 ± 6.6
Change	**−14.8 ± 6.4**	**0.3 ± 1.4**

[a]Test group was the active treatment group

subscale score from baseline to endpoint evaluation of −15.1.

T-Test for Two Correlated Samples A correlated sample *t*-test was used to compare the difference in the mean change in ABC score from study baseline to endpoint. The evaluation for participant groups separately found the mean change to be significant for the test group ($t = +10.6$; $df = 20$; $p < 0.001$), but not for the placebo group ($t = -1.0$; $df = 18$, $p = 0.33$).

T-Test for Independent Samples A *t*-test for two independent samples, used to compare the mean ABC score change from baseline to endpoint between the test and placebo groups, found that the mean difference of −15.1 was significant in favor of the participants in the test group ($t = -10.1$; $df = 38$; $p < 0.0001$).

3.4 Secondary Efficacy Outcome Analysis

3.4.1 Positive Responder Rate (PRR)

The evaluation of the difference in PRR between the procedure groups was performed as a predetermined secondary efficacy outcome measure to provide support for the primary efficacy analysis. The PRR was defined as satisfaction with both of the following: (a) ≥ 25% reduction from baseline to endpoint in the ABC score based on the participant's primary caregiver's rating and (b) CGI-I rating of 1 (very much improved) or 2 (much improved) at study endpoint as determined by the clinician's evaluation.

Participants attaining a ≥ 25% reduction from baseline to endpoint in the ABC irritability subscale score. Eighteen (86%) of the 21 test group participants attained a minimum of 25% reduction in the ABC score from baseline to endpoint, while none of the 19 placebo participants did. Table 12 shows the mean and standard deviation of the percent (%) change in ABC scores from baseline to endpoint for the test and placebo groups.

ABC Irritability Subscale A *t*-test for two independent samples was performed to compare the mean difference in percent change in ABC scores from baseline to endpoint between the test group and placebo groups. The mean difference of -52.5% was significant in favor of the test group participants ($t = -9.79$; $df = 38$; $p < 0.0001$).

CGI-I Ratings Seventeen (81%) of the 21 test group participants received a CGI-I rating of 1 or 2 at the study endpoint evaluation, while none of the 19 placebo participants did.

Positive Responder Rate Successes Table 13 shows the number and percentage of test and placebo group participants meeting the dual criteria for PRR. There was a difference of 81%

Table 12 Percentage change in ABC irritability subscale score by the procedure group

% change in ABC irritability score	Test[a] (n = 21)	Placebo (n = 19)
Mean ± SD	−51.0 ± 22.4	1.5 ± 6.6

[a]Test group was the active treatment group

Table 13 Positive responder rate by the procedure group

Participants	Test[a] (n = 21)	Placebo (n = 19)
Meeting success criteria (n, %)	17 (81)	0 (0)

[a]Test group was the active treatment group

Table 14 Comparison of the proportion of positive responder rates between the procedure groups

2 × 2 table	Positive responder rate (PRR)	Negative responder rate (NRR)
Test[a] group	17	4
Placebo group	0	19
$p < 0.00001$	17	23

[a]Test group was the active treatment group

in the proportion of participants who met the PRR between procedure groups: 81% of test group participants met the PRR criteria compared with none in the placebo group. Fisher's exact test for two independent proportions was conducted to compare the proportion of PRR between the groups (Table 14). The difference in this proportion was significant ($p < 0.00001$). The greater PRR from baseline to endpoint for the test group relative to the placebo group also was significant.

3.4.2 Aberrant Behavior Checklist (ABC) Global and Subscale Scores

The evaluation of the mean change from baseline to endpoint for each of the ABC global score and the remaining four ABC subscale scores (lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech) between the two procedure groups was performed as a predetermined secondary efficacy outcome measure to provide support for the primary efficacy analysis outcome. Table 15 shows the mean and standard deviation of baseline and endpoint ABC global and subscale scores and the changes for the test and placebo participants (Aman et al. 1985a, 1985b). The ABC global and subscale scores were evaluated with ANCOVA, with the baseline measure for each score as a covariate and the group as a main effect (Tables 16 and 17). The F values were statistically greater for the mean change for each of the ABC scores between groups ($p < 0.0001$). With removal of individual differences in baseline scores, the two adjusted means significantly differed ($p < 0.0001$), and the means were significant for the test but not for placebo group participants (Tables 18 and 19).

A *t*-test analysis for two independent samples comparing differences in the mean change in the ABC scores from baseline to endpoint between the two groups is provided in Table 20; the difference was significantly greater for the test than placebo group participants.

The evaluation of the mean change in each of the ABC global score and the five subscale sores (irritability/agitation, lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech) across the study duration between the procedure groups was performed as a predetermined supportive measure providing support for the primary efficacy analysis. The ABC scores were recorded at the following four evaluation points: baseline (pre-procedure), week 2 (interim procedure administration), week 4 (study endpoint), and week 8 (i.e., 4 weeks post-procedure). Table 21 shows these data for the test and placebo groups.

Table 15 ABC global and subscale scores from baseline to endpoint by the procedure group

		Test[a] (n = 21)	Placebo (n = 19)
		Mean ± SD	Mean ± SD
Global score	Baseline	107.3 ± 20.3	104.7 ± 28.7
	Endpoint	63.8 ± 30.5	105.4 ± 28.4
	Change	−43.5 ± 19.1	0.7 ± 2.6
Lethargy and social withdrawal	Baseline	23.1 ± 9.3	24.7 ± 5.1
	Endpoint	13.8 ± 8.8	24.7 ± 5.1
	Change	−9.3 ± 5.8	0.1 ± 0.2
Stereotypic behavior	Baseline	13.7 ± 4.1	12.3 ± 5.6
	Endpoint	8.2 ± 5.1	12.3 ± 5.6
	Change	−5.5 ± 4.0	0.0 ± 0.0
Hyperactivity and noncompliance	Baseline	32.8 ± 7.8	36.9 ± 7.9
	Endpoint	21.1 ± 9.5	37.3 ± 7.4
	Change	−11.7 ± 7.5	0.4 ± 1.1
Inappropriate speech	Baseline	7.2 ± 3.1	6.4 ± 4.0
	Endpoint	4.9 ± 2.4	6.4 ± 3.9
	Change	−2.3 ± 2.3	0.0 ± 0.3

[a]Test group was the active treatment group

Table 16 Change in ABC scores from baseline to endpoint, adjusted for baseline score

ABC global and subscales	Mean scores	Test[a] (n = 21)	Placebo (n = 19)
Global score	Observed	−43.53	0.74
	Adjusted	−43.60	0.82
Lethargy and social withdrawal	Observed	−9.29	0.05
	Adjusted	−9.44	0.22
Stereotypic behavior	Observed	−5.47	0
	Adjusted	−5.43	−0.05
Hyperactivity and noncompliance	Observed	−11.67	0.37
	Adjusted	−11.95	0.68
Inappropriate speech	Observed	−2.29	0
	Adjusted	−2.21	−0.08

[a]Test group was the active treatment group

Table 17 Significance of the mean baseline to endpoint change in the ABC global and subscale scores between the test and placebo groups

	Observed difference	Adjusted difference	F	p
Global score	44.3	44.4	99.0	<0.0001
Lethargy and social withdrawal	9.7	9.3	58.1	<0.001
Stereotypic behavior	5.5	5.4	33.8	0.000001
				<0.00005
Hyperactivity and noncompliance	12.0	12.6	50.3	<0.0001
Inappropriate speech	2.3	2.1	19.3	0.000091
				<0.0001

Figures 1, 2, 3, 4, 5, and 6 show the mean changes in each of the ABC global and five subscale scores across the study duration by the procedure group. The figures as well as Table 21 indicate that each ABC score in the test (active treatment group) decreased significantly from the baseline level across the three evaluation points; the decrease was progressively augmented over

Table 18 *t*-test analysis for the mean change in the ABC global and subscale scores for the test group participants

	t	df	p
Global score	+10.45	20	<0.0001
Lethargy and social withdrawal	+7.34	20	<0.0001
Stereotypic behavior	+6.34	20	<0.0001
Hyperactivity and noncompliance	+7.14	20	<0.0005
Inappropriate speech	+4.59	20	<0.0001

Table 19 *t*-test analysis for the mean change in the ABC global and subscale scores for the placebo group participants

	t	df	p
Global score	−1.25	18	0.23
Lethargy and social withdrawal	−1.00	18	0.33
Stereotypic behavior	−0.0	18	−1.00
Hyperactivity and noncompliance	−1.44	18	0.17
Inappropriate speech	0.0	18	1.00

Table 20 *t*-test analysis for the mean change in the ABC scores between the test and placebo groups

	t	df	p
Global score	−10.01	38	<0.0001
Lethargy and social withdrawal	−7.01	38	<0.0001
Stereotypic behavior	−6.02	38	<0.0001
Hyperactivity and noncompliance	−6.92	38	<0.0005
Inappropriate speech	−4.32	38	<0.0001

time, including a 4-week follow-up period during which no further treatment occurred. Conversely, there was no such change in the placebo group.

One-way ANOVA and Tukey's HSD post hoc analyses were performed to evaluate the mean change in each ABC global and subscale scores across the four study evaluation points in the test and placebo groups. Table 22 shows that the score improvement in each of the ABC subscales was significant across almost all the comparative evaluations in the test group. Conversely, score changes in the placebo participants were not statistically significant (Table 23).

3.4.3 Clinical Global Impressions Severity-of-Illness (CGI-S) Ratings

The evaluation of the change in CGI-S ratings from baseline to endpoint between the test and placebo groups was performed as a predetermined secondary efficacy outcome measure providing support for the primary efficacy analysis outcome. Table 24 shows the number of participants by the CGI-S rating at baseline and endpoint for both groups of participants. All 21 test (active treatment) participants showed a one-category or greater improvement in CGI-S ratings from baseline to endpoint. In contradistinction, the majority of placebo participants (17) showed no change in CGI-S rating, one demonstrated a worsening of one category, and another demonstrated an improvement of one-category rating from baseline to endpoint. A 2×3 Fisher's exact test for matched categorical data was conducted to compare the proportion of participants whose CGI-S rating improved, showed no change, or worsened from baseline to endpoint in the test and placebo groups (Table 25).

A difference in the proportion of participants whose CGI-S rating changed one or more categories from baseline to endpoint between the test and placebo groups was significant ($p < 0.00001$), with a greater proportion of test group participants who had improved CGI-S ratings from baseline to endpoint relative to the placebo group (Table 26). In both test and placebo groups, all participants (100%) were rated at baseline in the top three severity-of-condition ratings, i.e., marked, severe, and most extreme. All placebo group participants (100%) retained these top CGI-S ratings (categories 5–7 in Table 26) by week 8, while only 3 of the 21 of active test treatment (14%) received the same top ratings. This continuously progressive and substantial improvement for the test over placebo group participants was illustrated in Fig. 7 which indicates the percentage of participants who

Table 21 ABC global and subscale scores across the study duration by the test and placebo groups

		Test[a] (n = 21)	Placebo (n = 19)
		Mean ± SD	Mean ± SD
Global score	Baseline	107.3 ± 20.3	104.7 ± 28.7
	Week 2	89.3 ± 24.1	110.0 ± 19.4
	Week 4	63.8 ± 30.5	105.4 ± 28.4
	Week 8	48.8 ± 25.1	105.3 ± 31.6
Irritability	Baseline	30.5 ± 6.7	29.6 ± 6.8
	Week 2	23.4 ± 7.4	29.9 ± 7.5
	Week 4	15.7 ± 9.9	29.9 ± 6.5
	Week 8	11.8 ± 10.0	29.9 ± 6.6
Lethargy and social withdrawal	Baseline	23.1 ± 9.3	24.7 ± 5.1
	Week 2	18.2 ± 9.3	24.7 ± 5.1
	Week 4	13.8 ± 8.8	24.7 ± 5.1
	Week 8	10.7 ± 9.8	24.7 ± 5.1
Stereotypic behavior	Baseline	13.7 ± 4.1	12.3 ± 5.6
	Week 2	11.6 ± 4.4	12.3 ± 5.6
	Week 4	8.2 ± 5.1	12.3 ± 5.6
	Week 8	6.9 ± 5.1	12.6 ± 5.7
Hyperactivity and noncompliance	Baseline	32.8 ± 7.8	36.9 ± 7.9
	Week 2	30.3 ± 8.2	36.7 ± 7.8
	Week 4	21.1 ± 9.5	37.3 ± 7.4
	Week 8	16.0 ± 10.5	37.3 ± 7.4
Inappropriate speech	Baseline	7.2 ± 3.1	6.4 ± 4.0
	Week 2	5.8 ± 2.6	6.4 ± 4.0
	Week 4	4.9 ± 2.4	6.4 ± 3.9
	Week 8	3.5 ± 2.2	6.5 ± 3.9

[a]Test group was the active treatment group

received the 5–7 categories of CGI-S ranking across the study duration by the procedure group.

3.4.4 Clinical Global Impressions Improvement/Change (CGI-C) Ratings

The evaluation of CGI-C ratings at study endpoint between the procedure groups was performed as a predetermined secondary efficacy outcome measure to provide support for the primary efficacy analysis outcome. The number of participants by the CGI-C rating at endpoint for the test and placebo groups is shown in Table 27.

Twenty out of the 21 test group participants showed some degree of improvement in the autism-related symptoms at study endpoint relative to baseline, with the majority (13) receiving a rating of "much improved". Conversely, no placebo group participant was rated as demonstrating symptom improvement at endpoint relative to baseline, with the majority (17) rated as "no change" and the remaining 2 as "minimally worse". A proportion of participants in both test and placebo groups whose CGI-C rating at study endpoint, relative to baseline, showed "improvement" (CGS-C rating of 1, 2, and 3), "no change" (CGI-C rating of 4), or "worsening" (CGI-C rating of 5, 6, and 7) in symptoms, evaluated with 2 x 3 Fisher's exact test, is shown in Table 28. A difference in this proportion between the two groups was significant ($p < 0.00001$). There was a greater

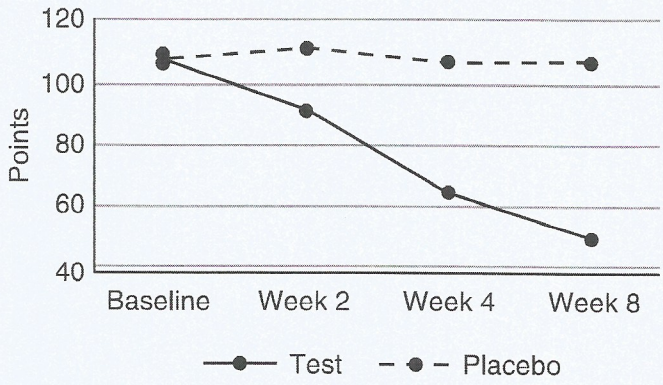

Fig. 1 Aberrant Behavior Checklist (ABC) global score in the test (active treatment) and placebo group participants

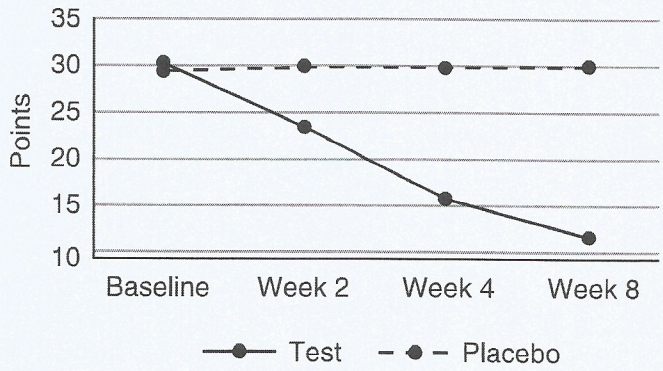

Fig. 2 Aberrant Behavior Checklist (ABC) irritability subscale score in the test (active treatment) and placebo group participants

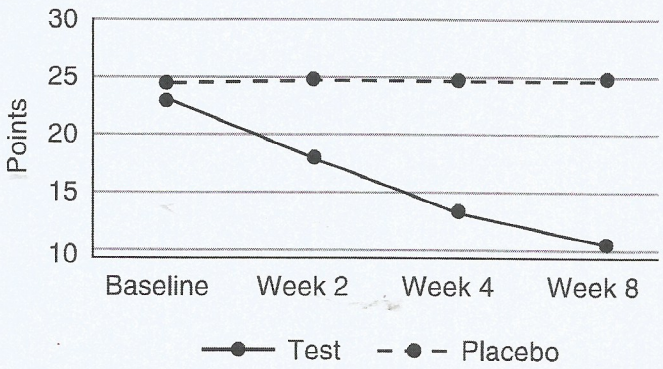

Fig. 3 Aberrant Behavior Checklist (ABC) lethargy/ social withdrawal subscale score in the test (active treatment) and placebo group participants

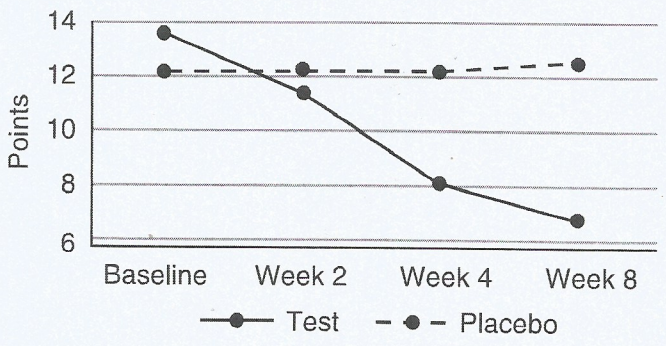

Fig. 4 Aberrant Behavior Checklist (ABC) stereotypic behavior subscale score in the test (active treatment) and placebo group participants

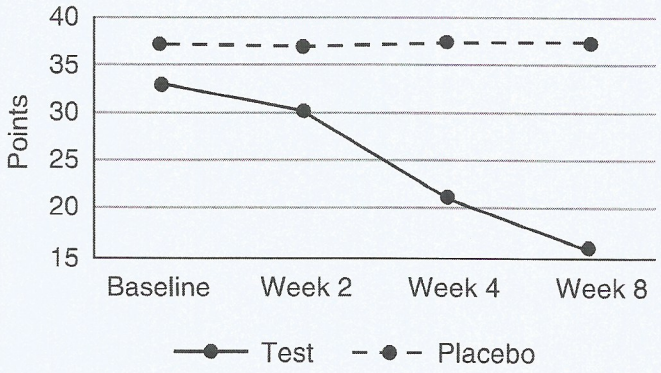

Fig. 5 Aberrant Behavior Checklist (ABC) hyperactivity/ noncompliance subscale score in the test (active treatment) and placebo group participants

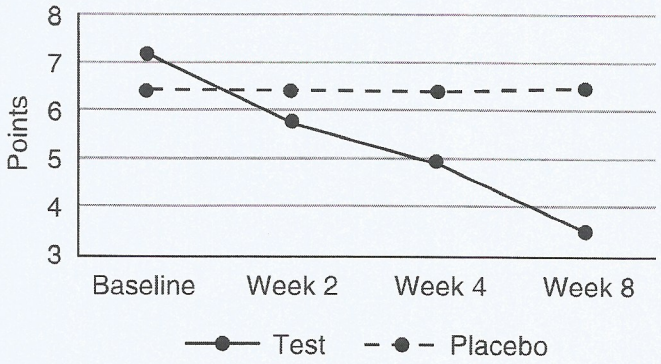

Fig. 6 Aberrant Behavior Checklist (ABC) inappropriate speech subscale score in the test (active treatment) and placebo group participants

Table 22 One-way ANOVA and Tukey's HSD post hoc follow-up results for the change in the Aberrant Behavior Checklist (ABC) score across the study duration in the test (active treatment) group participants

ABC scale/subscale	F	p	Tukey's HSD
Global score	101.6	<0.0001	Changes between each possible evaluation
			Combination was significant at $p < 0.01$
Irritability	114.5	<0.0001	Changes between each possible evaluation
			Combination was significant at $p < 0.01$
Lethargy and social withdrawal	49.6	<0.0001	Changes between each possible evaluation
			Combination was significant at $p < 0.01$, except week 4–8 which was significant at $p < 0.05$
Stereotypic behavior	38.2	<0.0001	Baseline to week 2 significant at $p < 0.05$
			All others significant at $p < 0.01$, except week 4–8 which was not significant
Hyperactivity and noncompliance	59.4	<0.0001	All significant at $p < 0.01$, except baseline to week 2 which was not significant
Inappropriate speech	26.9	<0.0001	All significant at $p < 0.01$, except week 2–4 which was not significant

Table 23 One-way ANOVA results for the change in Aberrant Behavior Checklist (ABC) score across the study duration in the placebo group participants

ABC scale/subscale	F	p
Global score	0.4	0.789
Irritability	0.4	0.739
Lethargy and social withdrawal	1.0	0.399
Stereotypic behavior	1.0	0.399
Hyperactivity and noncompliance	2.4	0.081
Inappropriate speech	0.4	0.739

Table 24 Clinical Global Impressions severity-of-illness (CGI-S) ratings at baseline and endpoint by the procedure group

	Test[a] (n = 21)		Placebo (n = 19)	
CGI-S category	Baseline	Endpoint	Baseline	Endpoint
7: Most extreme of all autism patients	3	–	–	–
6: Severe	14	2	15	16
5: Marked	4	1	4	3
4: Moderate	–	13	–	–
3: Mild	–	4	–	–
2: Borderline	–	1	–	–
1: Normal	–	–	–	–

[a]Test group was the active treatment group

Table 25 Fisher's exact test for matched categorical data to compare the proportion of participants whose Clinical Global Impressions severity-of-illness (CGI-S) ratings improved

2 × 3 table	Improved	Unchanged	Worsened	n
Test[a] group	21	0	0	21
Placebo group	1	17	1	19
Total	22	17	1	40

[a]Test group was the active treatment group; $p < 0.00001$

Table 26 Clinical Global Impressions severity-of-illness (CGI-S) ratings across the study duration by the procedure groups

	Test[a] (n = 21)				Placebo (n = 19)			
CGI-S	Baseline	Week 2	Week 4	Week 8	Baseline	Week 2	Week 4	Week 8
7: Most extreme	3	2	–	1	–	–	–	–
6: Severe	14	1	2	2	15	15	16	15
5: Marked	4	15	1	–	4	4	3	4
4: Moderate	–	3	13	9	–	–	–	–
3: Mild	–	–	4	6	–	–	–	–
2: Borderline	–	–	1	3	–	–	–	–
1: Normal	–	–	–	–	–	–	–	–

[a]Test group was the active treatment group; $p < 0.00001$

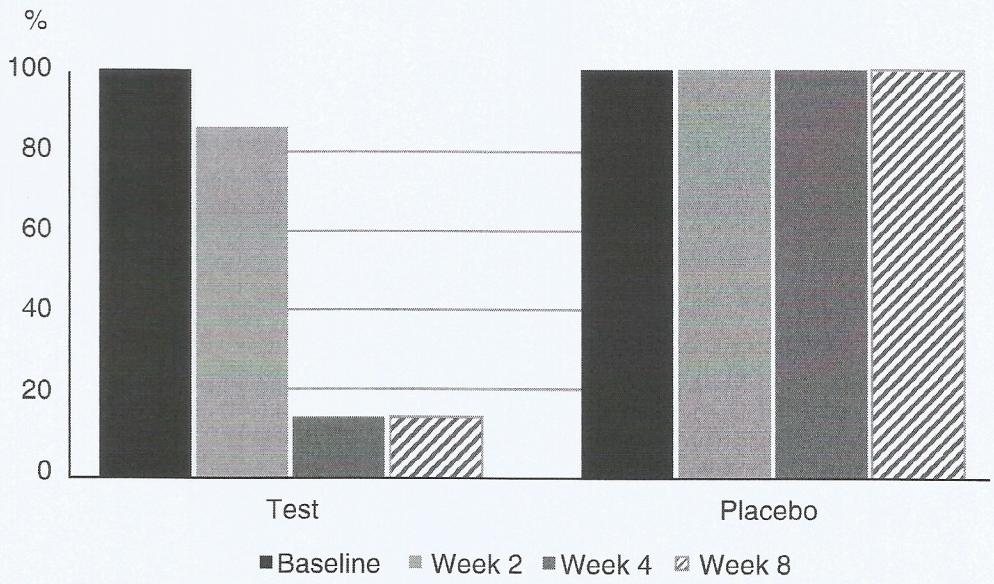

Fig. 7 Percentage of participants receiving a 5–7 rating in the severity-of-illness subscale of the Clinical Global Impressions Scale (CGI-S) across the study duration

Table 27 Clinical Global Impressions improvement/change subscale (CGI-C) ratings at the study endpoint by the procedure group

CGI-C category	Test[a] (n = 21)	Placebo (n = 19)
1: Very much improved	4	–
2: Much improved	13	–
3: Minimally improved	3	–
4: No change	1	17
5: Minimally worse	–	2
6: Much worse	–	–
7: Very much worse	–	–

[a]Test group was the active treatment group; $p < 0.00001$

Table 28 Fisher's exact test comparing the proportion of participants with Clinical Global Impressions improvement/change subscale (CGI-C) ratings of ASD symptoms at the study endpoint

2 × 3 table	Improved	Unchanged	Worsened	n
Test group[a]	20	1	0	21
Placebo group	0	17	2	19
Total	20	18	2	40

[a]Test group was the active treatment group; $p < 0.00001$

proportion of participants demonstrating "improvement" at study endpoint in the test than placebo group, which is viably attributed to the application of LLLT.

The evaluation of change in the CGI-C ratings across the study duration by the procedure group was performed as a predetermined supportive analysis to provide additional support for the primary efficacy analysis outcome. CGI-C ratings were recorded across the following evaluation points: after 2 weeks (interim procedure administration), 4 weeks (study endpoint), and 8 weeks (4 weeks post-procedure). Table 29 shows the number of participants by CGI-C rating category for the test and placebo groups. The CGI-C ratings for the test (active treatment) participants

Table 29 Clinical Global Impressions improvement/change subscale (CGI-C) ratings across the study duration by the procedure group

	Test[a] (n = 21)			Placebo (n = 19)		
CGI-C rating	Week 2	Week 4	Week 8	Week 2	Week 4	Week 8
1: Very much improved	–	5	10	–	–	–
2: Much improved	9	12	8	–	–	–
3: Minimally improved	11	3	3	–	–	–
4: No change	1	1	–	18	17	17
5: Minimally worse	–	–	–	1	2	2
6: Much worse	–	–	–	–	–	–
7: Very much worse	–	–	–	–	–	–

[a]Test group was the active treatment group; $p < 0.00001$

indicated a continuous progressive improvement in symptoms. As early as 2 weeks into the 4-week procedure, 20 out of the 21 participants received CGI-C ratings of improvement, relative to baseline, with 11 showing "minimal improvement" and 9 "much improvement". By week 8, the presentation of autistic symptoms and behaviors was reported as "very much improved" for almost half (48%) of active treatment participants. Conversely, there was essentially no change in the CGI-C ratings across the study duration for the placebo participants, indicating no observable symptomatic improvement.

4 Discussion

Baseline ABC irritability subscale scores indicated that LLLT was significantly more effective than placebo in treating symptoms of ASD in children and adolescents independent of baseline ABC scores, which accounted for 6% of the variance in the ABC score change from baseline to endpoint. The difference in the proportion of PPR between the LLLT and placebo groups was statistically significant ($p < 0.00001$).

Considering the baseline score as a covariate, F values were statistically significant ($p < 0.0001$) for the mean change from baseline to endpoint between the LLLT and placebo groups and within participant groups for both ABC global and subscale scores. Removing individual differences in the baseline score, the adjusted means significantly differed ($p < 0.0001$), supporting the conclusion that LLLT is more effective than placebo in effecting a positive change in the ASD symptoms.

All participants of the active treatment showed a one-category or greater improvement in CGI-S from baseline to endpoint, while 17 of the placebo participants showed no CGI-S rating change. The difference in the proportion of participants whose CGI-S rating changed one or more categories from baseline to endpoint between the two groups was significant ($p < 0.00001$). This difference is attributable to the efficacy of LLLT compared with placebo. All 21 active treatment participants showed a one-category or greater improvement in CGI-S from baseline to endpoint.

Twenty out of the 21 active treatment participants showed some degree of improvement in autism-related symptoms at endpoint relative to baseline. The majority (13) received ratings of "much improved". No placebo group participant demonstrated improvement in symptoms at endpoint relative to baseline. The majority (17) demonstrated "no change", and the remaining 2 placebo participants rated "minimally worse". We found that the ABC global and five subscale scores decreased progressively and significantly from baseline across each of the three successive evaluation points; the decrease progressed over time, including a 4-week follow-up during which no further LLLT occurred. Conversely, the placebo group demonstrated no significant change across the study duration, demonstrating the effectiveness of LLLT in reducing ASD-associated symptoms.

For both test and placebo group, all participants were rated at baseline in the top

three severity conditions. By week 8, all placebo participants retained a 5–7 CGI-S score, while only 3 of the 21 active treatment (14%) received this rating, which speaks for a progressive improvement in the symptom presentation across the study time. As early as 2 weeks into the 4-week active treatment, 20 out of the 21 test group participants received improved CGI-C ratings, with 11 participants showing "minimal" and 9 demonstrating "much improvement". By week 8, symptom presentation of ASD was reported as being "very much improved" for almost half (48%) of the test group participants, whereas no significant change in the CGI-C rating was noted for the placebo group participants.

There is a well-established literature on photobiomodulation, supporting improvement in dysfunctional neuronal activity with the use of low intensity red and near-infrared (NIR) light (Hiwaki and Miyaguchi 2018; Naeser et al. 2014). Ten-year experience in animal studies has indicated that transcranial photobiomodulation has a positive effect in animal models of traumatic brain injury (Wu et al. 2012a; Oron et al. 2007), Alzheimer's (Wu et al. 2012b), depression (Purushothuman et al. 2015), and stroke (Hiwaki and Miyaguchi 2018; Lapchak and deTaboada 2010; Oron et al. 2006), while human studies have included traumatic brain injury (Naeser et al. 2011), depression (Schiffer et al. 2009), and stroke (Zivin et al. 2009). Further, low-level light energy has been found safe for humans in the stroke studies, providing a high benefit-to-risk ratio, with no reported side effects of LLLT.

Almost all aspects of cognitive function require integration of widely distributed neural activity. Network analysis of human brain connectivity has reliably classified sets of neocortical areas essential for supporting optimized neuronal signaling and communication. Optimal "brain hubs" exist in the networks of effective connectivity, supporting the notion of the hub's function in a wide range of cognitive tasks and a dynamic coupling in and across effective functional networks. A high level of brain hub centrality renders these networks vulnerable to dysfunction and disconnection (van den Heuvel and Sporns 2013). Abnormal anatomical connectivity and performance of hub regions have been hypothesized to be associated with cognitive and behavioral dysfunction in numerous neurological and psychiatric disorders (Bullmore and Sporns 2012; Seeley et al. 2009). For example, analyses of structural and functional connectivity in schizophrenia have shown reduced frontal hub connectivity (Fornito et al. 2012).

We have recently noted that altered functional connectivity, i.e., synchronous brain activity, might be associated with the deficits characteristically found in ASD (Machado et al. 2015). Of specific importance is the integrity of functional connectivity in the default mode network (DMN), a network active during inactive resting states, and in cognitive functions linked to the ASD-related social dysfunction. Assaf et al. (2010) have found a decreased functional connectivity between the precuneus/medial/prefrontal/anterior/cingulate cortices and default mode network core areas, with the degree of functional connectivity in these regions inversely correlated with the ASD communication and social deficits. These results support the hypothesis that default mode networks' under-connectivity contributes to the core deficits seen in ASD.

Of particular interest is the association of default mode networks with ASD (Buckner et al. 2008). Numerous studies have found various "hubs" with the effectiveness of the entire network highly dependent on the hub status. The most common ASD-related hubs are those reported by Raichle et al. (2001) and Greicius et al. (2003) being associated with the ventromedial and dorsomedial prefrontal, posterior cingulate, precuneus, lateral parietal, and entorhinal cortices (Raichle 2015). Assaf et al. (2010) have examined three default mode sub-networks obtained from the resting fMRI scans of 16 ASD individuals and 16 matched controls, using independent component analysis. The ASD individuals demonstrate a reduced functional connectivity between the medial-prefrontal/anterior-cingulate/precuneus cortices and other default mode sub-networks areas. The degree of functional connectivity in these regions

is inversely associated with the severity of social and communication deficits.

LLLT promotes cell and neuronal repair (Dawood and Salman 2013) and brain network rearrangement (Erlicher et al. 2002) in many neurologic disorders identified with lesions in the hubs of default mode networks (Buckner et al. 2008). LLLT facilitates a fast-track wound-healing (Dawood and Salman 2013) as mitochondria respond to light in the red and near-infrared spectrum (Quirk and Whelan 2011). On the other hand, Erlicher et al. (2002) have demonstrated that weak light directs the leading edge of growth cones of a nerve. Therefore, when a light beam is positioned in front of a nerve's leading edge, the neuron will move in the direction of the light and grow in length (Black et al. 2013; Quirk and Whelan 2011). Nerve cells appear to thrive and grow in the presence of low-energy light, and we think that the effect seen here is associated with the rearrangement of connectivity.

Reports are now emerging that LLLT and photobiomodulation significantly upregulate brain-derived neurotrophic factor (BDNF), a factor highly associated with dendritic sprouting, neuroplasticity, and brain reconnectivity (Hamblin 2018). In particular, photobiomodulation influences the ubiquitous transcription factor CREB (cAMP-response element-binding protein) to increase BDNF and consequently dendrite growth (length, spine density, and branching in the hippocampal neurons). Functional magnetic resonance studies demonstrate the activity modulation in intrinsic brain networks, including default mode networks, likely to be dysfunctional in a variety of conditions. All of that supports the notion that LLLT can modify functional and effective connectivity in the neocortex. Research on photobiomodulation reveals the beneficial effects of LLLT for a rapidly expanding list of conditions, making this method increasingly accepted by the mainstream medicine, even though its mechanisms of action remains by far an area of limited knowledge.

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Conflicts of Interest None of the authors have any fiduciary interests in the research reported herein or with the source of funding.

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