Transcranial photobiomodulation in a single case of gene SCN2A-related autism

*Corresponding Author: Stefano Pallanti
Email: stefanopallanti@yahoo.it

Abstract

ASD is a multi-factorial disorder in nature with genetic mechanisms, immune dysregulations and neurofunctional alterations as pathogenic mechanisms. SCN2A, encoding the neuronal voltage-gated Na+ channel NaV1.2, is one of the most commonly affected loci linked to ASD. There are no established pharmacological treatment for the core features of ASD. Herein, we report the case of a young adult with gene SCN2-A-related autism and hypofrontality, which was treated with transcranial photobiomodulation (tPBM). The patient showed an improvement in repetitive behaviours, cognitive and behavioural rigidity and impulsive behaviours. This case report shows the potential of tPBM in the treatment of ASD due to a genetic mutation and characterized by structural and functional neural abnormalities. Mechanisms and implications are discussed.

Keywords: Transcranial photobiomodulation; Neuromodulation; Autism; SCN2A-related autism.

Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder with early onset, characterized by two core symptoms domains: social communication and repetitive behaviours [1]. ASD is a multi-factorial disorder in nature with genetic mechanisms, immune dysregulations and neurofunctional alterations as pathogenic mechanisms [2]. First, specific genetic syndromes like Rett syndrome or Fragile-X syndrome, or cytogenetic abnormalities are associated with ASD. Moreover, specific mutations have been identified in ASD [3]. SCN2A, encoding the neuronal voltage-gated Na+ channel NaV1.2, is one of the most commonly affected loci linked to Autism Spectrum Disorders (ASDs) [4]. Second, strong inflammation states are associated with ASD, including increased levels of cytokines [5]. Moreover, an excessive microglial activation (related to immune abnormalities) has been observed in multiple brain regions of people with ASD [6]. Third, altered functional and structural organization of the Default Mode Network (DMN) are prominent neurobiological features of ASD, as well as a shallower right TPJ sulcus, a thicker mPFC and abnormal cingulate cortex [7]. In conjunction with behavioural and emotional therapies [8], pharmacological approach is often considered [9,10]. Medications such as risperidone and aripiprazole have an effect on ASD related irritability and aggression [11], with risperidone being the only one drug approved by the FDA to treat the irritability symptoms [12]. However, there are no established pharmacological treatment for the core features of ASD.

Nowadays, there is still increasing the interest is non-invasive brain stimulation in the treatment of neurodevelopmental disorders, thanks to their ability to modulate neuroplasticity, behavioral and socio-emotional processes [13,14].

One of the new neuromodulation approaches is the transcranial photobiomodulation (tPBM), In PBM there is a non-invasive exposure of light, typically within the red to near-infrared (\(\lambda\approx600-1300\) nm) spectrum, to elicit physiological effects across several tissue systems [15]. PBM can include either coherent-light (lasers) or non-coherent light (light-emitting diodes, LEDs) [15] and its therapeutic mechanisms
involved increased metabolism, plastic modulation of neural networks and anti-inflammatory effects [16].

Considering the clinical phenotype of ASD, transcranial PBM (tPBM) appears as a potential optimal candidate for its treatment. A study with a mouse model of Valproic Acid (VPA)-induced autism showed that laser PBM with a wavelength of 830 nm as a neuroprotective effect, inducing an attenuation of cognitive dysfunction, repetitive behaviours and neuroinflammation [17]. Specifically, a reduction in the number of microglia in hippocampus was reported. The first study with PBM in human with ASD employed low-level laser therapy, which is a form of PBM, with a pulsed laser of 635 nm with a power output of 15 mW. Laser was delivered to the base of the skull and temporal areas children and adolescents. A reduction in the aberrant behaviours and an improvement in the clinical global impression scale were observed [18]. The first study adopting LED PBM was published by our group [19]. LED light has the advantage of irradiating larger areas of tissue and results in fewer side effects. 21 patients with a mean age of 9.1 were treated with LED PBM at 810 nm 5 days a week for 6 months. The protocol involves two sessions a day: one with light delivered at 10 Hz (alpha stimulation) and one at 40 Hz (Gamma stimulation). The main result was the reduction in ASD severity. Secondary measures showed a reduction in cognitive and behavioral rigidity and an improvement in parents-reported attention. Another study showed the effects of tPBM at a wavelength of 830 nm in adults with high-functioning ASD [20], reporting a reduction in the severity of ASD symptoms. All these findings converge to report that tPBM is a safe and feasible treatment approach for ASD. In this single study, we report the case of a young adult with gene SCN2A-related autism and hypofrontality, which was treated with tPBM and showed unbelievable outcomes.

Methods

Case description

All the clinical data of the patient were extracted from databases containing information on patients of the psychiatric clinic at the Institute of Neuroscience, Florence (Italy).

The patient, aged 24, presented a clinical picture characterised by difficulties in social interaction, generalised and performance anxiety, difficulty in modulating mood and easy irritability and difficulty in accepting changes.

In 2009, the first psychopathological assessments were carried out in which he was diagnosed with ASD. Moreover, the tendency to rigid submission to daily routines and habits was observed as well as a phantasmatic personality structure, explored through projective tests.

In July 2010, another psychopathological assessment was carried out in which an important generalised anxiety disorder was reported, associated with somatisation, grandiose ideas and accelerated speech. Oppositional defiant traits with occasional rule-breaking and impulsiveness were also highlighted. A highly immature personality structure also emerged, with a disharmonious profile, difficulties in emotional modulation, poor self-control and recourse to poorly evolving and dysfunctional defence mechanisms, such as switching to behavioural action in the face of frustration.

Following the assessment, a weekly psychotherapeutic course was undertaken, which was subsequently interrupted by the boy’s decision due to discomfort he felt in reaction to the sessions.

During the high school, parents and teachers reported good commitment and motivation in the school environment as well as an accentuation of anxiety reactions in the face of both scholastic and performance demands and a greater awareness of his difficulties, with a tendency to become anxious and disorganised even in the face of small mishaps and mistakes in daily life. They report, therefore, a rigidity in coping with the rhythms of daily life, presenting difficulties and sometimes resiting changing habits and needing ample notice of any changes. They also report extreme attention to schedules with significant anticipatory agitation in the face of appointments with related disorganised behaviours and anxiety. A scarce ability of self-regulation was observed. There was a permanent difficulty in interacting with the peer group. He also reported difficulty in managing his impulses, aggressive behaviours.

In 2020, structural and functional MRI showed hypofrontality, i.e. decreased neural activity in the frontal regions, an abnormal paracingular sulcus and a lower than normal position of the cerebellar tonsils at the level of the great occipital foramen (Figure 1).

Furthermore, he reported altered values in the Reuma test, meaning an ongoing inflammatory process. When a genetic test was conducted, a mutation in gene SCN2A was observed.

In July 2022, he was admitted to the outpatient psychiatric unit at the Institute of Neuroscience.

He received a diagnosis of ASD with genetic typing (SN-C2A). He was assessed with psychometric and neuropsychological measures. The Ritvo Autism Asperger Diagnostic Scale-Revised (RAADS-R) confirmed the presence of autistic traits. The Montefiore- Einstein Rigidity Scale (MERS) showed increased levels of cognitive and behavioural rigidity along with severe protest. The Reactivity, Intensity, Polarity and Stability questionnaire (RIPoSt-40) highlights emotional dysregulation and liability. Specifically, neuropsychological assessment included Connor’s Continuous Performance Task (CPT) and Stop Signal Task, showing control inhibition deficits.

In this case, PBM was considered and added to ongoing behavioral or pharmacological treatments, which remained unchanged throughout the stimulation period. Pharmacological therapy included Lorazepam (2 mg/die) and atomoxetine.

Procedure and stimulation parameters

tPBM was delivered using the commercially available Vielight®Neuro Gamma brain photo biomodulation stimulator. The gamma stimulator pulses light at 40 Hz light pulsing frequency and delivers 810 nm near infrared light via the transcranial LED clusters placed on the helmet.

The device is composed of a wearable headset with features microchip-boosted transcranial LED diodes. The tPBM headset consists of four clusters. The four LEDs deliver the NIR to the subdivisions of the DMN: The medial prefrontal cortex, the praeunecous area, and left and right angular gyrus. The intranasal application is positioned in the left nostril with the clip on the outside to deliver light to the ventral section of the brain, specifically to the ventromedial PFC. Device parameters are reported in Figure 2. tPBM was applied daily (5 days a week) for a total of 60 sessions.
Results

tPBM was well tolerated and no side effects were observed. At the end of treatment, an improvement in ASD core features was observed (Table 1). Indeed, standardized metrics reported a reduction in repetitive behaviours, measured through the The Adult Repetitive Behaviours Questionnaire-2 (RBQ-2), an improvement in impulsivity, measured through the UPPS-P Impulsive Behavior Scale, a reduction in cognitive and behavioural rigidity, measured through the MERS, and an improvement in empathy, assessed with the Empathy Quotient (EQ). Furthermore, an improvement in emotion liability, measured with the RIPOST was observed. Importantly, tPBM was associated with a significant reduction in related disability (SDS). At a 12-month follow-up improvement was stable.

Moreover, tPBM improved executive and attentional functions, as measured with the CPT and Stop Signal Task. Specifically, a profile of attentional function with a 75% of probability of being clinical reduced to a probability of 50%. Moreover, an increase in reaction time (T0:210 ms; T1:240 ms) was observed in SST, meaning an improvement in impulsivity.

Discussion

The presented case study of a young adult with SCN2A-related autism further highlights the potential of tPBM as a therapeutic option in ASD. Specifically, tPBM resulted to decrease ASD symptoms severity, like repetitive behaviours, impulsive behaviours, and behavioural rigidity. Moreover, executive and attentional functions improved. Indeed, the Stop Signal Reaction Time (SSRT) increased after the treatment, meaning an attenuation of impulsive behaviours. Improvement in ASD severity here reported is consistent with previous findings [18-20]. Also the improvement in attention was previously reported by [19]. This is the first time that an improvement in impulsive behaviours, corroborated by a neuropsychological test, is shown in ASD following tPBM. Importantly, no previous study reported whether tPBM could be effective in ASD with specific underlying genetic mutations and important structural and functional MRI abnormalities.

SCN2A, encoding the NaV1.2 sodium channel, is one of the commonly affected loci in ASD but also in epilepsy and infantile seizures [21]. In SCN2A-related epilepsy, mutations resulted in a gain of function which led to an increased neural excitability [21]. In children with SCN2A-related disorders the pathogenic variant ("mutation") in the gene SCN2A is associated with a dampened channel function, which impair the flow of sodium ions in the brain, leading to deficits in neural excitability [21]. This could explain the hypofrontality observed in our patient. Moreover, the loss of sodium reduced action potential backpropagation into dendrites, impairing synaptic plasticity and synaptic strength [22]. Interestingly, tPBM has been shown to increase the number of dendritic nodes and ends [23], restoring dendritic function [24], and improve synaptic plasticity [25]. Furthermore, a potential mechanism of tPBM is associated with cerebrovascular oxygenation of the prefrontal cortex [26]. Moreover, a systematic review showed strong support for long-range underconnectivity in ASD and that ASD is characterized by a general trend toward an under-expression of lower-band wide-spread integrative processes compensated by more focal, higher-frequency, locally specialized, and segregated processes [27].

tPBM at 40 Hz to the Default Mode Network (DMN) significantly increases the power of the higher oscillatory frequencies of alpha, beta and gamma and reduces the power of the slower frequencies of delta and theta in subjects in resting state [28]. Therefore, through a precision approach [29], tPBM could restore neural oscillations and altered brain wave patterns observed in ASD, leading to an improvement in ASD symptomatology.

Remarkably, the neural networks restorations should be stable in time. Indeed, in SCN2A-related ASD, the pathogenic mechanism leading to alterations is active only in early brain development, because in the mature brain NaV1.6 replaced NaV1.2 [21]. Coherently, herein we reported the sustained improvements at a 12-month follow-up, a finding that reinforces the potential durability of tPBM effects. These findings align with other studies reporting the benefits of tPBM in individuals with ASD [20]. Collectively, the evidence converges to suggest

Table 1: Psychometric test scores at the baseline, at the end of the treatment (after two months) and at a 12-month follow-up.

<table>
<thead>
<tr>
<th>Test name</th>
<th>Pre-Test</th>
<th>Post-Test</th>
<th>Difference</th>
<th>Follow-up-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBQ-2</td>
<td>1.93</td>
<td>1.35</td>
<td>-0.58</td>
<td>1.27</td>
</tr>
<tr>
<td>UPPS-P</td>
<td>71</td>
<td>34</td>
<td>-37</td>
<td>32</td>
</tr>
<tr>
<td>MERS</td>
<td>22</td>
<td>15</td>
<td>-7</td>
<td>16</td>
</tr>
<tr>
<td>EQ</td>
<td>29</td>
<td>32</td>
<td>+3</td>
<td>34</td>
</tr>
<tr>
<td>RIPOST</td>
<td>194</td>
<td>165</td>
<td>-29</td>
<td>139</td>
</tr>
<tr>
<td>SDS</td>
<td>26</td>
<td>5</td>
<td>-21</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 1: sMRI scan. sMRI scan 149 x 106 mm (144 x 144 DPI).

Figure 2: Parameters of the vielight PBM device (LED, Light-Emitting Diode). Parameters of the Vie light PBM device (LED, Light-Emitting Diode). 144 x 45 mm (96 x 96 DPI).
that tPBM is a safe and feasible therapeutic option for individuals with SCN2A-related ASD, offering potential improvements in core symptoms and associated challenges.

Furthermore, a gastrointestinal dysfunction has been identifying in genetically determined ASD cases [30]. Indeed, a disruption of the gut-brain axis has been implicated in ASD and correlated with brain gene expression changes, restrictive dietary patterns and pro-inflammatory cytokine profiles [31]. In this same sense, PBM has been shown to positively affect and control microbiome [32] and to regulate cytokines levels [33]. One interesting option, even if premature but to be explored is represented by the potential application of tPBM to modulate neural activity and positively impact core ASD features is promising. As the field advances, tPBM may emerge as a valuable addition to the toolkit of interventions for individuals with ASD, offering hope for improved quality of life and socio-emotional functioning.

**Conclusion**

In conclusion, the present case study contributes to the growing body of literature supporting tPBM as a novel approach for individuals with SCN2A-related ASD. The combination of genetic susceptibility, immune dysregulations, and neurofunctional alterations in ASD makes tPBM a compelling intervention. While further research is needed to elucidate the underlying mechanisms and optimize treatment protocols, the potential of tPBM to modulate neural activity and positively impact core ASD features is promising. As the field advances, tPBM may emerge as a valuable addition to the toolkit of interventions for individuals with ASD, offering hope for improved quality of life and socio-emotional functioning.

**Acknowledgement**

Informed consent: The patient gave his informed consent for the inclusion of his data in this case report.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because containing information that could compromise the privacy of research participants.

**References**


