ACADEMIA NEUROSCIENCE & BRAIN RESEARCH

Brief Research Report
Published: 5 June 2026
https://doi.org/10.20935/AcadNeurosci8343

Melatonin, angiotensin 1-7, and cannabidiol in refractory autoimmune disease: clinical case series

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Academic Editor: Lina Bunketorp-Käll

Abstract

Introduction: Dysregulation of the TH17/T regulatory (Treg) axis represents a frequently implicated pathway that may contribute to immune imbalance in selected autoimmune diseases, and experimental and clinical evidence suggests that several neuroendocrine systems—including melatonin, the endocannabinoid system, and the ACE2/angiotensin 1-7 axis—inhibit interleukin 17 (IL-17) signaling and physiologically modulate immune homeostasis.

Materials and methods: This retrospective, observational case series evaluated 70 consecutive patients with refractory autoimmune diseases who were nonresponsive to or declined conventional immunosuppressive therapies. Patients received an integrative neuroendocrine regimen consisting of oral melatonin (10–50 mg nightly), gastro-protected angiotensin 1-7 (0.5 mg twice daily), and cannabidiol (20 mg twice daily). Outcomes included changes in disease-specific autoantibody titers (anti-thyroglobulin antibodies and antinuclear antibodies), lymphocyte-to-monocyte ratio (LMR) as an exploratory biomarker of systemic inflammation, and clinical or radiological disease stability, particularly in multiple sclerosis.

Results: After 3 months, patients with Hashimoto's thyroiditis showed a significant reduction in anti-thyroglobulin antibody levels (−49%), while patients with other systemic autoimmune diseases exhibited a significant decline in antinuclear antibody titers (−60%). In the multiple sclerosis subgroup, 62% of patients achieved radiological disease stabilization, with a median follow-up of 46 months. Abnormally low baseline LMR values were normalized in 67% of patients experiencing disease flares at enrollment. The regimen was well tolerated, and no clinically significant adverse events requiring treatment discontinuation were observed.

Conclusions: In this heterogeneous cohort of patients with refractory autoimmune diseases, modulation of the neuroendocrine immune axis using melatonin, angiotensin 1-7, and cannabidiol was feasible, well tolerated, and associated with favorable serological and clinical trends. Given the retrospective, non-controlled design, these findings should be interpreted as hypothesis-generating. Controlled, randomized trials incorporating standardized immunological endpoints are warranted to validate the therapeutic potential of this integrative neuroimmune approach.

Keywords: *angiotensin 1-7, autoimmune diseases, cannabidiol, interleukin-17, mitochondria, melatonin, psycho-neuro-endocrine-immunology*

Citation: Lissoni P, Messina G, Monzon A, Tassoni S, Sassola A, Di Fede G, et al. Melatonin, angiotensin 1-7, and cannabidiol in refractory autoimmune disease: clinical case series. *Academia Neuroscience and Brain Research* 2026;2. https://doi.org/10.20935/AcadNeurosci8343

1. Introduction

Autoimmune diseases are fundamentally rooted in dysregulation of the intricate cytokine signaling molecules that mediate and regulate immunity, inflammation, and hematopoiesis [1], with mitochondrial damage and dysfunction being significant factors in the initiation and perpetuation of autoimmune conditions [2, 3]. An imbalance in proinflammatory versus anti-inflammatory cytokines is a hallmark of autoimmune conditions, leading to chronic inflammation and tissue damage. This can be conceptualized as a disruption in the relationships among TH1 lymphocytes (CD4+), T regulatory (Treg) lymphocytes (CD4+CD25+), and TH17 lymphocytes (CD4+CD17+) [4–7]. An enhancement of TH17 lymphocyte function in association with a diminished count and activity of both Treg and TH1 lymphocytes is typical of autoimmune diseases [1].

Recent advances in the field of psycho-neuro-endocrine-immunology demonstrate that this immune network is physiologically under neuroendocrine modulation [8]. Although most hormones, neurotransmitters, and neuropeptides may potentially influence the immune system, major neuroendocrine structures responsible for the psychoneurochemical control of chronic inflammation and tissue damage in autoimmune diseases are the pineal gland via melatonin (MLT) release [9–12] and the endocannabinoid system (ECS) [13–15]. In addition, a fundamental role of the renin–angiotensin converting enzyme (ACE)–ACE2 axis in the regulation of both immune and inflammatory status is now ascertained [16, 17]. Angiotensin (Ang) 1-7, the enzymatic product of ACE2, play anti-inflammatory, antitumor, and antithrombotic roles.

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The three types of compounds, MLT [18], ECS [19], and Ang 1-7 [20], inhibit IL-17 secretion. In addition, MLT enhances the expression of ACE2 and increases endogenous production of Ang 1-7 [21]. Then, the concomitant administration of MLT could reduce the dose of Ang 1-7 required to achieve clinical effects.

The concept of a neuroimmune pharmacological regimen for autoimmune diseases is gaining interest. Targeting IL-17 production through natural inhibitors is an attractive therapeutic strategy, potentially having fewer side effects compared to broad-spectrum immunosuppressants currently in use (e.g., the anti-IL-17A secukinumab® and ixekizumab®, or the anti-IL-17RA brodalumab®). Although these agents have gained their place in the treatment of psoriasis, psoriatic arthritis, and ankylosing spondylitis, they carry risks of infection and paradoxical inflammation [22, 23].

Preliminary clinical studies suggest the possibility of reversing the autoimmune processes by a neuroendocrine regime containing MLT, Ang 1-7, and cannabidiol (CBD) as a cannabinoid agent with a decline in autoantibody titers and a consequent improvement in clinical symptomatology [24]. The present study includes 70 consecutive patients affected by different types of autoimmune pathologies who did not receive benefits from the standard therapies with corticosteroid or immunosuppressive agents and were therefore treated with a neuroimmune regimen containing MLT, Ang 1-7, and CBD.

2. Materials and methods

2.1. Study design

This study is a retrospective, observational case series evaluating clinical and laboratory outcomes in patients with refractory autoimmune diseases treated with a neuroendocrine-based integrative regimen. No randomization, blinding, or control group was included. The study was designed to generate hypotheses regarding feasibility, safety, and potential biological effects rather than to establish causal efficacy.

2.2. Cohort

Seventy consecutive patients affected by different types of autoimmune pathologies were included in the study (M/F: 13/57; median age: 56; range: 19–91). The eligibility criteria were: (1) a clinical diagnosis of autoimmune disease, consisting of the presence of anti-thyroglobulin autoantibodies for the diagnosis of Hashimoto's thyroiditis, typical radiological features at nuclear magnetic resonance (NMR) imaging for the diagnosis of multiple sclerosis, and abnormal levels of antinuclear autoantibodies (ANAs) for the remaining pathologies considered; (2) a lack of response to the previous conventional therapies with corticosteroid and immunosuppressive agents or personal refusal to treatment, due to patient preferences, concerns about adverse effects, intolerance, access limitations, or socio-cultural factors. This heterogeneity represented a limitation of the study and may contribute to variability in observed responses.

The autoimmune pathologies included were Hashimoto's thyroiditis (24 patients), multiple sclerosis (MS) (21 patients), inflammatory bowel disease in 6 patients (Crohn's disease: 3; ulcerative colitis: 3), rheumatoid arthritis (5 patients), Sjögren syndrome (4 patients), psoriasis (3 patients), systemic lupus erythematous (2 patients), mixed connective tissue disease (MCTD) (2 patients), systemic scleroderma (2 patients), and uveitis (1 patient). Autoimmune conditions were grouped only for analyses involving non-disease-specific immunological markers, within a hypothesis-driven framework aimed at exploring shared immune features rather than disease-specific clinical effects. Due to limited sample sizes within individual autoimmune diagnoses, analyses were conducted at the group level to assess shared immunological features rather than disease-specific effects.

Serological outcomes included changes in anti-thyroglobulin antibodies and antinuclear antibody titers measured in all cases except for multiple sclerosis. A serological response was defined as a reduction $\geq$30% from baseline values. In multiple sclerosis patients, clinical outcome was defined as radiological disease stabilization, assessed through serial NMR imaging reports according to standard neuroradiological criteria (absence of new or enlarging lesions). The lymphocyte-to-monocyte ratio (LMR) was used as an exploratory biomarker of systemic inflammatory status.

After the approval of the local Ethical Committee of the Institute of Biological Medicine (protocol code 01/10; approved on 1 February 2020), the clinical protocol was explained to each patient and their relatives, and written consent was obtained. All procedures were conducted in accordance with the Declaration of Helsinki.

2.3. Drugs

All drugs were supplied by San Ruffino Laboratory (Smerillo, Fermo, Italy) and were administered per os. MLT was given at a 10 mg dose every night, generally 30 min prior to sleep, except for the MS patients who received 50 mg because of the partial dose-dependent efficacy in this specific disease [25]. Ang 1-7 was given in gastro-protected capsules with cyclodextrin [26] at a 0.5 mg dose twice daily. CBD (20 mg) was given twice daily.

Dosing was hypothesis-driven and informed by prior preclinical and translational studies demonstrating immunomodulatory effects relevant to TH17/Treg balance and inflammatory signaling. For MLT, the higher dose used in patients with multiple sclerosis was extrapolated from experimental autoimmune encephalomyelitis models [27, 28] and translational studies showing that immunomodulatory actions—such as suppression of proinflammatory cytokines (including IL-17-related pathways), inhibition of inflammasome activation, and mitochondrial protection—occur at doses exceeding those required for chronobiotic effects [29]. For Ang 1-7, dose selection was guided by experimental studies demonstrating anti-inflammatory and pro-resolving effects mediated through Mas receptor activation, including increases in regulatory T-cell markers and suppression of inflammatory cytokine signaling in immune-mediated disease models [17, 30, 31]. Its use and dosing in autoimmune contexts remain investigational. For CBD, dosing rationale is now explicitly linked to experimental data showing dose-dependent modulation of TH17/IL-17 responses, with low-to-moderate concentrations suppressing IL-17 production in autoimmune models, while higher or context-specific exposure may yield divergent effects [32, 33].

2.4. Assessment

Concerning laboratory data, normal values in our laboratory (95% confidence limits) were below 1:40 for ANA and below 40 IU/ml for anti-thyroglobulin autoantibodies. Because of its prognostic value, the lymphocyte-to-monocyte ratio (LMR) was examined in all cases. The normal values of LMR observed in our laboratory (95% confidence limits) were greater than 2.1. LMR was measured at monthly intervals, while autoantibody values were measured before the onset of therapy and at 3-month intervals. The clinical course of MS was assessed by NMR at 3-month intervals for the first year of therapy and then at 6-month intervals. Safety and tolerability were assessed through routine clinical evaluations, laboratory monitoring, and spontaneous reporting of adverse events during follow-up visits. No clinically significant adverse events or laboratory abnormalities requiring treatment discontinuation were observed during the observation period.

Clinical and laboratory assessments were performed as part of routine follow-up rather than at predefined study time points. Therefore, response timelines are reported descriptively and approximately, based on clinical records and patient reports. Disease stabilization was defined as the absence of clinical deterioration during follow-up, including no new disease-related symptoms, no documented progression of existing manifestations, and no need for escalation of immunomodulatory therapy. Stabilization did not imply clinical improvement or remission.

2.5. Statistical procedure

Because serological measurements were obtained before and after treatment in the same individuals, paired statistical analyses were performed. Given the non-normal distribution of antibody titers, as assessed by the Shapiro–Wilk test, the Wilcoxon signed-rank test was used for all pre–post comparisons. This non-parametric approach does not assume normality and is appropriate for immunological titration data. All analyses were conducted using individual patient-level data, allowing direct paired comparisons without assumptions of independence between baseline and follow-up measurements. Percentage changes and 95% confidence intervals were calculated directly from the observed paired differences. To account for multiple comparisons, the Bonferroni correction was applied; with two primary serological endpoints, an adjusted significance threshold of $p < 0.025$ was used. All statistical analyses were exploratory and hypothesis-generating, and results were interpreted within the limitations of a non-controlled observational design.

3. Results

3.1. Serological outcomes

In patients with Hashimoto's thyroiditis ($n = 24$), median serum anti-thyroglobulin antibody levels decreased from 246 IU/ml (interquartile range [IQR]: 127–630) at baseline to 106 IU/ml (IQR: 46–240) after 3 months of treatment, corresponding to a median relative reduction of approximately 47%. This reduction was statistically significant using the Wilcoxon signed-rank test ($p < 0.025$, Bonferroni-adjusted). Similarly, patients with other systemic autoimmune diseases and antinuclear antibody positivity ($n = 25$) showed a significant decline in ANA titers, from a median baseline value of 1:180 (IQR 1:180–1:320) to 1:80 (IQR 1:40–1:180) after 3 months, representing a median relative reduction of approximately 56% ($p < 0.025$, Wilcoxon signed-rank test) (**Table 1**). A serological response, defined as a reduction of ≥30% from baseline, was observed in 67% of patients with Hashimoto's thyroiditis and in 76% of patients with other systemic autoimmune diseases.

3.2. Multiple sclerosis outcomes

Among patients with multiple sclerosis ($n = 21$), radiological assessment based on serial NMR imaging reports indicated disease stabilization in 62% of cases. The median duration of radiological stability was 46 months (range: 9–68 months). Clinical observations included subjective improvement in neuropathic pain and motor function; however, these were recorded descriptively and were not assessed using standardized disability scales.

3.3. Lymphocyte-to-monocyte ratio

At enrollment, an abnormally low lymphocyte-to-monocyte ratio (LMR < 2.1) was observed in 6 out of 70 patients, all presenting with active disease exacerbation. Following the neuroendocrine intervention, LMR values normalized in four of these six patients (67%), coinciding with clinical remission of the acute phase.

Table 1 • Median (interquartile range) serum levels of anti-thyroglobulin (TG) antibodies in patients with Hashimoto's thyroiditis and antinuclear antibodies (ANAs) in patients with systemic autoimmune diseases at baseline and after 3 months of therapy with melatonin, angiotensin 1-7, and cannabidiol.

Patient group	*n*	Parameter	Baseline (median, IQR)	3 months (median, IQR)	Median % change	*p* value †
Hashimoto's thyroiditis	24	Anti-TG antibodies (IU/ml)	246 (127–630)	106 (46–240)	−47%	<0.025 *
Systemic autoimmune diseases	25	ANA titer ‡	1:180 (1:180–1:320)	1:80 (1:40–1:180)	−56%	<0.025 *

† Paired comparisons between baseline and 3 months were performed using the Wilcoxon signed-rank test. Bonferroni correction was applied for two comparisons (adjusted significance threshold of $p < 0.025$). * Statistically significant after correction for multiple comparisons. ‡ ANA titers are expressed as reciprocal dilution. TG: anti-thyroglobulin; ANA: antinuclear antibody; IQR: interquartile range. *n*: number of patients.

3.4. Safety and tolerability

The neuroendocrine regimen was generally well tolerated. Safety assessment was based on prospective clinical monitoring, including systematic reporting of adverse events and serial laboratory evaluations (hematology, liver, and renal function tests). No clinically relevant toxicities or treatment-limiting adverse events were observed during the study period. Rather, consistent side benefits were observed: a significant relief of subjective reports of asthenia, a reduction in patient-reported impressions of anxiety and chronic pain, and qualitative observations related to improved sleep patterns and mood. Specific rapid responses were noted in psoriasis (skin lesion clearance) and rheumatoid arthritis (significant pain reduction).

3.5. Temporal description

When changes were observed, they occurred over variable timeframes, generally ranging from weeks to months, with substantial interindividual variability. Not all patients exhibited changes within the same period, and some showed no apparent response during follow-up. The exact onset and duration of changes could not be systematically determined.

4. Discussion

This retrospective observational study suggests that modulation of the neuroendocrine immune axis using MLT, Ang 1-7, and CBD is associated with favorable serological and clinical trends in a heterogeneous cohort of patients with refractory autoimmune diseases. The present findings should be interpreted within the exploratory framework of a non-controlled case series and are intended to generate hypotheses rather than establish causal efficacy. The combined analysis reflects a conceptual approach to shared immune dysregulation and should not be interpreted as evidence of homogeneous mechanisms or treatment responses across different autoimmune diseases. Because responses were not evaluated at standardized intervals, the temporal patterns described herein should be interpreted cautiously and should not be considered representative of treatment kinetics.

Autoimmune diseases share common immunopathological features, notably an imbalance between proinflammatory TH17 lymphocytes and immunosuppressive Treg cells, accompanied by sustained cytokine-mediated inflammation and mitochondrial dysfunction [1–3]. Dysregulation of the TH17/T-reg axis and mitochondrial dysfunction represent frequently implicated, but not universally present, pathways that may contribute to immune imbalance in selected autoimmune diseases and clinical contexts. In this study, patients with different autoimmune diagnoses were analyzed together but stratified by disease category, based on the shared involvement of the IL-17/Treg axis, with the rationale for grouping these conditions being biological and hypothesis-driven rather than clinical or diagnostic.

The present study was not designed to evaluate disease-specific clinical efficacy, but rather to explore shared immunological patterns across a heterogeneous group of autoimmune and neuroinflammatory conditions. The combined analysis focused on non-disease-specific immunological markers (e.g., autoantibody titers and immune balance indicators) that reflect systemic immune activity rather than disease-specific pathology. Given the limited sample size within individual diagnoses, separate subgroup analyses would have been underpowered and potentially misleading. Pooling these conditions allowed for a descriptive assessment of group-level trends while maintaining appropriate caution in interpretation. Importantly, diseases were analyzed separately when disease-specific markers were involved, and no assumption of uniform clinical behavior or treatment response across conditions was made. The observed stabilization of disease activity in multiple sclerosis and the reductions in autoantibody titers in other autoimmune pathologies examined support the concept that targeting common immune regulatory pathways may be relevant across distinct autoimmune phenotypes.

Since the abnormally enhanced endogenous production of IL-17 is the main factor responsible for the inhibition of Treg cell immunosuppressive function [1], further clinical studies are needed to establish whether the control of the autoimmune processes reported herein is associated with a concomitant decline in IL-17 secretion, as well as an increase in Treg cell number and activity. This also applies in general to the discussion that follows, since the lack of experimental evidence for mechanisms, such as cytokine profiles or mitochondrial activity markers, makes it necessary to present these points as hypotheses rather than established conclusions.

Although IL-17 levels, Treg cell counts, and mitochondrial function were not directly measured in this study, the clinical and serological trends observed are consistent with previously reported immunomodulatory properties of MLT, ECS, and Ang 1-7. These agents have been shown in experimental and clinical contexts to modulate cytokine signaling, reduce oxidative stress, and counteract proinflammatory pathways linked to chronic immune activation. Regarding dosing, the relatively high melatonin dose was selected based on prior experimental and clinical evidence suggesting dose-dependent immunomodulatory, antioxidant, and mitochondrial effects that extend beyond its chronobiotic action [34]. The Ang 1-7 dose was selected based on preclinical and translational studies indicating anti-inflammatory, immunoregulatory, and mitochondrial-protective properties across immune-mediated conditions [35, 36]. However, the immunological effects of MLT, CBD, and Ang 1-7 are context-dependent and not uniformly anti-inflammatory across all settings. The present study does not allow conclusions regarding the relative contribution of individual therapeutic components, nor does it establish superiority of the combined regimen over monotherapy. These questions will require dedicated controlled trials.

The lymphocyte–monocyte ratio (LMR) was selected as an exploratory biomarker reflecting systemic immune balance and inflammatory tone. Complete blood count-derived ratios, including LMR, have been increasingly recognized as accessible indicators of immune activation in chronic inflammatory and autoimmune conditions [37–39]. Reduced LMR (or elevated monocyte-relative indices) has been associated with increased disease activity and severity in immune-mediated disorders, including systemic lupus erythematosus and autoimmune neurological diseases, and correlates with validated disease activity scales such as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Clinical Assessment Scale in Autoimmune Encephalitis (CASE), and modified Rankin scores. These findings support the biological relevance of LMR as a marker of inflammatory burden, while recognizing that it is not a direct clinical endpoint [40].

Similarly, autoantibody titers are well-established biomarkers in autoimmune diseases, with recognized roles in diagnosis and, in selected contexts, in monitoring disease activity and therapeutic response. For example, anti-dsDNA titers in systemic lupus erythematosus and anti-CCP antibodies in rheumatoid arthritis have been linked to disease activity, flare risk, and specific clinical phenotypes [41, 42]. Nonetheless, expert reviews emphasize that autoantibody levels often show imperfect and disease-specific correlations with clinical severity and must be interpreted cautiously, particularly in heterogeneous or exploratory cohorts [43]. Thus, changes in LMR and autoantibody titers are intended as biological correlates of immune modulation, rather than substitutes for validated clinical outcome measures.

Beyond the reduction in autoantibodies, the marked improvement in asthenia and mood suggests a restoration of mitochondrial homeostasis. MLT and CBD act as mitochondrial-targeted antioxidants that neutralize ROS and preserve the electron transport chain, addressing the energetic deficit typical of chronic inflammation. The normalization of the LMR further validates this regimen as a systemic stabilizer of the innate and adaptive immune responses.

Safety and tolerability were favorable, with no clinically significant adverse events observed during follow-up. Nevertheless, adverse event monitoring was based on routine clinical assessments and patient reporting, and subclinical effects cannot be excluded. The absence of formal pharmacovigilance infrastructure, predefined toxicity grading, and long-term follow-up limits definitive safety conclusions. Larger, controlled studies are necessary to establish a comprehensive safety profile.

While clinical stabilization in multiple sclerosis patients was confirmed by longitudinal NMR assessments following established neuroradiological criteria, the original imaging files are not included in this report due to strict institutional privacy protocols and the multi-centric origin of the initial diagnostic scans. However, the qualitative and quantitative radiological reports were verified by the clinical team to determine disease status (active vs. stable), as summarized in Section 3.

Several limitations of this study must be acknowledged, including the retrospective design, lack of a control group, heterogeneous patient population, limited statistical power, and absence of direct immunological measurements. These factors preclude definitive conclusions regarding efficacy and mechanism of action. The heterogeneity of autoimmune conditions limits disease-specific interpretation, and the combined analysis should be regarded as descriptive and hypothesis-generating. The heterogeneity of autoimmune conditions and the lack of sufficient sample size for individual disease subgroups precluded separate subgroup analyses. Therefore, findings should be interpreted as reflecting systemic autoimmune activity rather than disease-specific responses.

The absence of monotherapy or placebo control groups limits causal inference and precludes assessment of the additive or synergistic effects of the combined intervention. Accordingly, findings should be interpreted as descriptive of within-group changes rather than comparative efficacy. The absence of predefined longitudinal assessment points limits the ability to precisely characterize timelines of response. Clinical outcomes such as disease stabilization were assessed using qualitative criteria rather than disease-specific activity indices, due to the heterogeneity of autoimmune conditions included. As such, conclusions regarding clinical effects should be interpreted cautiously.

5. Conclusions

This retrospective observational case series suggests that an integrative neuroendocrine regimen combining MLT, Ang 1-7, and CBD is feasible, well tolerated, and associated with encouraging serological and clinical signals in patients with refractory autoimmune diseases. However, the present data do not provide direct evidence of improved mitochondrial function, immune modulation, neurological recovery, or metabolic benefit, as these domains were not formally assessed using mechanistic assays or standardized clinical measurements. Given the absence of a control group, randomization, standardized clinical outcome measures, and direct mechanistic assessments, no conclusions regarding therapeutic efficacy, disease modification, or biological mechanism can be drawn. Any discussion of these processes should therefore be considered interpretative and hypothesis-generating, based on indirect observations and the existing literature rather than on direct experimental confirmation. The findings highlight the need for future controlled studies incorporating appropriate control groups, validated clinical scales, and direct mechanistic measurements to rigorously evaluate the biological and clinical relevance of the proposed hypotheses.

Acknowledgments

The authors would like to thank the patients and research assistants for their participation and support. The authors acknowledge the use of M365 Copilot for language editing. The tool was applied to enhance clarity and scholarly tone, and all edits were carefully reviewed and validated by the authors to ensure accuracy, compliance with academic standards, and research integrity. The authors fully support Academia.edu Journals' adherence to the COPE position statement regarding the use of AI and AI-assisted technologies in manuscript preparation and confirm that this use has been managed responsibly and ethically.

Funding

This research received no external funding.

Author contributions

Conceptualization, P.L. and D.P.C.; methodology, G.M., A.M., S.T., A.S., G.D.F. and A.C.S.e.S.; formal analysis, P.L., D.P.C. and A.C.S.e.S.; investigation, G.M., A.M., S.T., A.S. and G.D.F.; writing—original draft, D.P.C.; writing—review and editing, D.P.C., P.L., G.M., A.M., S.T., A.S., G.D.F. and A.C.S.e.S. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

Data availability statement

The data supporting the findings of this publication can be made available upon request.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Ethical Committee of the Institute of Biological Medicine (protocol code 01/10; approved on 1 February 2020).

Informed consent statement

Written informed consent for participation was obtained from all participants involved in the study.

Additional information

Received: 24 March 2026

Accepted: 23 May 2026

Published: 5 June 2026

Academia Neuroscience and Brain Research papers should be cited as *Academia Neuroscience and Brain Research 2026*, ISSN 3071-4087, https://doi.org/10.20935/AcadNeurosci8343. The journal's official abbreviation is *Acad. Neurosci. Brain Res.*

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