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Research article

Effects of running before pregnancy on long-term memory and hippocampal alterations induced by prenatal stress

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ABSTRACT

Studies have shown that an adverse environment in utero influences fetal growth and development, leading to several neuroendocrine and behavioral changes in adult life. Nevertheless, the mechanisms involved in the long-term benefits of pregestational exercise are still poorly understood. Thus, this study aimed to evaluate the effects of physical exercise before the gestational period on memory behavior and gene expression in the hippocampus of adult mice submitted to prenatal stress. Female Balb/c mice were divided into three groups: control (CON), prenatal restraint stress (PNS), and exercise before the gestational period plus PNS (EX + PNS). When adults, male and female offspring were submitted to the object recognition test followed by the hippocampal evaluation of BDNF exons I and IV mRNA expression, as well as hypothalamic-pituitary-adrenal axis related genes. Pregestational exercise did not prevent the decreased recognition index, as well as GR and CRHR1 gene expression observed in PNS males. Conversely, prenatal stress did not influence female memory behavior. Moreover, exercise attenuated the effects of prenatal stress on female BDNF IV gene expression. The results indicate that pregestational exercise was able to prevent the effects of maternal stress on hippocampal BDNF IV gene expression in females, although no effects were seen on the stress-induced memory impairment in males.

1. Introduction

Stress during pregnancy has been reported as a serious current health problem. Studies have shown that an adverse environment in utero can influence fetal growth and development, leading to several neuroendocrine and behavioral changes in adult life [22,37]. The exposure to high levels of maternal glucocorticoids, such as cortisol (corticosterone in rodents), affects the fetus leading to a cerebral reduction in both glucocorticoid (GR) and mineralocorticoid (MR) receptor expression, which are important targets for the control of the hypothalamic-pituitary-adrenal (HPA) axis [32]. Reduced expression of these receptors may result in decreased glucocorticoid-controlled negative feedback and, consequently, increased HPA axis activity in the offspring [32]. Evidence also demonstrated that prenatal stress might promote changes in circulating corticotropin-releasing hormone (CRH) levels, which is also an important target in the regulation of behavioral responses [15,30,42].

Moreover, prenatal stress can affect synaptic plasticity and neurogenesis in the hippocampus, which plays a key role in the regulation of cognition and mood [18,44]. The brain-derived neurotrophic factor (BDNF), a neurotrophin related to the central nervous system development, has been extensively associated to cognitive impairments observed in animals submitted to early-life stress [7]. The BDNF gene has eight 5' exons (I-VIII) and one 3' exon (IX), whereas the exons I and IV appear to be strongly regulated by neuronal activity [23]. Although the relationship between early-life stress and BDNF I is poorly understood to date, studies with maternal separation have shown decreased BDNF IV acetylation and gene expression in the hippocampus of stressed rodents [33,39]. A previous study has demonstrated that rodents submitted to prenatal stress had significant alterations in BDNF regulatory regions (exons I-IV and VI-IX) in the prefrontal cortex and hippocampus, besides decreased performance in behavioral tasks [9]. Several biological mechanisms are responsible for promoting the benefits induced by physical exercise, including the optimization of HPA axis response and

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increased expression of growth factors and neural plasticity [20,24,41]. Studies reported that exercise during the gestational period has beneficial effects on the offspring anxiety tasks, such as increased time in the open arms in the elevated plus-maze test, reduced corticosterone levels and increased cerebral expression of BDNF in experimental models of early-life stress [1,14,36]. Moreover, recent data shows that exercise before pregnancy decreases corticosterone secretion and CRHR1 gene expression in the prefrontal cortex of prenatally stressed mice [19].

Although exercise appears to have protective and therapeutic effects in the treatment of neurologic diseases, the mechanisms involved in the long-term benefits of pregestational exercise are still poorly understood. Thus, this study aimed to evaluate the effects of physical exercise before the gestational period on memory behavior and gene expression in the hippocampus of male and female adult mice submitted to prenatal stress. We hypothesized that pregestational exercise would contribute to preventing long-term prenatal stress alterations in the cognition and in HPA axis markers, in a sex-dependent effect.

2. Material and methods

2.1. Animals

Male and female Balb/c mice were acquired from the Center for Experimental Biological Models (CEMBE) of the Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS). Animals were kept in a controlled temperature environment (24 ± 2 °C), light/dark cycle of 12 h, with free access to food and water. The experimental protocol was approved by the Ethics Research Committee of PUCRS (protocol number 15/00446).

2.2. Experimental design

Adult females (8-week old) were divided into three experimental groups: (i) CON – control ($n = 9$); (ii) PNS – prenatal restraint stress ($n = 8$); (iii) EX + PNS - physical exercise before the gestational period and prenatal restraint stress ($n = 9$). Animals from the CON group were kept in their cages and only handled during the cleaning routine.

The female's estrous cycle was verified before mating by microscopic visualization of the collected vaginal material. During the fertile period (nigh of proestrus), females and males were mated overnight. With the confirmation of mating (G0), pregnant females were caged individually and randomized according to the experimental group. After birth (PND1), the litters were randomly adjusted to 6 animals per dam. Dams remained with their litters until weaning at the 21 st day of life (PND 21). When adults (PND60), mice were submitted to the object recognition test. Two weeks after (PND74), animals were euthanized and the hippocampi were collected for the evaluation of BDNF I, BDNF IV, MR, GR and CRHR1 gene expression.

2.3. Prenatal stress

Females from PNS and EX + PNS groups were submitted to prenatal restraint stress. The restraint stress was performed using a closed cylinder, made of acrylic crystal, with 34 mm of height, 42 mm of width, 100 mm of circumference and 10 lateral holes of 6 mm for entrance and exit of air. The stress was performed from the 8th day of gestation, for 30 min, on intercalated days until the day of parturition [19,38]. Pregnant CON females remained undisturbed in their cages during the prenatal period.

2.4. Treadmill exercise

Females from the EX + PNS group were daily submitted to an exercise session on a motorized treadmill, during the 3 weeks that preceded the day of mating (G0). The exercise protocol consisted of 60 min sessions at a speed of 10 m/min, 5 days a week [19,39]. Before the beginning of the protocol, animals were habituated to the room for 30 min. No stimulus, such as electric shock, was applied to motivate animals to run. If animals refused to run, presented difficulties in following the protocol or any visual signs of distress, they were excluded from the study. Animals from the CON and PNS groups performed only spontaneous activities in their cages.

2.5. Object recognition test

Male and female mice at PND60 were submitted to the object recognition test in an open field arena (45 × 45 × 15 cm). The task of recognition comprises three phases: habituation, familiarization and test. On the first day, during the habituation phase, each animal was placed in the open field to explore it in the absence of any object for 10 min. On the following day, during the familiarization phase, mice were placed in the arena with 2 identical objects (A + A), in adjacent corners (approximately 2 cm away from the wall) for 10 min. The animals were returned to their cages and, after 24 h, were submitted to the recognition memory evaluation test. In the assessment of recognition, object A was replaced by object B and animals were exposed for 10 min to these objects. The objects were always positioned in the same place and position, in opposite corners of the arena. The time spent exploring each object was recorded. In the interval of all phases, the apparatus and objects were cleaned with 70 % alcohol to prevent olfactory stimulus. The recognition index was determined as the time spent in the novel object relative to the total time of object exploration (time spent in the novel object + time spent in the familiar object) [11].

2.6. mRNA levels

After two weeks of the behavioral test, the animals were euthanized by decapitation. The brains were removed and stored in RNA-later (Applied Biosystems, USA) for 24 h at 4 °C and then transferred to −80 °C until final processing. Hippocampi were homogenized with a mechanical homogenizer and total cellular RNA from tissue was extracted by the Trizol method (ThermoFisher – Scientific, USA). The RNA was reconstituted in 20 μL of nuclease-free water (Ambion® - ThermoFisher – Scientific, USA) and reverse transcribed (GoScript ™ Reverse Transcription System Protocol – Promega, USA). The final concentration of cDNA was analyzed by the fluorimetric method (Qubit® - ThermoFisher – Scientific, USA) using a commercial kit (Qubit® dsDNA HS Assay - ThermoFisher – Scientific, USA).

For the RT-qPCR reaction (Step One Plus - ThermoFisher – Scientific, USA), 16 ng of cDNA were used. The samples were prepared in duplicates and the relative expression of mRNA was calculated by the ΔΔCt method using the males from CON group as reference. The GAPDH was used as the reference endogenous gene. A negative control for each primer was used on each plate to check for possible contamination. mRNA analysis were calculated based on the incorporation of the SYBR® Green fluorescence marker (ThermoFisher – Scientific, USA) into the double cDNA ribbon for each amplification reaction. The following primers for each gene were used: BDNF I (forward 5 'GCGTTGAGAAAGCTGCTTCAG 3'; reverse 5' GAATGAGCGAGGTTACCAATGA 3'), BDNF IV (forward 5 'GCAGCTGCCTTGATGTTTAC 3'; reverse 5 'CCGTGGACGTTTACTTCTTTC 3'), GR (forward 5 'GGAATAGGTGCCAAGGGTCT 3', reverse 5 'GAGCACACCAGGCAGAGTTT 3'), MR (forward 5 'CCAGTTCTCCGTTCTCTGTA 3'; reverse 5 'CTTGAGCACCAATCCGGTAG 3'), CRHR1 (forward 5 'TGAGTGTTAGCGATGCCTTG 3 '; reverse 5' TCCTACCACTGAGGACTGG 3 '), and GAPDH (direct 5 'GGGGAGCCAAAAGGGTCATC 3'; reverse 5 'GACGCCTGCTTCACCACCTTCTTG 3').

2.7. Statistical analysis

The normality of data was verified using the Shapiro-Wilk test. Outliers were excluded from analyses. In order to evaluate differences

between the experimental groups (CON, PNS, and EX + PNS) and the interaction with sex (males and females), two-way ANOVA followed by Fisher's LSD post-test was used. Data were expressed using mean and standard error of the mean (SEM). In all cases, the level of significance was set at 5% ($p \leq 0.05$). Data were analyzed using the software SPSS 18.0 (SPSS Inc., USA) and graphs were made using Prism GraphPad (version 8.0, GraphPad Software Inc, USA).

3. Results

3.1. Pregestational exercise does not alter the memory effects induced by prenatal stress

Memory was evaluated using the object recognition test (Fig. 1A). Pairwise comparisons revealed that stress in males decreased ($p = 0.04$) the recognition index when compared to the CON group and exercise before pregnancy (EX+PNS) was not able to prevent ($p = 0.42$) this effect (Fig. 1B). No significant effects were found for both stress and exercise in females (Fig. 1B). However, CON females demonstrated a significant ($p = 0.03$) decrease in the recognition index when compared to CON males (Fig. 1B).

3.2. Pregestational exercise attenuates BDNF exon IV increase in PNS females

Considering the results found for memory, we have investigated the BDNF exons I and IV gene expression in the hippocampus. For the BDNF exon I, significant effects for sex ($F_{(1,28)} = 11.29$; $p = 0.002$) were found. Moreover, BDNF exon IV showed significant effects for sex ($F_{(1,25)} = 23.17$; $p < 0.0001$), group ($F_{(2,25)} = 13.57$; $p = 0.0001$) and interaction between group and sex ($F_{(2,25)} = 12.36$; $p = 0.0002$). Pairwise comparisons showed no significant differences for the BDNF exon I mRNA expression between groups (Fig. 2A). Prenatally stressed females (PNS group) showed a significant ($p < 0.0001$) increase in the expression of BDNF IV mRNA in the hippocampus compared to the CON group and exercise before pregnancy prevented this effect ($p < 0.0001$) (Fig. 2B).

In the analysis of sex differences, PNS females showed increased BDNF I ($p = 0.01$) and BDNF IV ($p < 0.0001$) mRNA expression when compared to males from their respective experimental groups (Fig. 2A and B).

3.3. Pregestational exercise does not prevent the effects induced by prenatal stress on GR and CRHR1 gene expression in males

We have also evaluated the mRNA expression of genes associated with the HPA axis control in the hippocampus. Significant effects for sex ($F_{(1,39)} = 5.58$; $p = 0.02$) were found in the MR gene expression analysis. However, there were no significant differences in MR gene analysis in the hippocampus for both genders (Fig. 3A). We have observed a significant effect for group in the analyses of GR ($F_{(2,31)} = 5.70$; $p = 0.007$) and CRHR1 ($F_{(2,24)} = 3.86$; $p = 0.035$) gene expression. In males, prenatal stress induced a significant decrease in the GR ($p = 0.02$) and CRHR1 ($p = 0.03$) mRNA expression and pregestational exercise was not able to prevent it (Fig. 3B and C, respectively). As observed in the object recognition test, there were no significant effects of stress or exercise in the mRNA gene expression for females (Fig. 3).

Regarding sexual differences, a significant MR gene expression increase in PNS females ($p = 0.04$) was observed when compared to PNS males (Fig. 3A). No other significant difference was found.

A summary of the main results is presented as a supplemental Table 1.

4. Discussion

Our findings demonstrated that stress from the second week of gestation induced long-term changes in the offspring in a sex-dependent manner, evidenced mainly by the memory impairment and the expression of important HPA axis regulators in males. In addition, exercise before pregnancy was not able to prevent the effects of prenatal stress on these markers. However, in females, the effects of prenatal stress on BNDF exon IV gene expression was attenuated by maternal exercise before the gestational period, although no memory alterations were seen.

Early-life stress has already been associated with several changes in cognitive behaviors in a sex-dependent manner [3,12,21]. Our data corroborate with other evidence demonstrating that prenatally stressed males are more vulnerable to learning and memory impairments, probably due to decreased neurogenesis in the hippocampus [13]. Furthermore, a study in human showed that prenatal stress is associated with increased cortisol reactivity coupled with a deficiency in executive functions only in boys [25]. Considering that exercise improves cognition and increases cerebral growth factors, we have evaluated the

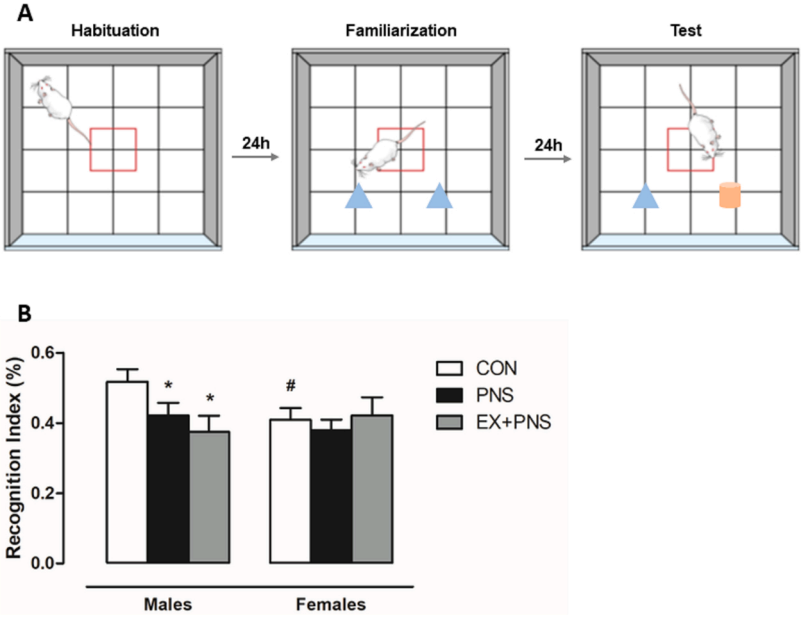

Fig. 1. Sex-specific effects of pregestational exercise on the object recognition test in prenatally stressed mice. Experimental design of the object recognition test (A). The recognition index was evaluated in both males and females (B). PNS males showed decreased recognition index and exercise before pregnancy was not able to prevent this effect. No significant differences between groups were found for females. Data are presented as mean and standard error of the mean and were analyzed using two-way ANOVA. $^{*}p < 0.05$ indicates significant differences compared to CON group in the equivalent sex; and $^{\#}p < 0.05$ indicates significant sex differences in the same group. $n = 6$-15 mice/group. CON: control; PNS: prenatal restraint stress; EX + PNS: physical exercise before the gestational period and prenatal restraint stress.

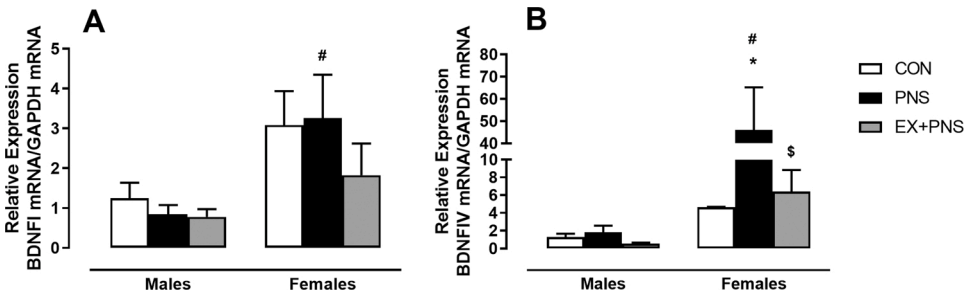

Fig. 2. Effects of pregestational exercise on BDNF I and IV mRNA expression in the hippocampus of prenatally stressed mice. The gene expression of BDNF I (A) and BDNF IV (B) were assessed in both male and female hippocampus. PNS females revealed a significant increase in the expression of BDNF IV mRNA in the hippocampus and exercise before pregnancy prevented this effect. Moreover, PNS females showed a significant increase in the BDNF I and IV mRNA expression when compared to males from the same experimental group. No significant differences were found for males. Data are presented as mean and standard error of the mean and were analyzed using two-way ANOVA. $^{*}p < 0.05$ indicates significant differences compared to CON group in the equivalent sex; and $^{\#}p < 0.05$ indicates significant sex differences in the same group. n= 4-8 mice/group. CON: control; PNS: prenatal restraint stress; EX + PNS: physical exercise before the gestational period and prenatal restraint stress.

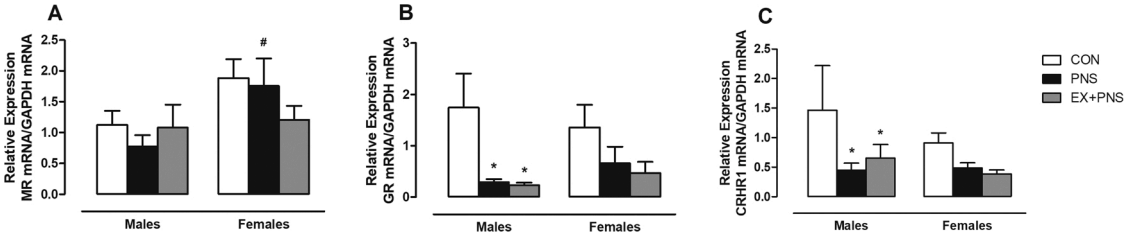

Fig. 3. Effects of pregestational exercise on MR, GR, and CRHR1 mRNA expression in the hippocampus of prenatally stressed mice. The gene expression of MR (A), GR (B) and CRHR1 (C) were assessed in both male and female hippocampus. EX + PNS and PNS males showed a significant decrease in GR and CRHR1 mRNA expression compared to the CON group. There was an increased MR gene expression in PNS females when compared to males from the same group. No significant effects of stress or exercise in the mRNA gene expression for females were found. Data are presented as mean and standard error of the mean and were analyzed using two-way ANOVA. $^{*}p < 0.05$ indicates significant differences compared to CON group in the equivalent sex; and $^{\#}p < 0.05$ indicates significant sex differences in the same group. n = 4-8 mice/group. CON: control; PNS: prenatal restraint stress; EX + PNS: physical exercise before the gestational period and prenatal restraint stress.

long-term effects of pregestational exercise in a memory task in the adult offspring. To date, no studies have evaluated the effects of exercise only before pregnancy on cognitive impairments. However, it has already been shown that animals that perform forced exercise and stop the protocol for 21 days lose the beneficial effects of exercise on neuronal cell activity in the hippocampus [28]. The results presented here show that exercise was not able to prevent, in males, the harmful effects of prenatal stress on the object recognition test.

The BDNF is extensively studied due to its important role in cell survival and particularly in the synaptic plasticity regulation, which can influence many cognitive behaviors [23,34]. Studies have already demonstrated the association of early-life stress and alterations in the regulation of the BDNF gene. Female mice from maternal separation showed a decreased mRNA expression of BDNF IV, which was not reversed by treadmill exercise [39]. Similarly, prenatal stress also decreased the expression of BDNF in the hippocampus and amygdala of male mice, accompanied by an increase in exon IV methylation in these regions [4]. We did not find significant differences in the expression of BDNF exons I and IV in males from any of the experimental groups studied. Interestingly, the pregestational exercise attenuated the upregulation of exon IV in the hippocampus of prenatally stressed females. These findings in females regarding the expression of BDNF IV may have influence from sex hormones. Estradiol is the main female hormone and its administration is related to increased neurogenesis and HPA axis activity inhibition [10,46]. Moreover, studies have suggested that the increase of this hormone activates the expression of tropomyosin-related kinase B (receptor for BDNF) [31]. Indeed, the relationship between stress and the regulatory mechanisms of BDNF still seems to be controversial, since different stress protocols, regions, and genders evaluated can produce distinct changes in the BDNF responsiveness.

Although the precise mechanisms of how maternal exercise counteracts prenatal stress remain unclear, it has been associated to improvements in the offspring brain function and development, contributing to long-term physiological and behavioral changes in adulthood [29,35,43]. One possible mechanism would be enhancing hippocampal neurogenesis, which has been already demonstrated as a consequence of voluntary wheel running during pregnancy in mice [43]. In addition, studies with rodents have demonstrated the association of physical exercise during pregnancy with beneficial effects on several parameters observed after prenatal stress, including decreased anxiety and depressive behavior and improved cognition, probably from mechanisms related to increased cell proliferation, neuronal activity and survival [1,16,29,43].

Regular physical exercise has been reported to have positive effects on several biological systems, including decreased HPA stress response [17]. The modulation of glucocorticoid secretion in exercised animals has been suggested as one of the factors in the control of neurogenesis [5]. Furthermore, glucocorticoids appear to be strongly related to memory. For example, the administration of dexamethasone, or the inhibition of GR with antagonists, have been shown to generate cognitive impairment in memory tasks [26,45]. Thus, as expected, we have observed a decreased GR mRNA expression in male mice exposed to prenatal stress. Moreover, changes in CRHR1 have been associated with stress-related diseases, such as impaired fear and anxiety behavior [2].

In a prenatal stress model, a decrease in the amygdala CRHR1 mRNA expression was demonstrated for a second generation of male rats, associated with an increase in the anxiety-like behavior [15]. However, this receptor also seems to be important in hippocampal plasticity since it has already been shown that animals lacking CRHR1 exhibit impaired behavior [6]. In the present results, exercise before pregnancy was not able to prevent the long-term effects of prenatal stress in these markers. We hypothesized that these findings could be related to the sex-dependent changes observed in the behavioral object recognition test. The hippocampus is a key region for memory mechanisms and GR and CRHR1 have been shown to play an important role in this function [8]. Thus, it appears that exercise before pregnancy does not act positively to reverse the effects of stress on these markers in the hippocampus. Our findings are supported by a previous study showing that individuals who stop exercising tend to exhibit behavioral changes related to impaired GR and CRHR1 signaling, such as anxiety and depression [40]. Conversely, using an early-life stress model, a study demonstrated that forced physical exercise might increase the GR density in the dentate gyrus of exercised individuals, leading to an improvement in the symptoms involved to the stress response [27].

In conclusion, our results indicate that pregestational exercise was able to prevent the effects of maternal stress on hippocampal BDNF IV gene expression in females, although no effects were seen on the stress-induced memory impairment. Moreover, no early exercise-induced effect was found on males submitted to prenatal stress in both the object recognition test and the molecular markers. The findings support previous evidence showing that early-life stress promotes sex-dependent effects on regulatory mechanisms of cognitive behaviors and open a window to further investigate possible beneficial effects of exercising before pregnancy.

CRediT authorship contribution statement

Carolina Luft: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft. **Isadora Perez Levices:** Investigation, Data curation, Writing - review & editing. **Mariana Severo da Costa:** Investigation, Data curation, Writing - review & editing. **Jarbas Rodrigues de Oliveira:** Conceptualization, Supervision, Writing - review & editing, Funding acquisition. **Márcio Vinícius Fagundes Donadio:** Conceptualization, Methodology, Supervision, Writing - review & editing, Funding acquisition, Project administration.

Declaration of Competing Interest

The authors declare they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neulet.2021.135659.

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