IECBS 2022

MDPI

Type of the Paper (Proceedings, Abstract, Extended Abstract, Editorial, etc.)

Sex-dependent variations in voluntary exercise of 14-month-old 3xTgAD mice associated with novelty inhibition†

Daniel Alveal-Mellado [1,2], Lydia Giménez-Llort [1,2,*]

[1] Institut de Neurociències, Universitat Autònoma de Barcelona, Spain; daniel.alveal@autonoma.cat
[2] Dept Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Spain; lidia.gimenez@uab.cat
* Correspondence: lidia.gimenez@uab.cat;.
† Presented at the 3rd International Electronic Conference on Brain Sciences, 1–15 October 2022; Available online: https://iecbs2022.sciforum.net/

Abstract: Alzheimer's Disease (AD) patients suffer from circadian rhythm alterations involving sleep, thermoregulation, and movement activity disorders. The latter affects their daily patterns of physical activity (PA) and willingness to perform voluntary exercise, impeding benefit from routine PA practice. Neuropsychiatric symptoms (NPS) have been postulated to influence human physical activity engagement. However, there is no clarity on whether animal models can replicate these effects. Here, we evaluated the behavioral circadian rhythmicity of voluntary physical exercise (VPE) in a group of 14-month-old 3xTg-AD animals of both sexes at advanced stages of the disease and compared their performance according to the presence of NPS-like symptoms. Mice (n=9 females and n=7 males) were provided with an in-cage running wheel for 30 days with daily control of the diurnal and nocturnal amount of VPE performed. Using a Linear Mixed Model Analysis, we found that all animals kept similar nocturnal patterns of VPE. However, sex-dependent differences associated with previous novelty inhibition (NI) response, an NPS-like symptom frequently observed in this model, were found during diurnal periods. Thus, males with high NI showed significantly higher levels of VPE compared with high NI females. No sex differences were found in low NI animals. Our results suggest that the influence of NPS-like symptoms in VPA engagement may vary depending on the sex of 3xTg-AD mice. Further studies are needed to help elucidate molecular and genetic factors associated with these differences.

Keywords: Alzheimer disease; mice; animal model; sex difference; running; exercise.

Citation: Lastname, F.; Lastname, F.; Lastname, F. Title. *Biol. Life Sci. Forum* **2022**, 2, x. https://doi.org/10.3390/xxxxx

Academic Editor: Firstname Lastname

Published: date

1. Introduction

Healthy lifestyle habits such as maintaining high levels of physical activity (PA) have proved able to prevent cognitive decline and modify the neuropathological changes occurred in Alzheimer's Disease (AD) [1,2].

Apart from the progressive cognitive decline observed in AD patients, neuropsychiatric symptoms (NPS) are commonly reported. These include a wide spectrum of heterogeneous clinical phenomena involving affective disorders (i.e., anxiety and depression), behavioral disturbances (i.e., apathy and mood fluctuation), and psychotic symptoms (i.e., hallucinations and delusions) [3].

In addition, circadian rhythm dysfunctions (CRD) are present in AD. Thus, sleep, thermoregulation, and movement activity disorders appear in the individual's early stages of the disease [4].

Previous reports [5,6] have postulated that NPS and CRD may negatively influence engagement in routine exercise in patients with AD, impeding the benefit of routine PA practice.

Nowadays, non-human AD models' usage is paramount to explaining the mechanisms behind NPS and CRD in AD. Interestingly, the triple transgenic AD model (3xTg-AD) has replicated NPS-like symptoms through a novelty-induced behavioral inhibition in the corner test (CT) [7]. However, their interaction with CRD and its influence on PA levels remain unclear.

In the present experiment, we aim to identify the influence of NPS-like symptoms in daily levels of PA performed by a group of triple transgenic (3xTg-AD) animals.

2. Material and methods

Sixteen 14-month-old animals (n=9 females and n=7 males) at advanced stages of the disease from the Spanish colony of homozygous 3xTg-AD mice were included in the experiment.

Animals were housed in groups of 2-3 and provided an in-cage running wheel (RW) for 30 days.

The system allowed the assessment of circadian motor activity by recording revolutions on the wheel, which were registered at 8:00 h (Nocturnal activity) and 20:00 h (Diurnal activity).

Neophobia was evaluated in the CT. Subsequently, animals were classified as presenting high (below the 33rd percentile in the number of corners in 60s) or low (above the 33rd percentile in the number of corners in 60s) novelty inhibition (NI).

3. Results

We found that all animals kept similar nocturnal patterns of VPE. However, sex-dependent differences associated with previous novelty inhibition (NI) response in the CT, an NPS-like symptom frequently observed in this model, were found during diurnal periods. Therefore, males with high NI showed significantly higher levels of VPE compared with high NI females. No sex differences were found in low NI animals.

4. Conclusions

Our results suggest that the influence of NPS-like symptoms in VPA engagement may vary depending on the sex of 3xTg-AD mice. However, further studies are needed to help elucidate molecular and genetic factors associated with these differences.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions: Both authors equally contributed to the performance and analysis of the experiments. Both authors revised and approved the final poster.

Funding: The colonies are currently sustained by Fet-Open ArrestAD European Union's Horizon 2020 research and innovation program under grant agreement No 737390 to L.G.-L.. Also, D.A-M is recipient of a CONICYT-ANID/73200493 grant from the Chilean government.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Tolppanen, A.-M.; Solomon, A.; Kulmala, J.; Kåreholt, I.; Ngandu, T.; Rusanen, M.; Laatikainen, T.; Soininen, H.; Kivipelto, M. Leisure-Time Physical Activity from Mid- to Late Life, Body Mass Index, and Risk of Dementia. Alzheimer's Dement. 2015, 11, 434-443.e6.

2. Honea, R.A.; Thomas, G.P.; Harsha, A.; Anderson, H.S.; Donnelly, J.E.; Brooks, W.M.; Burns, J.M. Cardiorespiratory Fitness and Preserved Medial Temporal Lobe Volume in Alzheimer Disease. Alzheimer Dis. Assoc. Disord. 2009, 23, 188–197.

3. Ritchie, K.; Lovestone, S. The Dementias. In Proceedings of the Lancet; Elsevier Limited, November 2002; Vol. 360, pp. 1759–1766.4.

4. Videnovic, A.; Lazar, A.S.; Barker, R.A.; Overeem, S. 'The Clocks That Time Us'—Circadian Rhythms in Neurodegenerative Disorders. Nat. Rev. Neurol. 2014, 10, 683.

5. Watts, A.S.; Mortby, M.E.; Burns, J.M. Depressive Symptoms as a Barrier to Engagement in Physical Activity in Older Adults with and without Alzheimer's Disease. PLoS One 2018, 13.

6. Cote, A.C.; Phelps, R.J.; Kabiri, N.S.; Bhangu, J.S.; Thomas, K. Evaluation of Wearable Technology in Dementia: A Systematic Review and Meta-Analysis. Front. Med. 2021, 7, 501104.

7. Blázquez, G.; Cañete, T.; Tobeña, A.; Giménez-Llort, L.; Fernández-Teruel, A. Cognitive and Emotional Profiles of Aged Alzheimer's Disease (3×TgAD) Mice: Effects of Environmental Enrichment and Sexual Dimorphism. Behav. Brain Res. 2014, 268, 185–201.