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*Proceeding Paper*

# Sex-Dependent Variations in Voluntary Exercise of 14-Month-Old 3xTg-AD Mice Associated with Novelty Inhibition †

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**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. Herein, 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 us to elucidate molecular and genetic factors associated with these differences.

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



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## 1. Introduction

Longitudinal studies have reported an association between healthy lifestyle habits, such as maintaining high levels of physical activity (PA), and a decreased incidence of Alzheimer's Disease (AD). Moreover, the cognitive decline and neuropathological changes following AD seem to be ameliorated in physically active populations [1,2].

Apart from the progressive cognitive decline observed in AD patients, neuropsychiatric symptoms (NPS) are commonly reported. These include a wide spectrum of a 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, the usage of non-human AD models' is paramount for 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 on daily levels of PA performed in a group of triple transgenic (3xTg-AD) animals.

## 2. Materials 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 for 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 60 s) or low (above the 33rd percentile in the number of corners in 60 s) 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 us elucidate the molecular and genetic factors associated with these differences.

**Supplementary Materials:** The presentation material of this work is available online at https://www.mdpi.com/article/10.3390/IECBS2022-12946/s1.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the Departament de Medi Ambient i Habitatge, Generalitat de Catalunya (CEEAH 3588/DMAH 9452) on the 8 March 2019.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**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.

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