

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

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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.

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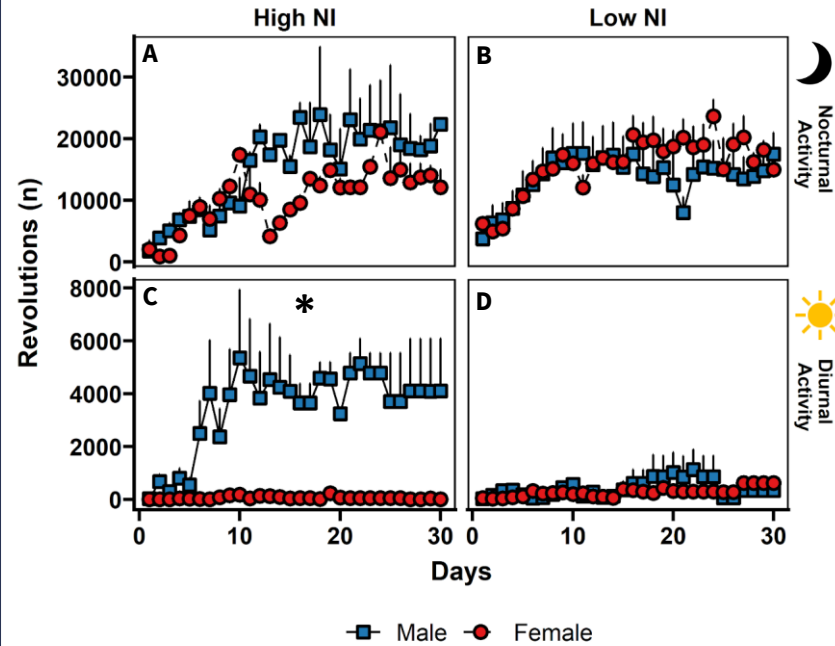


Fig. 2. Circadian rhythmicity of Voluntary Physical Exercise (VPE). A and B. Nocturnal variation in VPE. No sex differences were found in the CT comparing high or low NI responses. C and D. Diurnal activity variation in VPE. Males in the group of high NI responses showed higher levels of VPE (C). * $p < 0.05$. Results are expressed as the mean \pm standard error of the mean (SEM).

AIMS

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.

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).

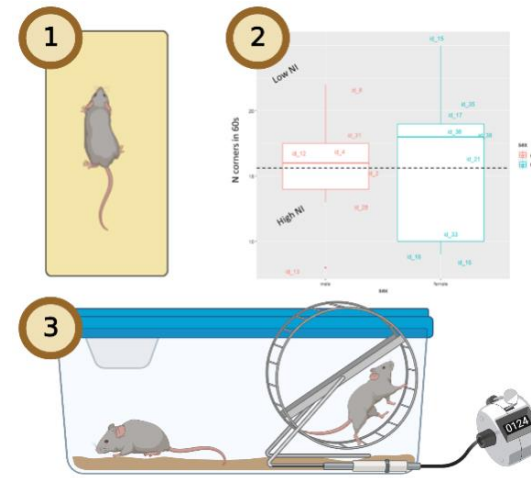


Fig 1. Experimental Methodology. 1) Neophobia was evaluated in the corner test CT. 2) Distribution of animals according to the number of corners explored in the CT. High-NI and Low-NI responses were identified. 3) Illustration of the "Activity Wheel Cage System for mice, Techniplast, Buguggiate, Italy" used in the study.

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.

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.