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| Elucidating the behavioral and mitochondrial correlates of early handling**Markus Nussbaumer** 1,2#, **Christina Thomou** 1,2, **Eleni Grammenou** 1,2, **Chrysoula Komini** 1,2, **Angeliki-Maria Vlaikou** 1,2, **Maria P. Papageorgiou** 1,2 and **Michaela D. Filiou** 1,2\*1 Biomedical Research Institute, Foundation for Research and Technology-Hellas Ioannina, Greece2 Laboratory of Biochemistry, Department of Biological Applications and Technology, University of Ioannina, Ioannina, Greece# Presenting author: Markus Nussbaumer, email: [nussbaumermarkus.80@gmail.com](nussbaumermarkus.80%40gmail.com)\* Corresponding author: Michaela D. Filiou, email: [mfiliou@uoi.gr](mfiliou%40uoi.gr) |

abstract

Early Handling (EH) is an early life intervention consisting of the brief and repeated separation of the pups from their mother during the first days after birth. Our study explored the effects of EH on maternal behavior as well as on male and female pup behavior in adulthood and investigated the implication of brain mitochondria in modulating the effects of EH in the offspring.

We addressed these questions in different anxiety backgrounds by using high anxiety-related behavior (HAB) and normal anxiety-related behavior (NAB) mice. We assessed the effects of EH on maternal behavior in HAB and NAB mice by observing dams from postnatal day 2 to 7. We studied the EH effects on HAB and NAB pup behavior by performing an elaborate behavioral test battery (social preference-avoidance test, dark-light box test, open field test, forced-swim test). For our molecular analysis, we looked for changes in metabolic pathways and mitochondrial dynamics, a term collectively addressing the molecular machinery of mitochondrial biogenesis, fission, fusion and mitophagy.

EH did not affect maternal behavior in neither HAB nor NAB dams, however, we found significant differences between the basal (non-handling group, ΝΗ) HAB and NAB dams. Interestingly, EH exerted anxiolytic effects in dark-light box test in HAB-EH compared to HAB-NH male pups. Following up these results in the prefrontal cortex and hippocampus, we found that EH resulted in mRNA level alterations of key players of the mitochondrial dynamics machinery in HAB-EH compared to HAB-NH male pups. Protein levels of mitochondrial metabolic functions were not affected by EH in HAB male pups. Overall, these findings highlight an implication of mitochondrial dynamics in the anxiolytic effects of EH in HAB male mice. Unraveling the EH-driven behavioral and molecular correlates and elucidating how EH influences adult behavior may facilitate the discovery of novel therapeutic targets for anxiety disorders.

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