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Hellenic Foundation for Research & Innovation

## Description of the funded research project

# 1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment

**Title of the research project:** Pharmacogenetics of Habituation

**Principal Investigator:** Efthimios Skoulakis

**Reader-friendly title:** Habituation defects as a screen for schizophrenia genes

**Scientific Area:** Life Sciences

**Institution and Country:** Biomedical Sciences Research Center “Alexanderf Fleming” Greece

**Host Institution:**

**Collaborating Institution(s):**

**Project webpage (if applicable):**

**Budget:** €179.685

**Duration:** 36 months

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**Habituation** is a form of behavioral plasticity that permits animals to ignore repetitive or prolonged non-reinforced stimuli that likely underlies selective attention. Defective habituation has been linked to schizophrenia. Although neurons and mechanisms that govern habituation of sensory neurons have been described, little is known about the mechanisms that govern habituation in the Central Nervous system (CNS), which mediate decisions to attend or ignore stimuli. We have developed two different and complementary assays to study habituation to mechanosensory and odor stimuli in Drosophila and have identified at least one essential postsynaptic site for stimulus evaluation in its CNS, the Mushroom Bodies. We have performed screens for mutants affecting these processes and have identified and characterized mutants that fail to habituate, a situation we posit akin to Schizophrenia in humans because of the following: Schizophrenics also display difficulty in habituation. Secondly, we show that the defective habituation phenotype of the fly mutants is reversible by Clozapine or Risperidone, antipsychotic drugs used to over the last 50 years to treat human schizophrenics and whose mechanisms of action remain far from clear to date. Finally, mutants in Drosophila orthologs of human genes associated with schizophrenia by GWAS studies display defective habituation phenotypes. We propose to gain insights into mechanisms that govern habituation in Drosophila as we assert that our findings will be catalytic in understanding the genetic etiology of human habituation defects such as Schizophrenia and the mode of action of typical antipsychotic drugs used to treat the disease.

**At the moment there is no systematic method to screen for potential Schizophrenia and Autism Spectrum Disorder genes or a system to functionally validate human genes whose polymorphisms are ASD associated via GWAS. The proposed approach is also expected to enrich in such genes and initiate a discovery pipeline. The work on habituation will lead into other Schizophrenia and Autism-proxy behaviors is a novel idea, but it solidly based on extant work and lab expertise.**

**The proposed work aims to establish a validated Schizophrenia and ASD model in Drosophila, essential to functionally test along the Schizophrenia-like habituation defective mutants we have isolated, the comorbidity between these two diseases hypothesis. In addition, it will provide a method to functionally test schizophrenia-linked human genes from GWAS studies. Finally, we posit that establishment of a facile genetic model for schizophrenia will have a *major impact* on the search and validation for the genetic contribution to the Disorder and potentially will lead towards its pharmaceutical amelioration**

**The ELIDEK grant allows us to establish and validate this novel system, including use of antipsychotics in Drosophila in a major pharmacogenetic approach to understand the genetics of Schizophrenia and Autism Spectrum Disorders. With the expected results and publications, we are aiming at applying for much larger EU (ie Horizon, ERC) or International funding and if successful it will will be only because the ELIDEK funding enabled it.**

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