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| pořadí v jakém návrhy přišly | pracoviště | název projektu/řešitel  |
|  | Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital in Prague | **EYE MOVEMENTS IN THE DEEP PHENOTYPING OF EARLY NEURODEGENERATION**Prof. Evžen Růžička, MD, DSc. |
|  | Institute of Physiology, 1st Faculty of Medicine, Laboratory of Neurosciences | **THE BIOLOGICAL RHYTHMS AFFECTED BY MUSCARINIC RECEPTORS**Jaromír Mysliveček, M.D., Ph.D. |

**1.Title of the research project:**

**EYE MOVEMENTS IN THE DEEP PHENOTYPING OF EARLY NEURODEGENERATION**

**Description:**

Idiopathic rapid eye movement sleep behavior disorder (iRBD) manifested by the absence of muscle atonia and dream enactment behaviors, is a recognized initial form of neurodegenerative disease. After 10 years or more since iRBD diagnosis, up to 3/4 of patients develop alpha-synucleinopathies, including Parkinson's disease (PD), multiple system atrophy, or Lewy body disease. Early detection of neurodegeneration before the clinical onset of symptoms is a prerequisite for studying the mechanisms of disability and/or for early initiation of targeted symptomatic, neuroprotective or neurorestorative therapy. To accurately discern the phenotype of the disease and classify it into one of the forms differing in the degree of impairment of motor, cognitive and autonomic functions, deep phenotyping procedures have recently been introduced (Delude 2015). These consist of a detailed description of the characteristic features that contribute to the recognition of the sub-phenotypes of the disease. While disability may be undetectable by clinical examination in the earliest stages of neurodegeneration, targeted instrumental analyses have been used to study motor stereotypes such as gait and speech (Krupička et al. 2020, Viteckova et al. 2020, Rusz et al. 2022). Since the initial neurodegenerative changes in alpha-synucleinopathies affect the brainstem nuclei, it can be expected that eye movements, in particular saccades and smooth pursuit will also be affected in addition to sleep disturbances. To date, eye movements have only been studied in a single cohort of iRBD patients prospectively followed at our centre, which demonstrated a high rate of antisaccade errors, considered to be a manifestation of prefrontal cortex dysfunction (Hanuška et al. 2019). Thus, the objectives of the proposed Junior project will be to 1) use video-oculography to test whether gaze abnormalities in patients with iRBD can serve as an early predictor of the clinical manifestation of synucleinopathy; 2) to investigate gaze abnormalities in iRBD patients as a biomarker of future cognitive decline corresponding to prefrontal cortex dysfunction; and 3) to investigate the relationships between eye movement abnormalities and gait and speech impairments in iRBD and in early stages of PD.

**References:**

Delude CM. Deep phenotyping: The details of disease. Nature 2015;527(7576):S14-5.

Hanuška J, Rusz J, Bezdicek O, Ulmanová O, Bonnet C, Dušek P, Ibarburu V, Nikolai T, Sieger T, Šonka K, Růžička E. Eye movements in idiopathic rapid eye movement sleep behaviour disorder: High antisaccade error rate reflects prefrontal cortex dysfunction. J Sleep Res 2019;28(5):e12742.

Krupička R, Krýže P, Neťuková S, Duspivová T, Klempíř O, Szabó Z, Dušek P, Šonka K, Rusz J, Růžička E. Instrumental analysis of finger tapping reveals a novel early biomarker of parkinsonism in idiopathic rapid eye movement sleep behaviour disorder. Sleep Med 2020;75:45-49.

Rusz J, Janzen A, Tykalová T, Novotný M, Zogala D, Timmermann L, Růžička E, Šonka K, Dušek P, Oertel W. Dysprosody in Isolated REM Sleep Behavior Disorder with Impaired Olfaction but Intact Nigrostriatal Pathway. Mov Disord 2022;37(3):619-623.

Viteckova S, Rusz J, Krupicka R, Dusek P, Růžička E. Instrumental analysis of gait abnormalities in idiopathic rapid eye movement sleep behavior disorder. Mov Disord 2020;35(1):193-195.

**Qualifications:**

* Ph.D. degree in neuroscience or related fields (up to 5 years from graduation)
* Ability to communicate in both spoken and written English, and at least basic Czech (to communicate with patients)
* High motivation, ability to conduct collaborative research.

**Funding:**

Position will be co-financed from projects funded by the Ministry of Health of the Czech Republic (AZV) and by Charles University (Cooperatio Neuroscience, Exceles).

**Workplace:**

Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital in Prague

**Supervisor:**

Prof. Evžen Růžička, MD, DSc.

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**Position available from:** January 1, 2023

Applicants must submit required documents to: Anna Jezberová anna.jezberova@lf1.cuni.cz

**2. Title of the research project:**

**THE BIOLOGICAL RHYTHMS AFFECTED BY MUSCARINIC RECEPTORS**

**Description:**

Muscarinic receptors (MRs) are typical members of the G protein-coupled receptor (GPCR) family and exist in five subtypes from M1 to M5. MRs are involved in many functions, such as learning [1], spinal locomotor networks [2], locomotion [3], biological rhythms [4], cardiovascular physiology [5], bronchoconstriction [6], and gastrointestinal tract functions [7], and they are also involved in pathologies, such as schizophrenia [8] and Parkinson’s disease [3].

Recently, the role of MRs in biological rhythm regulation was determined [9-11].

The project aims to study the specific role of MR subtypes in the biological rhythms, mainly motor activity, temperature, and heart rate. As the differences have been identified between males and females, another aspect of the project will be the role of sex hormones in the regulation of specific biological rhythms. The second part of the project will be the comparison of behavior dependency on biological rhythm. The identification of brain structures responsible for biological rhythm regulation will be another aim of the present project. As another aspect of biological rhythm regulation, the biological rhythm of key cholinergic molecules (MRs, acetylcholinesterases, choline transporter, vesicular acetylcholine transporter) will be studied too. The project will comprise neurochemical, receptor binding, behavioral, and telemetry experiments with specific treatments with sex hormones.

**References**

1. Fernández de Sevilla, D.; Núñez, A.; Buño, W. Muscarinic Receptors, from Synaptic Plasticity to its Role in Network Activity. *Neuroscience* **2021**, *456*, 60-70, doi:<https://doi.org/10.1016/j.neuroscience.2020.04.005>.

2. Mille, T.; Quilgars, C.; Cazalets, J.-R.; Bertrand, S.S. Acetylcholine and spinal locomotor networks: The insider. *Physiological Reports* **2021**, *9*, e14736, doi:<https://doi.org/10.14814/phy2.14736>.

3. Ztaou, S.; Amalric, M. Contribution of cholinergic interneurons to striatal pathophysiology in Parkinson's disease. *Neurochem. Int.* **2019**, *126*, 1-10, doi:<https://doi.org/10.1016/j.neuint.2019.02.019>.

4. Myslivecek, J.; Farar, V.; Valuskova, P. M(4) muscarinic receptors and locomotor activity regulation. *Physiol. Res.* **2017**, *66*, S443-s455.

5. Saternos, H.C.; Almarghalani, D.A.; Gibson, H.M.; Meqdad, M.A.; Antypas, R.B.; Lingireddy, A.; AbouAlaiwi, W.A. Distribution and Function of the Muscarinic Receptor Subtypes in the Cardiovascular System. *Physiol. Genomics* **2017**, doi:10.1152/physiolgenomics.00062.2017.

6. Kistemaker, L.E.M.; Gosens, R. Acetylcholine beyond bronchoconstriction: roles in inflammation and remodeling. *Trends Pharmacol. Sci.* **2015**, *36*, 164-171, doi:<http://dx.doi.org/10.1016/j.tips.2014.11.005>.

7. Tobin, G.; Giglio, D.; Lundgren, O. Muscarinic receptor subtypes in the alimentary tract. *J. Physiol. Pharmacol.* **2009**, *60*, 3-21.

8. Dean, B.; Scarr, E. Muscarinic M1 and M4 receptors: Hypothesis driven drug development for schizophrenia. *Psychiatry Res.* **2020**, *288*, 112989, doi:<https://doi.org/10.1016/j.psychres.2020.112989>.

9. Riljak, V.; Janisova, K.; Myslivecek, J. Lack of M4 muscarinic receptors in the striatum, thalamus and intergeniculate leaflet alters the biological rhythm of locomotor activity in mice. *Brain Struct Funct* **2020**, *225*, 1615–1629, doi:10.1007/s00429-020-02082-x.

10. Valuskova, P.; Riljak, V.; Forczek, S.T.; Farar, V.; Myslivecek, J. Variability in the Drug Response of M4 Muscarinic Receptor Knockout Mice During Day and Night Time. *Front. Pharmacol.* **2019**, *10*, doi:10.3389/fphar.2019.00237.

11. Valuskova, P.; Forczek, S.T.; Farar, V.; Myslivecek, J. The deletion of M4 muscarinic receptors increases motor activity in females in the dark phase. *Brain Behav* **2018**, *8*, e01057, doi:10.1002/brb3.1057.

**Qualifications:**
Ph.D. in neurosciences, physiology, cell biology, biochemistry or equivalent. Prior experience with behaviour research and neurochemistry will be appreciated.

**Funding:**
Charles University Program Cooperatio

**Workplace:**
Institute of Physiology, 1st Faculty of Medicine, Laboratory of Neurosciences

**Supervisor:**
Jaromir Myslivecek, M.D., Ph.D.

**Position available from:**

January 1, 2023