1. PHD PROJECT DESCRIPTION (4000 characters max., including the aims and work plan)

Project title:

Development of eye motion-based biomarkers for the detection and monitoring of neurodegenerative diseases.

1.1. Project goals

- To develop methods for quantitative analysis of eye motion characteristics acquired with high speed and high resolution retinal eye-tracking system. This includes segmentation (classification of motion events of various types) and parametrization (quantitative description of motion events - hundreds of parameters can be calculated)
- To develop statistical and artificial intelligence methods for classification, knowledge extraction, data reduction, diagnostics, monitoring of neurodegenerative diseases and vision disorders from eye-motion traces.
- To develop digital phenotype of human subject using eye motion trajectories and methods for monitoring its changes in time from immediate alterations due to state of the subject (fast daily changes due to fatigue, depression, any kind of weakness), or long term processes such as aging, through changes caused by disease or treatment.

1.2. Outline

The human eye is the window to the body and the brain. The retina, many cortical and subcortical brain areas, and the brainstem or cerebellum are involved in visual perception and eye movement control and execution. Therefore, the eye is a source of sensitive and specific biomarkers for early detection and progress. These diseases can be indicated by accurate quantification of changes in ocular dynamics. Several papers and monographs discuss different eye movement paradigms and the scientific rationale for studying eye movements in patients with psychiatric and neurologic disorders.

The long-term vision aims to lay down the scientific foundation of retinal biomarker-based ND diagnosis and develop a new method based on the relations between oculomotor characteristics of the human eye and brain activity. A new method may significantly improve the diagnostics, monitoring, and care of neurodegenerative disorders such as Alzheimer's Disease (AD) and Dementia with Lewy Bodies (DLB). Early detection and monitoring of progression are key to a personalized medical approach. Targeted therapies with efficient monitoring prevent complications and rapid worsening of the disease and allow for on-time modifications. It can also reduce new drug development time, and facilitate widely accessible, affordable test standards in healthcare. A breakthrough technology like this reassures impacted people that there are ways to alleviate the consequences of their illness and improve their quality of life.

This project, will aim at establishing the relationship between subtle changes in oculomotor characteristics (i.e., gaze fixation patterns, saccades, tremor and drift) and the progress of neurodegenerative disorders (such as AD or DLB). It requires adapting our proof-of-concept retinal tracker for clinical practice and exploiting its unprecedented resolution to reveal oculomotor characteristics of the eye that were so far hidden from researchers.

1.3. Work plan

- Literature review and introduction to retinal eye-tracking technology and existing prototypes.
- Development of the battery of visual psychophysical experiments from simple fixation to mentally demanding exercises with saccadic tasks and more complex paradigms.
- Development of tools for automatic classification, knowledge extraction, data reduction of motion events registered during experiments with the test battery.
- Experiments with human subjects in laboratory and in collaborating clinics.
- Development of candidates for biomarkers for diagnostics, monitoring of neurodegenerative diseases and vision disorders.

1.4. Literature *(max. 10 listed, as a suggestion for a PhD candidate)*

1) W. H. Organization, Neurological disorders: Public health challenges (World Health Organization, 2006).
2) S. Gauthier, P. Rosa-Neto, J. Morais, and C. Webster, "World alzheimer report 2021: Journey through the diagnosis of dementia," Alzheimer's Disease International (2021).
3) M. R. MacAskill, and T. J. Anderson, "Eye movements in neurodegenerative diseases," Current opinion in neurology 29, 61-68 (2016).
4) C. K. Sheehy, E. S. Bensinger, A. Romeo, L. Rani, N. Stepien-Bernabe, B. Shi, Z. Helft, N. Putnam, C. Cordano, J. M. Gelfand, R. Bove, S. B. Stevenson, and A. J. Green, "Fixational microsaccades: A quantitative and objective measure of disability in multiple sclerosis," Multiple Sclerosis Journal 26, 343-353 (2020).
5) C. C. Wu, B. Cao, V. Dali, C. Gagliardi, O. J. Barthelemy, R. D. Salazar, M. Pomplun, A. Cronin-Golomb, and A. Yazdanbakhsh, "Eye movement control during visual pursuit in parkinson's disease," Peerj 6 (2018).
6) A. Serra, C. G. Chisari, and M. Matta, "Eye movement abnormalities in multiple sclerosis: Pathogenesis, modeling, and treatment," Frontiers in neurology 9 (2018).
7) R. Rodríguez-Labrada, Y. Vázquez-Mojena, and L. Velázquez-Pérez, "Eye movement abnormalities in neurodegenerative diseases," Eye Motility (2019).
8) 10. P. J. Benson, S. A. Beedie, E. Shephard, I. Giegling, D. Rujescu, and D. St Clair, "Simple viewing tests can detect eye movement abnormalities that distinguish schizophrenia cases from controls with exceptional accuracy," Biol Psychiat 72, 716-724 (2012).
9) 13. O. Hansson, "Biomarkers for neurodegenerative diseases," Nature medicine 27, 954-963 (2021).
10) 14. M. M. Bartuzel, K. Wróbel, S. Tamborski, M. Meina, M. Nowakowski, K. Dalasiński, A. Szkulmowska, and M. Szkulmowski, "High-resolution, ultrafast, wide-field retinal eye-tracking for enhanced quantification of fixational and saccadic motion," Biomed Opt Express 11, 3164-3180 (2020).

1.5. Required initial knowledge and skills of the PhD candidate

- Background in physics, mathematics, informatics or similar. Knowledge in optical physics and optical imaging will be an advantage.
- Basics in computer programming (preferably Python, Labview, Matlab, C/C++/C#),

knowlegde of GPU programming will be an advantage.
- Knowledge of English is mandatory.

1.6. Expected development of the PhD candidate's knowledge and skills

It is expected that the PhD candidate will develop the following main skills during the PhD:

- The capacity to plan, implement and critically analyse novel experimental methodology related to retinal eye tracking.
- The capacity to create, implement and modify algorithms required in the processing of eye-tracker data.
- The capacity to independently carry out clinical studies using retinal eye-tracker, with guidance from the supervisory team.
- The capacity to clearly communicate research ideas and results in English, both in written and oral formats. Particular emphasis will be placed on writing journal papers and delivering conference presentations.