PROJECT 1

DoS: Federica Agosta

Title: Exploring the role of neurodegenerative pathology and vascular disease in the Parkinson's disease evolution

Curriculum: Neuroscience and Experimental Neurology

Residency Program: Neurology

Link to OSR/UniSR personal page: https://www.unisr.it/en/docenti/a/agosta-federica

Project description (*Number of characters, including spaces*: 2.000 - 3.000):

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD). It is characterized by progressive loss of dopaminergic neurons in the nigrostriatal circuit and intracytoplasmic fibrillary aggregates of α-synuclein (Lewy bodies) over the whole central nervous system. Motor symptoms are cardinal features for PD diagnosis. In addition, non-motor and cognitive/behavioural symptoms can occur, even in the prodromal phase. A link between clinical manifestations and the pathological stage of the disease has been suggested. There is, however, a variable expression of motor and non-motor symptoms along the disease course and among patients, suggesting variable neurodegenerative processes and/or the contribution of additional factors. Actually, the treatment of PD is symptomatic, with the possibility of a wide choice of dopaminergic drugs, first of all the levodopa treatment.
It is known that 90% PD cases have no identifiable genetic causes. In consideration of the heterogeneity of PD phenotypes and disease progression, the identification of risk factors, as well as protective factors, might have a key role to understand disease onset, progression or the expression of troublesome treatment adverse effects.
In the general population, some of the most frequent risk factors for morbidity and mortality are vascular risk factors (VRF), such as hypertension and dyslipidemia. Small vessel disease and white matter hyperintensities (WMH) as its surrogate marker are known to predict cognitive and motor decline in the elderly, in AD and in vascular dementia. Results regarding the link between VRF and PD, in terms of disease onset and progression, remains controversial. WMHs have been associated with cognitive decline, postural impairment and gait disorder, but the relationship between vascular and neurodegenerative pathologies is still unknown. MRI can be used to assess WMHs and their intrinsic structural damage, normal appearing WM and grey matter (GM) structural alterations, as well as the impact of both vascular and neurodegenerative changes on connectivity in widespread neural systems. Understanding the impact of different risk factors, including VRF, on the brain in-vivo in patients with PD will increase our knowledge of disease pathophysiology and allow modifying the natural history of the disease.

In this framework, the aims of the project are:

- To collect and process clinical, cognitive, behavioural, multiparametric MRI data, both structural and functional, from a large cohort of PD patients with a longitudinal study design;
- To explore the interaction between VRF, subsequent cerebrovascular (WMH burden, distribution and intrinsic damage) and spreading of neurodegenerative pathology in GM

and WM in PD patients, as assessed using structural and functional MRI, in the different stages of the disease;

- To assess the relative contribution of cerebrovascular and neurodegenerative MRI features on motor and non-motor disability progression and responsiveness to treatment in PD patients;
- To explore the relationship between neuroinflammation and vascular pathology that might accompany the neurodegenerative process.

Skills to be acquired by the student:

1) Expertise in PD management in terms of diagnosis, clinical evaluation and treatment, including the assessment of risk factors.
2) Ability to develop objective clinical outcome measures to improve the motor and non-motor evaluation of PD.
3) Ability to develop MRI experimental designs to study brain functional and structural brain properties in PD.
4) Ability to pre-process and analyze clinical and MRI (structural and functional) data.
5) Capability to work in team and development of strong collaborations with different research units.
6) Ability to meaningfully interpret the results obtained from the project and write a manuscript.

References (max. 3)

1) Ascherio A et al., *The epidemiology of Parkinson's disease: risk factors and prevention.* Lancet Neurol. 2016 Nov;15(12):1257-1272.
2) Imperiale F et al., *Brain structural and functional signatures of impulsive-compulsive behaviours in Parkinson's disease*. Mol Psychiatry. 2018 Feb;23(2):459-466.
3) Galantucci S et al., *Structural Brain Connectome and Cognitive Impairment in Parkinson Disease.* Radiology. 2017 May;283(2):515-525.