PROJECT 1

DoS:      Dr. Silvia Paola Caminiti

Title:    The effects of genotype, biological and environmental factors on neurodegeneration mediated brain dysfunction


Project description (Number of characters, including spaces: 2,000 - 3,000):

Several neurodegenerative diseases are associated with a misfolded and aggregated protein, hence the term “proteinopathies” to emphasize the biological basis of these disorders. Several studies have increasingly highlighted that the same neuropathology can trigger different clinical phenotypes [1]. The clinical phenotypes in addition are dependent on fix (e.g., genotype and gender) and flexible (e.g., education, occupation and leisure activity) factors. The concept of brain reserve (BR) is fundamental on this ground, whereby education, occupation and other lifestyle and inherited factors may contribute to differences in brain structure and function that modulate resistance against the development of neurodegenerative pathology and resilience (coping) in the face of pathology [2]. Notably, mounting evidence supports sex- and gender associated differences in risk for different proteinopathies and their clinical manifestations [3]. However, the interaction among genotype, biological, epidemiological, and environmental factors on neurodegenerative mechanisms yet to be explored. There is a need for studies evaluating the effect of these variables on the specific-disease risk and related clinical manifestation. A better understanding of the roles of biological, environmental and genetic differences in the mechanisms underlying proteinopathies-spectrum of diseases will play a key role in the prognostic considerations and development of treatments trials.

The main objective of this project is to assess the contribution of genetic, biological and environmental factors to amyloid, tau and α-synuclein neurodegenerative processes and related clinical phenotypes. We will adopt multi-factorial protocol which integrates epidemiological (gender), genetic features (e.g. APOE ε4, LRRK2 and GBA) and clinical data, environmental factors (e.g. occupation and education), neuroimaging measures (FDG-PET, MRI and fMRI), and biomarkers from cerebrospinal fluid. The pooled data for this project will provide the opportunity to evaluate the influences of genetic, environmental and sex/gender differences within amyloidopathy and tauopathies, focusing on Alzheimer’s disease-spectrum (AD-s), and within α-synucleinopathies, focusing on Lewy Bodies diseases-spectrum (LBD-s). We will include ~500 patients belonging to LBD-s (~100 from HSR internal dataset and ~400 from PPMI dataset) and ~500 patients belonging to AD-s (~100 from HSR internal dataset and ~400 from ADNI database).

The doctoral research 1) will assess whether genetic (e.g. APOE ε4, LRRK2 and GBA), environmental (e.g. education and occupation) and sex/gender differences factors can influence amyloid, tau and α-synuclein deposition and mediated brain dysfunction (FDG-PET, MRI and fMRI); 2) will evaluate the co-pathologies prevalence in relationship to these factors; 3) will examine the contribution of each factor in the different disease courses throughout a longitudinal research setting.
Skills to be acquired by the student:

1. Design and plan a scientific experiment, cope with problems, and find solutions;
2. Interpretation of test results from neuropsychological and clinical assessment;
3. Interpretation of biomarker metrics including MRI, fMRI, DTI, FDG-PET
4. *In vivo* molecular biomarkers analysis and interpretation, including CSF and PET measures of different proteinopathies (amyloid and tau).
5. Analytical skills from pre-processing to statistical analysis and interpretation;
6. Learning different functional connectivity (metabolic and rs-fMRI) analyses by using specific programs and software (e.g. MATLAB, SPM, FSL, MRico and BrainNet);
7. Statistical analysis for biomarkers evaluation, including computation of the main accuracy indices, ROC curve analysis, logistic regression models and survival analysis, by using the main softwares for statistical data analysis, including SPSS, Matlab and R;
8. Paper writing and oral communication abilities (build up concise and logically-written materials, organize and communicate effectively in oral presentations to small and large groups).

References (max. 3)

