**PROJECT 2**

**DoS**: Federica Agosta

Title: Tracking and predicting neurodegeneration spreading across the brain connectome: defining mathematical models to predict patterns of pathology propagation in FTLD syndromes

Curriculum: Neuroscience and Experimental Neurology

Link to OSR/UniSR personal page: http://www.unisr.it/dottorati-2/15134-2/

**Project description** (*Number of characters*, *including spaces*: 2.000 - 3.000):
Current knowledge of neurodegenerative diseases is limited by poor understanding of how they progress through the central nervous system. It has recently been hypothesized that clinical progression in these conditions involves the systematic spreading of protein misfolding along neuronal pathways. Protein aggregates would trigger misfolding of adjacent homologue proteins in newly-affected regions, and this would propagate in a "prion-like" fashion across anatomical connections. Although prion-like spread of misfolded proteins is a plausible mechanism of disease progression, it needs substantiation by longitudinal data. The project will apply emerging network science tools to longitudinal, structural and functional brain connectivity 3T magnetic resonance imaging data from patients with frontotemporal lobar degeneration (FTLD) – a devastating, relentlessly progressive, young onset, neurodegenerative disorder. The study will involve both sporadic and familial cases, including presymptomatic gene mutation carriers. We will use *ad hoc* mathematical frameworks to provide *in vivo* support to the prion-like spreading hypothesis. This will be achieved both independently of and accounting for the longitudinal connectome changes in patients. We will also evaluate how patients' functional and structural network connectomes at disease onset influence region-specific vulnerability to neurodegeneration (measured as severity of brain atrophy) and clinical evolution of FTLD syndromes after two years. If the measured brain network properties and "true" atrophy development are estimated to be associated by the statistical models, then network analysis could be used to create a predictor of brain atrophy progression, and thus clinical evolution, which would be a valuable prognostic tool for neurologists. The ground-breaking nature of the experiments planned in this project will pave the way to the development of novel tools for understanding the biological underpinnings of other central nervous system proteinopathies such as Alzheimer's disease and Parkinson's disease, and to identifying individualized, early interventions to modify disease progression.

**Skills to be acquired by the student:**

The student should be a bioengineer. During the project the student will acquire the following skills:

1) Pre-processing of MRI data (structural, HARDI, resting state functional MRI)
2) MRI analysis to assess longitudinal changes in brain atrophy
3) Brain connectome construction and analysis of healthy subjects and patients with frontotemporal dementia
4) Implementation and estimation of mathematical imaging-based models to predict network and clinical evolution
5) Interpretation of network analysis data in patients with frontotemporal dementia
6) Drafting of research reports and articles

**References** (max. 3)

Agosta F, Weiler M, Filippi M. Propagation of Pathology through Brain Networks in Neurodegenerative Diseases: From Molecules to Clinical Phenotypes. CNS Neurosci Ther 2015;21:754-767

Filippi M, Basaia S, Canu E, Imperiale F, Meani A, Caso F, Magnani G, Falautano M, Comi G, Falini A, Agosta F. Brain network connectivity differs in early-onset neurodegenerative dementia. Neurology 2017;89:1764-1772

Agosta F, Sala S, Valsasina P, Meani A, Canu E, Magnani G, Cappa SF, Scola E, Quatto P, Horsfield MA, Falini A, Comi G, Filippi M. Brain network connectivity assessed using graph theory in frontotemporal dementia. Neurology 2013;81:134-143