PROGETTO

Supervisore: Prof. Massimo Filippi

Titolo */Title:* Defining a multimodal machine-learning algorithm to predict disability outcomes in Frontotemporal Lobar Degeneration

Curriculum: Molecular Medicine, Neuroscience and Experimental Neurology

Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento: https://www.unisr.it/docenti/f/filippi-massimo

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Frontotemporal lobar degeneration (FTLD) is a term that encompasses progressive behavioral derangements and language deficits associated with atrophy of frontotemporal lobes. Different proteins accumulate in susceptible regions, the major ones being tau and TDP43. According to the areas affected, clinical variants range from the behavioral variant of FTD (1), to primary progressive aphasias (2) and motor phenotypes (motor neuron disease and atypical parkinsonisms) (3, 4). 30% of cases are familial, involving different genes (C9orf72, MAPT and GRN being the most common) (5). Given the multilevel heterogeneity of this syndrome, it is challenging to define predictors of disease outcomes.

Rationale and hypothesis

Extensive clinical trials for FTLD are in progress, with a demand for clearer definitions of disease outcome measures to ensure precise monitoring of therapeutic interventions. Tau and TDP43 accumulation is spatially and temporally complex and the understanding of their trajectories of deposition is incomplete. Advanced MRI can detect preclinical alterations and anticipate disease trajectories (6), providing hints for disease propagation models (i.e. through brain connectome). Various factors, such as the clinical presentation phenotype, patterns of atrophy at MRI, serum and cerebrospinal fluid (CSF) biomarkers indicating underlying (co-)pathology, and genetic influences, potentially impact which and when disease milestones will be reached. No reliable predictive model exists that could forecast the evolution of this spectrum of neurodegenerative diseases (7).

Objectives and specific aims

This study aims to investigate through a multimodal approach which predictors better forecast disease evolution in terms of milestones of disease severity. A machine learning approach will define the contribution of each baseline biomarker in predicting disease trajectories. The prediction model will be implemented with clinical measures of disease severity (CDR-FTD (8), UPDRS (9), motor signs, limb weakness, hypo/hyperreflexia), neuropsychological and neuroimaging data (atrophy, i.e. neurodegeneration), CSF and plasmatic biomarkers (neurodegeneration, inflammation, glial cell activation), and genetic data for FTLD-related mutations (determinants and modifiers of underlying pathology). Given the high variability of FTLD phenotypes, multiple outcome measures will be

considered to reach the highest degree of generalizability. These will include: motor outcomes (ability to walk independently), language outcomes (ability to comprehend/produce speech), behavioral outcomes (impairment in daily activity caused by behavioral alterations), executive outcomes (inability to drive, manage finances, prepare meals).

Expected outcomes

The contribution of each factor will be weighted to reach a composite disability outcome that would help clinicians predict, with a baseline assessment, pattern and rapidity of disease evolution and loss of autonomy.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

Diagnosis, treatment and monitoring of FTLD patients. Active collection and analysis of clinical data and biological material (blood and cerebrospinal fluid). Analysis of neuropsychological data. MRI acquisition. Advanced MRI analysis. Implementation of machine learning algorithms. Drafting of research reports and articles.

Bibliografia (max. 15)

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