PROJECT 1

DoS: FRANCESCO BENEDETTI

Title: Neurocognitive and neuropsychiatric long-term sequelae of COVID-19: advanced machine learning and key enabling technologies to improve wellbeing and quality of life.

Link to OSR/UniSR personal page:
https://www.unisr.it/docenti/b/benedetti-francesco
https://research.hsr.it/en/divisions/neuroscience/psychiatry-and-clinical-psychobiology/index.html

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

Coronavirus disease 2019 (COVID-19) has evolved into a worldwide pandemic with more than 230 million individuals infected and 4.7 million deaths as of September 2021. Despite most people survive to the virus, there are increasing reports of persistent and prolonged post-acute effects of COVID-19 which hamper the functioning and quality of life of the survivors. Beside the specific organ somatic consequences, a wide literature is consistently highlighting long lasting neurocognitive deficits, also defined as “brain fog”, chronic fatigue syndromes and the onset or psychopathological symptoms, mainly related to anxiety and depression. These long-term effects persist over more than one year after the clearance of the virus, and translate in an increasing burden of disease and years lived with disability, impacting both, quality of life and the socio-economic status of patients, and the welfare system which takes care of them.

Studies on the relationship between post COVID-19 neurocognitive deficits, brain structure and function, and the clinical conditions of the patients, are in its infancy, but preliminary data obtained in our research unit allow to hypothesize that regional brain microstructure and functional and structural connectivity could mediate the relationship between a COVID-19 and its psychopathological sequelae, and are in agreement with current perspectives on the brain structural and functional underpinnings of depressive psychopathology, and the effect of neuroinflammation in mood disorders: also considering the bidirectional link between COVID-19 and psychiatric conditions: post-acute COVID-19 neurocognitive phenotypes are associated with anxiety and depression, and pre-existing major mood disorders foster worse COVID-19 outcomes.

The current PhD project is focused on:

1) Assessing the epidemiology of these long-term effects, and their impact on participants quality of life, through online surveys in Italian general population (sample size: n=700) (1 year); and in patients enrolled at COVID-19 Follow-up Outpatients clinic at IRCCS Ospedale San Raffaele S.R.L., which is monitoring patients since March 2020 (n=200, followed at 1, 3, 6, and 12 months after clearance of the virus).

2) Providing an in-deep clinical (medical data related to COVID-19 and related pathologies), neurocognitive, and neural phenotyping (structural and functional neuroimaging; n=100) of COVID-19 survivors, aiming at defining the biological underpinnings of post-COVID neurocognitive deficits. This task will also exploit new technologies for the quantification of circulating peripheral markers of neuronal damage (e.g., neurofilament light chain) that our research group contributed to validate in brain neuroinflammation and acute COVID, to predict its fatal outcomes.

3) Identifying specific vulnerable subpopulations by applying advanced unsupervised machine learning techniques (such as topological data analysis, penalized regressions, support vector machine, multiple kernel learning optimized through bootstrapping and nested cross-validation procedures), that will allow to identify meaningful clusters of individuals characterized by specific relationships between sociodemographic, neurocognitive, clinical and functioning variables (1-2 years); this will be applied both, to data gathered in general population and in the deep phenotyping of COVID-19 survivors;

4) The PhD student will directly participate to the activities performed in Ospedale San Raffaele S.R.L., in a 6 months stage, aimed at defining needs, to implement effective interventions on the clinical processes exploiting key enabling technologies (1-2 years); these will include machine learning algorhythms to predict patients' outcomes; computer-aided cognitive remediation; internet-based platforms.

5) Developing and assessing the effectiveness of specific psychological (neurocognitive remediation and brief intervention of psychological support) and environmental empowerment and brain stimulation interventions (e.g., bright light, TDCS, etc) aimed at potentiating cognitive functions and improving the symptomatology and quality of life of COVID-19 survivors (1-3 years). This will be performed in proof-of-concept, pilot studies performed in the COVID-19 outpatients who show specific deficits or clinical syndromes after their in-deep phenotyping (1-3 years).

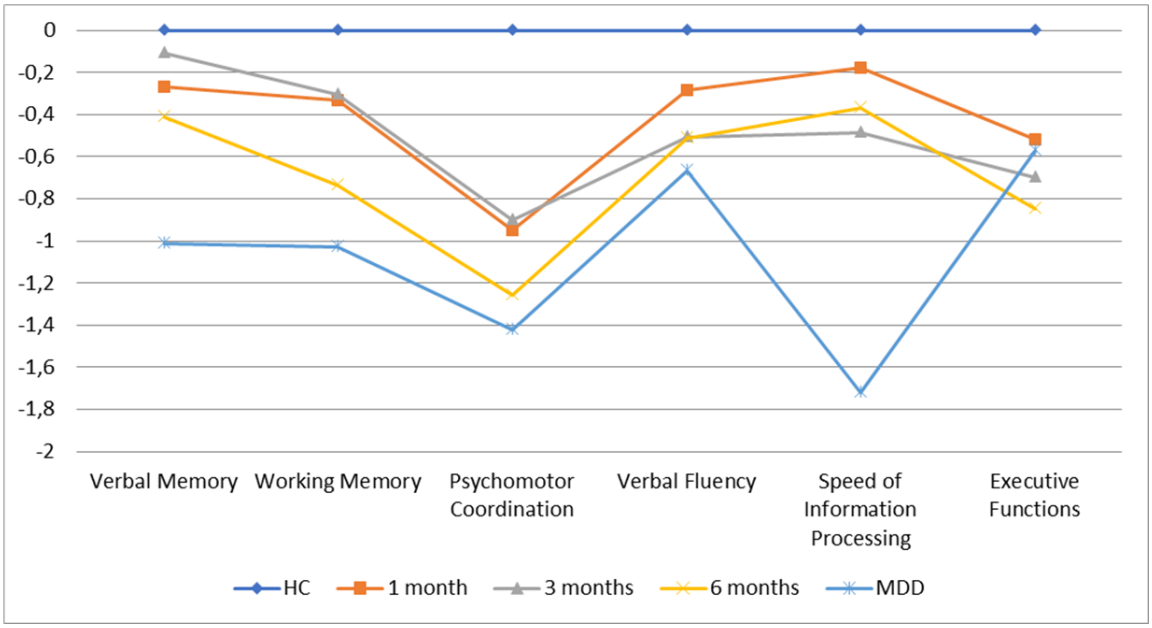
Skills to be acquired by the student:

The candidate will actively participate to all phases of the project: from design of the protocols and surveys, data collection, to the analyses of the data though cutting-edge statistical methods (e.g. TDA) including multimodal neuroimaging analyses (resting state and task based fMRI, including connectivity analyses, structural imaging for grey matter volumes and thickness, and white matter integrity).

Feasibility:

This project will be carried out within the main research frame of the research unit Psychiatry and Clinical Psychobiology at Ospedale San Raffaele SRL, currently funded for an ongoing research on the role of neuroinflammation in mood disorders (European Union H2020 SC1-PM-02-2017 New concepts in patient stratification: "MOODSTRATIFICATION: Immune Signatures for Therapy Stratification in Major Mood Disorders" Grant agreement ID: 754740).

Preliminary findings:



Preliminary findings. Neuropsychological profiles on the Brief Assessment of Cognition in Schizophrenia (BACS) for COVID-19 survivors at 1, 3 and 6 months, compared to healthy controls and major depression.

References (max. 3)

Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, Melloni EMT, Furlan R, Ciceri F, Rovere-Querini P; COVID-19 BioB Outpatient Clinic Study group, Benedetti F. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav Immun. 2020 Oct;89:594-600. doi: 10.1016/j.bbi.2020.07.037. Epub 2020 Jul 30. PMID: 32738287; PMCID: PMC7390748.

Mazza MG, Palladini M, De Lorenzo R, Magnaghi C, Poletti S, Furlan R, Ciceri F; COVID-19 BioB Outpatient Clinic Study group, Rovere-Querini P, Benedetti F. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: Effect of inflammatory biomarkers at three-month follow-up. Brain Behav Immun. 2021 May;94:138-147. doi: 10.1016/j.bbi.2021.02.021. Epub 2021 Feb 24. PMID: 33639239; PMCID: PMC7903920.

Vai B, Mazza MG, Delli Colli C, Foiselle M, Allen B, Benedetti F, Borsini A, Casanova Dias M, Tamouza R, Leboyer M, Benros ME, Branchi I, Fusar-Poli P, De Picker LJ. Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: a systematic review and meta-analysis. Lancet Psychiatry. 2021 Sep;8(9):797-812. doi: 10.1016/S2215-0366(21)00232-7. Epub 2021 Jul 17. PMID: 34274033; PMCID: PMC8285121.

De Lorenzo R, Loré NI, Finardi A, Mandelli A, Cirillo DM, Tresoldi C, Benedetti F, Ciceri F, Rovere-Querini P, Comi G, Filippi M, Manfredi AA, Furlan R. Blood neurofilament light chain and total tau levels at admission predict death in COVID-19 patients. J Neurol. 2021 May 10:1-7. doi: 10.1007/s00415-021-10595-6. Epub ahead of print. PMID: 33973106; PMCID: PMC8108733.

Company:
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