

most frequent complaints of long COVID patients [4]. These symptoms threaten the quality of life and the societal functioning of a significant proportion of the active population. Despite post-viral or post-infectious neuropsychiatric symptomatology has been recognized and studied prior to the COVID-19 pandemic, crucial knowledge about the neurobiological mechanisms underlying these symptoms is still lacking.

Objectives: The aims of the study are to describe the standardized evaluation of the psychological and cognitive function of long COVID patients and their evolution, to compare immunological and HPA-axis related biomarkers between long COVID patients and healthy controls, to explore cross-sectional and longitudinal associations between immunological measures and long COVID symptoms.

Study design: Cov-N-Psy is a longitudinal observational study. Three groups will be included from 2021 until 2023: long COVID patients with neuropsychological complaints (P), COVID-survivors without persistent complaints (Ca) and healthy volunteers without a history of COVID-19 (Cb). The total sample size is estimated on 130. Inclusion criteria for patients are (a) 18-70 years, (b) prolonged neuropsychological symptoms following a confirmed diagnosis of COVID-19 and (c) medical assessment done to exclude other causes. Ca and Cb participants are excluded in case of current psychological or cognitive symptoms and Cb participants are included only in the absence of a psychiatric history. Four visits are organized: at baseline, three, six and twelve months. The study is organized in three work packages (WP). WP1 includes a blood withdrawal and psychometric questionnaires and is part of every visit. WP2 includes the cortisol awakening response (CAR) measurement in saliva and takes place on the baseline visit for every participant and on the third visit for patients. Finally, WP3 includes an extensive neurocognitive assessment at baseline for patients and Ca controls and on the third visit for patients.

Lab measurements: The immunological measures in peripheral blood include SARS-CoV-2 antigenemia, leukocytes, cytokines, kynurenine pathway metabolites and human endogenous retrovirus-W envelope protein (HERV-W ENV) levels. The HPA-axis is evaluated using the cortisol awakening response (CAR) in saliva.

Statistics: Statistical analyses will be performed using JMP Pro 16.0. We will analyze the cross-sectional and longitudinal association between neuropsychological symptoms and inflammation using linear mixed models.

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Conflict of interest:

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BRAIN METABOLITES ASSOCIATE WITH WHITE MATTER INTEGRITY AND COGNITIVE DEFICITS IN PATIENTS RECOVERED FROM COVID-19: A MAGNETIC RESONANCE SPECTROSCOPY STUDY

M. Biondi¹, S. Poletti^{1,2}, B. Bravi^{1,3}, M. Paolini^{1,4}, M. Palladini^{1,3}, M.G. Mazza¹, P. Rovere-Querini^{5,6}, F. Benedetti^{1,2} ¹IRCCS San Raffaele Scientific Institute, Division of Neuroscience- Psychiatry and Clinical Psychobiology Unit, Milan, Italy; ²Vita-Salute San Raffaele University, Neuropsychiatric Sciences, Milan, Italy; ³Vita-Salute San Raffaele University, Psychology, Milan, Italy; ⁴Vita-Salute San Raffaele University, Neuroscience, Milan, Italy; ⁵Vita-Salute San Raffaele University, Internal Medicine, Milan, Italy; ⁶IRCCS San Raffaele Scientific

Institute, Division of Immunology- Transplantation and Infectious Diseases Unit, Milan, Italy

Background: Evidence on the neuropsychiatric consequences of COVID-19 are growing, and depressive symptoms and cognitive deficits now appear to be a relatively frequent outcome of the infection, being strictly interrelated [1,2]; much less however is known about their pathophysiology, although some recent MRI studies started to associate post-COVID neuropsychiatric symptoms with alterations in brain structure and function [3,4]. On the other hand, to date only few studies with limited sample size used brain spectroscopy to investigate COVID-related neuropathology [5]. Therefore in the present study we employed single voxel brain spectroscopy to investigate brain metabolites levels and their relationship with neuropsychiatric sequelae and white matter integrity in patients recovering from COVID-19 infection.

Methods: Our study was performed on 64 patients who were hospitalized at San Raffaele Hospital for a SARS-CoV-2 infection, recruited in the context of an ongoing prospective cohort study. The presence of depressive and cognitive symptomatology was assessed in the context of an unstructured clinical interview conducted by well-trained psychologists. Patients underwent 3-Tesla MRI scanning acquiring T1-weighted and Diffusion Weighted Images (DWI). ¹H-MRS was performed on a voxel placed in the DLPFC and concentration of brain N-acetyl-aspartate (NAA) and Glutamate (Glu) were estimated using LCModel. DWI normalization, correction for motion and eddy current, and tensor fitting were carried out using FSL 6.0. The association between brain metabolites levels, cognitive and depressive symptomatology and time elapsed from the infection to the MRI scan were investigated using age, sex and BMI as nuisance variables. Furthermore the associations between brain metabolites levels and Fractional Anisotropy (FA), Axial (AD), Mean (MD), and Radial Diffusivity (RD) were investigated, again entering age, sex and BMI as covariates.

Results: Time from infection to MRI scan was found to positively affect brain NAA levels ($\beta = 0.33$, $p=0.008$), while it had no effect on Glu ($\beta = 0.03$, $p=0.815$). Subjects with cognitive deficits had significantly lower levels of NAA ($p=0.005$) and Glu ($p=0.013$). When testing the effect of brain metabolites on white matter integrity, both NAA and Glu levels were associated with higher levels of FA (NAA: $p<0.001$; Glu: $p<0.001$) and lower of RD (NAA: $p=0.004$; Glu: $p=0.007$) and MD (NAA: $p=0.011$; Glu: $p=0.018$).

Conclusion: In our study we found NAA to progressively increase as a function of time elapsed from the infection to the MRI. Taking into account that NAA is considered to be a marker of neuronal viability, this finding could be suggestive of a brain recovery process after the infection. In line with this hypothesis, NAA and Glu levels were found to be lower in subjects with post-covid cognitive symptoms, and to be positively associated with white matter integrity. Our study therefore suggests that brain spectroscopy could provide novel insight into the pathophysiology of post-covid neuropsychiatric sequelae.

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