www.elsevier.com/locate/euroneuro
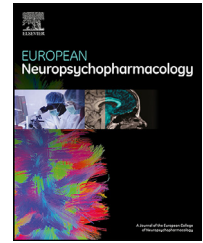
SHORT COMMUNICATION

Lower levels of glutathione in the anterior cingulate cortex associate with depressive symptoms and white matter hyperintensities in COVID-19 survivors

Sara Poletti[a,b,*], Marco Paolini[a,b], Mario Gennaro Mazza[a,b], Mariagrazia Palladini[a,b], Roberto Furlan[a,b], Patrizia Rovere Querini[a,b], Covid BioB Outpatients Clinic Study Group[a,b], Francesco Benedetti[a,b]

[a] Vita-Salute San Raffaele University, Milano, Italy
[b] Psychiatry & Clinical Psychobiology, Division of Neuroscience, Scientific Institute IRCCS Ospedale San Raffaele, Milano

Abstract
SARS-CoV-2 is a novel coronavirus that mainly affects the respiratory system. However, clinical manifestations such as neurological symptoms, psychopathological outcomes and brain alterations suggest brain involvement during SARS-CoV-2 infection. Depressive symptoms and cerebral white matter hypodensities/hyperintensities (WMH) have been widely reported in COVID-19 survivors and have been shown to persist after recovery from infection. At the same time viral Infections, including COVID-19, have been shown to lead to oxidative stress. Glutathione (GSH) is the main antioxidant in the brain and reduced GSH levels have been implicated both in COVID-19 and depression. We therefore hypothesise that reduced GSH levels may be associated with depressive symptoms and WMH in COVID-19 survivors. Forty-nine participants (age 18–70) surviving COVID-19 underwent magnetic resonance imaging to measure WMH and brain GSH levels in the ACC, blood sampling to measure systemic inflammation and psychopathological assessment for depressive symptoms. ACC concentrations of GSH inversely associated with

* Corresponding author at: San Raffaele Turro, Via Stamira d'Ancona 20, 20127 Milano, Italy.
E-mail address: poletti.sara@hsr.it (S. Poletti).

both depression scores and the number and volume of WMH. The volume of WMH also positively associated with depressive symptomatology. Finally, systemic inflammation negatively predicted GSH concentration in ACC. In conclusion, we observed overlapping associations of GSH levels in ACC, WMH and severity of depression in COVID-19 survivors, and confirmed the central role of systemic inflammation, thus warranting interest for further study of oxidative stress and antioxidants in the post-acute COVID-19 syndrome.

1. Introduction

SARS-CoV-2 is a novel coronavirus that mainly affects the respiratory system. However, other vital organs such as the heart, liver, kidney and brain can be affected by the infection (Nalbandian et al., 2021). Clinical manifestations suggestive of brain involvement during SARS-CoV-2 infection include, beside neurological symptoms, psychopathological outcomes and brain alterations. The occurrence of depressive symptoms in COVID-19 survivors has been widely reported and has been shown to persist up to twelve months after recovery from infection (Mazza et al., 2021a) and is considered one of the major causes of disability in COVID-19 survivors (Mazza et al., 2020b, 2021b).

Studies investigating the impact of COVID-19 infection on the brain have reported the presence of diffuse cerebral white matter hypodensities/hyperintensities (WMH) in several brain regions including prefrontal cortex, anterior cingulate cortex (ACC) and insula (Najt et al., 2021) brain regions consistently implicated in mood and anxiety disorders. Indeed, recent study from our group showed that the severity of depressive symptoms in COVID-19 survivors is associated with white and grey matter alterations in ACC and insula (Benedetti et al., 2021).

Viral Infections can cause a decrease in antioxidant defences leading to oxidative stress. This seems to be the case also in COVID-19 patients were a high neutrophil to lymphocyte ratio, an inflammatory index associated with high levels of reactive oxygen species, has been reported (Laforge et al., 2020). Oxidative stress is now recognized as one of the mechanisms involved in the pathophysiology of the disease (Suhail et al., 2020). In the brain, reactive astrocytes and activated microglia are able to produce free radicals that, together with a decreased level of antioxidants, may lead to neuronal damage.

Glutathione (GSH) is the main antioxidant in the brain. Depletion of GSH has been implicated in many chronic degenerative diseases and, in SARS-CoV-2, GSH deficiency has been associated with acute respiratory distress syndrome, multi-organ failure, and death (Polonikov, 2020). Further, a significant decline in GSH level has been reported in post-mortem cerebral cortex of COVID-19 patients (Boroujeni et al., 2021). Finally, supplementation of GSH has been shown to help recovery from respiratory distress in patients infected with COVID-19 (Guloyan et al., 2020), whereas N-acetylcysteine administration has been shown to increase GSH levels in the brain (Holmay et al., 2013), to reduce oxidative stress markers, and to increase cerebral glucose metabolism and improve cognition (Monti et al., 2020).

Alterations of brain metabolites have been reported in depressed patients, suggesting that a similar mechanism could underlie the psychopathological consequences of COVID-19. In particular, reduced levels of GSH have been observed in depressed patients (Nobis et al., 2020), whereas higher glutamate levels have been showed in unmedicated depressed patients. Further, GSH levels in the occipital cortex have been negatively associated with anhedonia severity whereas glutamate levels correlate with depression severity (Lapidus et al., 2014).

Considering the shared potential protective role of GSH both in COVID-19 and in depressed patients we investigated the possible association between GSH levels in the ACC, depressive symptomatology and WMH in COVID-19 survivors. Further, being GSH involved in the immune response we investigated the association between indices of inflammation and brain GSH levels.

2. Methods

2.1. Participants and data collection

Forty-nine participants (age 41–70) surviving COVID-19, have been recruited from January 7 to July 13 2021, during an ongoing prospective cohort study on COVID-19 sequelae at IRCCS San Raffaele Hospital in Milan (De Lorenzo et al., 2020). Diagnosis of COVID-19 was made after clinical and radiological findings at the admission to the Emergency Department, as confirmed by positive real-time reverse-transcriptase polymerase chain reaction from a nasopharyngeal and/or throat swab. Exclusion criteria were: intensive care unit treatment during the acute phase, presence of major medical disorders, presence of a coarse brain disorder prior to the onset of COVID-19, recent brain lesions typical of COVID such as multifocal cortical infarcts or microhaemorrhagic lesions. The institutional review board approved the study in accordance with the principles in the Declaration of Helsinki. Written informed consent was obtained from all participants after description of the study. Time between hospital admission and MRI scanning ranges from 3 to 12 months with a mean of 4 months.

Depressive psychopathology was self-rated on the Zung Self-Rating Depression Scale (ZSDS), a valid instrument to differentiate depressed from non-depressed groups in COVID-19 survivors (Mazza et al., 2020a). MRI was obtained within one week after the clinical assessment.

Inflammatory markers (CRP, neutrophils, lymphocytes, and platelets) at hospital admission were extracted from charts and a systemic immune-inflammation index (SII) was calculated (SII = platelets X neutrophils / lymphocytes).

2.2. MRI data processing and statistical methods

MRI scanning was performed on a 3.0 Tesla scanner (Ingenia CX, Philips, The Netherlands) using a 32-channel sensitivity encoding

(SENSE) head coil. A structural MRI study was performed first to rule out brain lesions and to localize the volume of interest (VOI) for the spectroscopy study, acquiring T1 images, T2 fast spin-echo (FSE), and coronal fluid-attenuated inversion recovery (FLAIR) images. T1 and T2-weighted FLAIR images were visually inspected as part of the quality check procedure.

The number and volume of WMH were first observed upon visual inspection and later confirmed via the SPM12 toolbox LST (v. 3.0.0), using the Lesion growth algorithm LGA with the default threshold 0.3.

^{1}H-MRS data were acquired using a point resolved spectroscopy (PRESS) sequence (TR 2000 ms, TE 42 ms, 128 acquisitions) from a VOI of $30 \times 15 \times 15$ mm size positioned at the level of the ACC. Unsuppressed water reference spectra were acquired from the same VOI.

[1]H-MR spectra were then analysed using LCModel version 6.3.0. as described in (Poletti et al., 2020) and the tissue within the MRS voxel was segmented with Gannet 3.1 toolbox (Edden et al., 2014). All subjects had values of Cramér-Rao lower bound less than 20%. Water-scaled metabolite levels referenced to total creatine (Cr+PCr) have been used.

2.3. Statistical analyses

Statistical analyses were performed using STATISTICA (StatSoft Statistica 11, Tulsa, OK, USA). The effect of GSH on the severity of psychopathology and WMH were tested through ANCOVAs adding age, sex, duration of hospitalization, and BMI as nuisance covariates. Tests were 2-tailed and an alpha level of 0.05 indicated statistically significant results.

To test the effect of inflammation on GSH levels, and considering the *a priori* expected significant interaction with other independent factors (age, sex) and the non-normal distribution of inflammatory biomarkers, independent variables (SII, CRP) were entered into a Generalized Linear Model (GLZM) analysis of homogeneity of variances with an identity link function. The significance of the effects was calculated with Wald W^2 test.

Considering the high number of males and the potential impact of smoke and hypertension on brain levels of GSH and WMH, sex differences and the effects of smoke and hypertension have been tested through *t*-test.

3. Results

Clinical and demographic characteristics of the sample as a whole and according to sex are resumed in Table 1. In agreement with our previous findings, females had higher depressive symptoms whereas male had longer duration of hospitalization (Mazza et al., 2020b, 2021b). Females were also younger than males and had fewer WMH. No differences based on smoking status, or presence of hypertension was observed for GSH levels and WMH. Time from hospital discharge until study participation was 61±41 days. No association was observed between the time from discharge to MRI scanning and GSH values or depressive symptoms. Further, no association was observed between GSH levels and GM, WM, and CSF fractions in the MRS voxel.

ACC concentrations of GSH negatively predicted depression scores at the ZSDS ($F = 4.51$; df=1, 43; $\beta= -0.32$; $p = 0.039$) (Figure 1). Further, GSH concentrations negatively predicted the number ($F = 4.21$; $\beta= -0.31$; $p = 0.046$) and the volume of WMH ($F = 4.35$; df=1, 43; $\beta= -0.31$; $p = 0.042$) (Figure 2). The volume of WMH

also positively associated with depressive symptomatology ($F = 6.40$; df=1, 43; $\beta= -0.36$; $p = 0.015$) (Figure 3). Whereas no difference between male and females was observed in the association of GSH concentrations with depressive symptoms and WMH, the association between WMH and depressive symptoms is present in males but not in females. No association was observed between Cr+PCr and WMH and depression.

Finally, systemic inflammation (SII level) predicted GSH concentration in ACC. A GLZM analysis of the effects of SII and CRP at hospital admission on GSH, also considering sex, age, and the change of SII from hospital admission to discharge (delta SII) as factors, showed significant effects of SII (lower GHS in patients with higher SII: $W = 12.74$, $\beta=-0.0001$, $p<0.001$) on GSH levels.

4. Discussion

This is the first study to investigate the effect of brain GSH on post- COVID sequelae. Our main finding is a negative association between GSH level in the ACC and both depressive symptoms, and WMH, suggesting that lower levels of brain GSH may be involved in the development of diffuse cerebral WMH and depression in COVID-19 survivors. Moreover, we found that higher baseline systemic inflammation predicted lower GSH levels.

Although the direct effect of SARS-CoV-2 on the brain is still unclear, during the infection an acute systemic inflammatory status could facilitate the entry of cytokines and other inflammatory mediators in the brain and a subsequent activation of the microglia. Once activated, microglia can enter either an M1 proinflammatory state characterized by the release of proinflammatory molecules and oxidative nitroxidative species, or an alternative M2 state characterized by the release of anti-inflammatory molecules and antioxidants (Lindenau et al., 1998). However, an imbalance between the M1/M2 states may deplete GSH levels, thus raising the oxidative stress. In this context the present findings highlight a negative relationship between systemic inflammation and brain GSH level.

Lower levels of brain GSH and increased oxidative stress have been widely reported both in depressed and in COVID-19 patients (Czarny et al., 2018). In agreement with these findings, here we found that lower GSH levels in the ACC associates with depressive symptomatology in COVID-19 survivors. The ACC is a central structure of the cortico-limbic circuit which is involved in the control of emotions and in the cognitive generation of affect. The ACC has been extensively studied in mood disorders and alterations in grey matter volume and functional connectivity have been reported in depressed patients (Vai et al., 2020). ACC volume is proportional to the severity of mild depressive symptoms in the general population, whereas ACC functional connectivity is proportional to symptoms severity in depressed patients. Interestingly, in a recent study from our group, ACC volume were found to be reduced in post-COVID depressed patients (Benedetti et al., 2021).

WMHs are a manifestation of small vessel disease and their pathophysiology is based on chronically reduced blood flow, although inflammation and oxidative stress are also thought to play a role. Accordingly, WMHs appear to be con-

Table 1 Clinical and demographic characteristics of the sample; severity of depressive symptoms and post-traumatic distress; and medical comorbidities and cardiovascular risk factors.

|	Whole sample mean±SD	males mean±SD	females mean±SD	t/χ p
Age	55.5 ± 8.05	57.44 ± 7.74	50.50 ± 6.72	2.94 0.004
Sex (M/F)	36/13			
Hospitalized (managed at home)	43 (6)	35 (1)	8 (5)	11.31<0.001
Duration of hospitalization (Days)	15.84 ± 15.24	18.72 ± 16.14	7.85 ± 8.64	2.30 0.025
SII at hospitalization	1766.46 ± 1355.29	1855.99 ± 1329.64	1259.14 ± 1515.1	0.99 0.326
CRP at hospitalization (mg/l)	78.25 ± 73.13	84.87 ± 76.87	47.04 ± 43.66	1.25 0.218
BMI	27.30 ± 4.18	27.69 ± 3.09	26.21 ± 6.35	1.09 0.279
White Matter Hyperintensities Volume (ml)	0.92 ± 1.59	1.02 ± 1.63	0.22 ± 0.17	1.83 0.073
White Matter Hyperintensities Number	6.13 ± 4.66	6.94 ± 4.59	3.87 ± 2.44	2.37 0.021
Smoke (Y/N)	16 (33)	14 (12)	2 (11)	1.23 0.267
Hypertension (Y/N)	15 (34)	13 (13)	2 (11)	2.94 0.229
ZSDS Index score	46.61 ± 13.54	43.86 ± 13.44	53.37 ± 11.65	2.29 0.031
GSH/Cr+PCr	0.27 ± 0.02	0.28 ± 0.03	0.27 ± 0.02	0.51 0.610
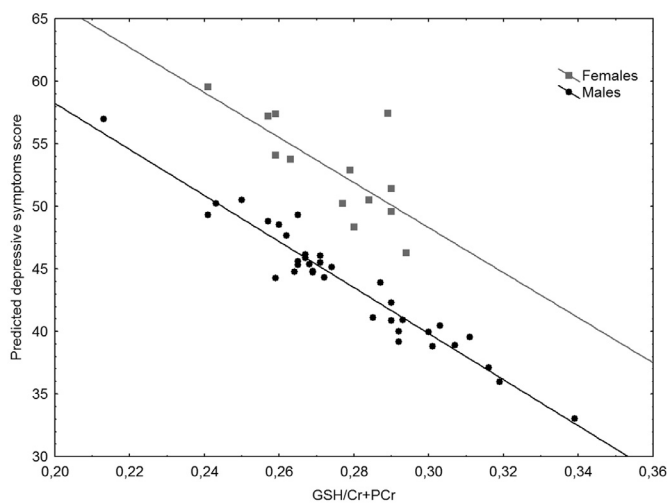
Fig. 1 Effect of Glutathione (GSH) on depressive symptoms as measured with the ZSDS. Predicted score are adjusted for covariates (age, sex, duration of hospitalization, BMI).
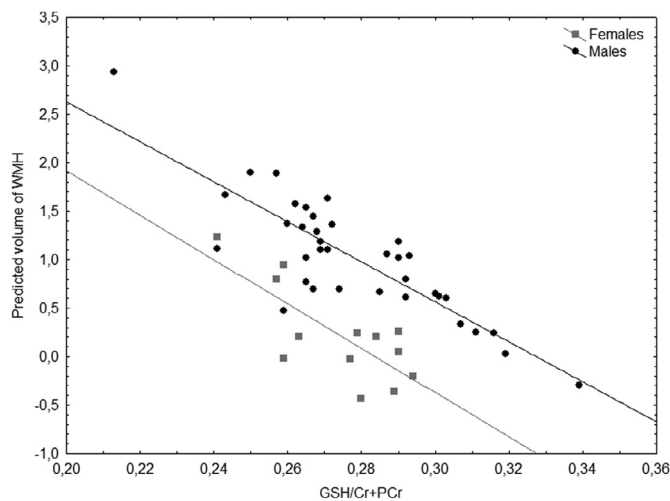

Fig. 2 Effect of Glutathione (GSH) on white matter hyperintensities (WMH). Predicted score are adjusted for covariates (age, sex, duration of hospitalization, BMI).
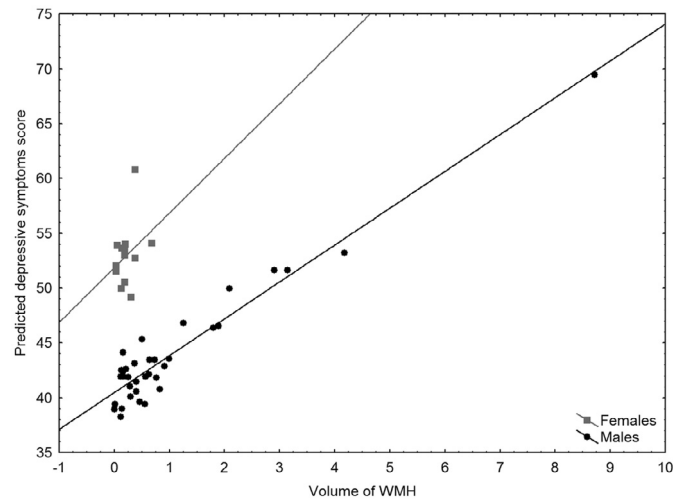
Fig. 3 Effect of white matter hyperintensities (WMH) on depressive symptoms as measured with the ZSDS. Predicted score are adjusted for covariates (age, sex, duration of hospitalization, BMI).

nected to vascular risk factors (such as smoking, hypertension, obesity and diabetes)(Wardlaw et al., 2015) known to be associated with a low-grade inflammatory state and oxidative stress. Interestingly these vascular risk factors are commonly shared between depressed patients and COVID-19 patients. WMHs have been linked to a higher risk of depressive symptomatology and cognitive impairment in stroke and dementia patients (Wardlaw et al., 2015). Considering that GSH is not homogenously distributed and that oligodendrocytes have relatively low levels of GSH and high levels of iron, making them more vulnerable to oxidative stress (Rae and Williams, 2017), we could speculate that the lower GSH level observed in our cohort of post COVID-patients could facilitate damages to the WM microstructure and explain the association between GSH depletion and increased WMHs. Furthermore, axonal suffering during COVID-19 has been previously revealed by higher blood levels of neurofilament light chain, a cytoskeletal filament protein of central and peripheral neurons which is released during disease progression in a variety of neurological diseases, and which can be an indicator of brain damage during COVID-19 (De Lorenzo et al., 2021). Interestingly, WMHs volume was found to be associated both with lower GSH levels in the ACC, underling the role of oxidative stress in their development, and with depressive symptomatology, as is also the case in patients that develop depression late in life (Herrmann et al., 2008). The effect of WMHs on depressive symptomatology was evident only in males, while no effect was found in females, despite the presence of higher depressive scores; this might suggest two different pathophysiological routes for the development of post COVID-19 depressive symptomatology, in males being linked to a higher degree of vascular risk factors, small vessel disease and the development of WMHs. In agreement with a higher incidence of COVID-19 in males, our sample was unbalanced for sex, further, the females group was small thus severely limiting the generalizability of this finding.

Taken together these findings suggest a shared pathophysiology between GSH levels in ACC, WMHs volume and depressive symptomatology in patients surviving COVID-19 infection. We speculate that inflammation and oxidative stress triggered by the viral infection could further reduce brain GSH levels, impairing the brain oxidative balance (reflected in lower GSH concentration in ACC) and inducing endothelial and small vessel dysfunction. These pathophysiological alterations could underlie the development of WMH and could also confer a higher vulnerability for the development of depressive and post traumatic symptomatology after severe COVID-19 infection.

Limitation of the study include the widely heterogeneous drug treatments administered during the course of the illness that could have influenced GSH levels; the different timing of MRI acquisitions from hospital discharge; and the correlational nature of the study which hampers causa interpretation of our finding. Finally, although WMHs were mainly localized near ventricles and in frontal and parietal regions they were not co-localized with the GSH measurement. Levels of GSH have been reported to be correlated between cortical regions so we can hypothesize that GSH levels measured in the ACC are reflective of those of other brain regions where WMHs are preferentially located. However, future studies are needed to further investigate this issue with a multi-voxel approach and a more precise localization of WMHs.

In conclusion, these limitations do not bias the main finding of overlapping associations of GSH levels in ACC, WMH and severity of depression in COVID-19 survivors and the central role of systemic inflammation underlying the long-term sequelae of SARS-Cov2 infection, thus warranting interest for further study of oxidative stress and antioxidants in the post-acute COVID-19 syndrome. Further, future studies should investigate whether treatment with precursors of GSH such as N-Acetyl-Cysteine may dampen the detrimental effect of COVID-19 on the brain and of the neuropsychiatric sequelae of the disease.

Contributors

FB and SP conceived the study. MGM, MP, and FB contributed to the inclusion of patients and acquisition of the data. SP and MP designed the analysis. SP and MP carried out

the analysis and interpreted the data, with contributions from FB, MGM, and MP. SP and MP wrote the initial draft of the manuscript. All authors contributed to the final version, gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Role of funding source

None.

Conflict of Interest

None.

Acknowledgments

References

Benedetti, F., Palladini, M., Paolini, M., Melloni, E., Vai, B., De Lorenzo, R., Furlan, R., Rovere-Querini, P., Falini, A., Mazza, M.G., 2021. Brain correlates of depression, post-traumatic distress, and inflammatory biomarkers in COVID-19 survivors: a multimodal magnetic resonance imaging study. Brain Behav Immun Health, 100387.

Boroujeni, M.E., Simani, L., Bluyssen, H.A.R., Samadikhah, H.R., Zamanlui Benisi, S., Hassani, S., Akbari Dilmaghani, N., Fathi, M., Vakili, K., Mahmoudiasl, G.R., Abbaszadeh, H.A., Hassani Moghaddam, M., Abdollahifar, M.A., Aliaghaei, A., 2021. Inflammatory Response Leads to Neuronal Death in Human Post-Mortem Cerebral Cortex in Patients with COVID-19. ACS Chem. Neurosci. 12, 2143-2150.

Czarny, P., Wigner, P., Galecki, P., Sliwinski, T., 2018. The interplay between inflammation, oxidative stress, DNA damage, DNA repair and mitochondrial dysfunction in depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 80, 309-321.

De Lorenzo, R., Conte, C., Lanzani, C., Benedetti, F., Roveri, L., Mazza, M.G., Brioni, E., Giacalone, G., Canti, V., Sofia, V., 2020. Residual clinical damage after COVID-19: a retrospective and prospective observational cohort study. PLoS One 15, e0239570.

De Lorenzo, R., Loré, N.I., Finardi, A., Mandelli, A., Cirillo, D.M., Tresoldi, C., Benedetti, F., Ciceri, F., Rovere-Querini, P., Comi, G., 2021. Blood neurofilament light chain and total tau levels at admission predict death in COVID-19 patients. J. Neurol. 1-7.

Guloyan, V., Oganesian, B., Baghdasaryan, N., Yeh, C., Singh, M., Guilford, F., Ting, Y.S., Venketaraman, V., 2020. Glutathione Supplementation as an Adjunctive Therapy in COVID-19. Antioxidants (Basel) 9.

Herrmann, L.L., Le Masurier, M., Ebmeier, K.P., 2008. White matter hyperintensities in late life depression: a systematic review. J. Neurol. Neurosurg. Psychiatry 79, 619-624.

Holmay, M.J., Terpstra, M., Coles, L.D., Mishra, U., Ahlskog, M., Oz, G., Cloyd, J.C., Tuite, P.J., 2013. N-Acetylcysteine boosts brain and blood glutathione in Gaucher and Parkinson diseases. Clin. Neuropharmacol. 36, 103-106.

Laforge, M., Elbim, C., Frere, C., Hemadi, M., Massaad, C., Nuss, P., Benoliel, J.J., Becker, C., 2020. Tissue damage from neutrophil-induced oxidative stress in COVID-19. Nat. Rev. Immunol. 20, 515-516.

Lapidus, K.A., Gabbay, V., Mao, X., Johnson, A., Murrough, J.W., Mathew, S.J., Shungu, D.C., 2014. In vivo (1)H MRS study of potential associations between glutathione, oxidative stress and anhedonia in major depressive disorder. Neurosci. Lett. 569, 74-79.

Lindenau, J., Noack, H., Asayama, K., Wolf, G., 1998. Enhanced cellular glutathione peroxidase immunoreactivity in activated astrocytes and in microglia during excitotoxin induced neurodegeneration. Glia 24, 252-256.

Mazza, M.G., De Lorenzo, R., Conte, C., Poletti, S., Vai, B., Bollettini, I., Melloni, E.M.T., Furlan, R., Ciceri, F., Rovere-Querini, P., Benedetti, F., 2020a. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. Brain Behav. Immun. 89, 594-600.

Mazza, M.G., De Lorenzo, R., Conte, C., Poletti, S., Vai, B., Bollettini, I., Melloni, E.M.T., Furlan, R., Ciceri, F., Rovere-Querini, P., group, C.-B.O.C.S., Benedetti, F., 2020b. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. Brain Behav. Immun. 89, 594-600.

Mazza, M.G., Palladini, M., De Lorenzo, R., Bravi, B., Poletti, S., Furlan, R., Ciceri, F., group, C.-B.O.C.S., Rovere-Querini, P., Benedetti, F., 2021a. One-year mental health outcomes in a cohort of COVID-19 survivors. J. Psychiatr. Res. 145, 118-124.

Mazza, M.G., Palladini, M., De Lorenzo, R., Magnaghi, C., Poletti, S., Furlan, R., Ciceri, F., Rovere Querini, P., Benedetti, B., 2021b. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. Brain Behav. Immun..

Monti, D.A., Zabrecky, G., Leist, T.P., Wintering, N., Bazzan, A.J., Zhan, T., Newberg, A.B., 2020. N-acetyl Cysteine Administration Is Associated With Increased Cerebral Glucose Metabolism in Patients With Multiple Sclerosis: an Exploratory Study. Front Neurol 11, 88.

Najt, P., Richards, H.L., Fortune, D.G., 2021. Brain Imaging in Patients with COVID-19: a Systematic Review. Brain, behavior, & immunity-health, 100290.

Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M.V., McGroder, C., Stevens, J.S., Cook, J.R., Nordvig, A.S., Shalev, D., Sehrawat, T.S., Ahluwalia, N., Bikdeli, B., Dietz, D., Der-Nigoghossian, C., Liyanage-Don, N., Rosner, G.F., Bernstein, E.J., Mohan, S., Beckley, A.A., Seres, D.S., Choueiri, T.K., Uriel, N., Ausiello, J.C., Accili, D., Freedberg, D.E., Baldwin, M., Schwartz, A., Brodie, D., Garcia, C.K., Elkind, M.S.V., Connors, J.M., Bilezikian, J.P., Landry, D.W., Wan, E.Y., 2021. Post-acute COVID-19 syndrome. Nat. Med. 27, 601-615.

Nobis, A., Zalewski, D., Waszkiewicz, N., 2020. Peripheral Markers of Depression. J Clin Med 9.

Poletti, S., Mazza, M.G., Vai, B., Lorenzi, C., Colombo, C., Benedetti, F., 2020. Proinflammatory Cytokines Predict Brain Metabolite Concentrations in the Anterior Cingulate Cortex of Patients With Bipolar Disorder. Front Psychiatry 11, 590095.

Polonikov, A., 2020. Endogenous Deficiency of Glutathione as the Most Likely Cause of Serious Manifestations and Death in COVID-19 Patients. ACS Infect Dis 6, 1558-1562.

Rae, C.D., Williams, S.R., 2017. Glutathione in the human brain: review of its roles and measurement by magnetic resonance spectroscopy. Anal. Biochem. 529, 127–143.

Suhail, S., Zajac, J., Fossum, C., Lowater, H., McCracken, C., Severson, N., Laatsch, B., Narkiewicz-Jodko, A., Johnson, B., Liebau, J., Bhattacharyya, S., Hati, S., 2020. Role of Oxidative Stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) Infection: a Review. Protein J. 39, 644–656.

Vai, B., Parenti, L., Bollettini, I., Cara, C., Verga, C., Melloni, E., Mazza, E., Poletti, S., Colombo, C., Benedetti, F., 2020. Predicting differential diagnosis between bipolar and unipolar depression with multiple kernel learning on multimodal structural neuroimaging. Eur. Neuropsychopharmacol. 34, 28–38.

Wardlaw, J.M., Valdes Hernandez, M.C., Munoz-Maniega, S., 2015. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J. Am. Heart Assoc. 4, 001140.