After recovering from COVID-19, a large proportion of patients suffer from long-lasting post-COVID symptoms, even after mild or asymptomatic forms of the disease. The most frequent, persistent, and disabling symptoms of long-COVID are neurological, known as ‘‘neuro-long COVID”. In this article, the Italian researchers used ‘‘paired-pulse” transcranial magnetic stimulation (ppTMS) to investigate the motor cortex excitability in a group of individuals diagnosed with post-COVID syndrome and cognitive deficits.

The TMS is a non-invasive research tool used to investigate cortical excitability, connectivity, and plasticity. γ -aminobutyric acid (GABA) and glutamate regulate the neurobiochemical circuits studied by the pp TMS protocols. Intracortical facilitation (ICF) reflects glutamatergic signaling. Reduced ICF was found in patients with dementia. Short-interval intracortical inhibition (SICI) reflects fast inhibitory post-synaptic potentials in corticospinal neurons mediated through $GABA_A$ receptors and short-latency afferent inhibition related to cholinergic circuits. Long-interval intracortical inhibition (LICI) depends on slow inhibitory post-synaptic potentials mediated through $GABA_B$ receptors. Short-latency afferent inhibition (SAI) reflects the excitatory effect of cholinergic thalamocortical projections on the inhibitory GABAergic cortical network. SAI is thought to be a sensitive biomarker of neurodegenerative diseases and dementia.

GABA, as a major inhibitory neurotransmitter in the central nervous system, activates GABAA and GABAC receptors (ligand-gated Cl-channels), and G protein-coupled GABAB receptors. The activation of GABAB receptors generates slow inhibitory postsynaptic potentials. Prior studies reported that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) depletes GABA through several mechanisms: 1. The binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) receptor disrupts the protective function of the renin-angiotensin system and lowers GABA. 2. SARS-CoV-2 S protein contains a GABA-mimicking sequence or a short linear motif that can usurp host GABAergic signaling directly. 3. The SARS-CoV-2 proteins nonstructural protein 6 (NSP6), open reading frame 8 (ORF8), and open reading frame 3 (ORF3a) interact directly with host mammalian target of rapamycin complex 1 (mTORC-1), interleukin 17 (IL-17), and transmembrane protein 16F (TMEM16F), inducing premature endothelial cell senescence, a phenotype characterized by low GABA. 4. The SARS-CoV-2 protein ORF3a interacts with toll-like receptor 4, triggering the senescence of endothelial cells and lowering GABA. 5. The SARS-CoV-2 nonstructural protein 4 (NSP4), nonstructural protein 8 (NSP8), and open reading frame 9c (ORF9c) decrease GABA by disrupting the mitochondria and triggering vascular senescence. (Afera A. et al. Neuronal and Non-Neuronal GABA in COVID-19: Relevance for Psychiatry, Reports

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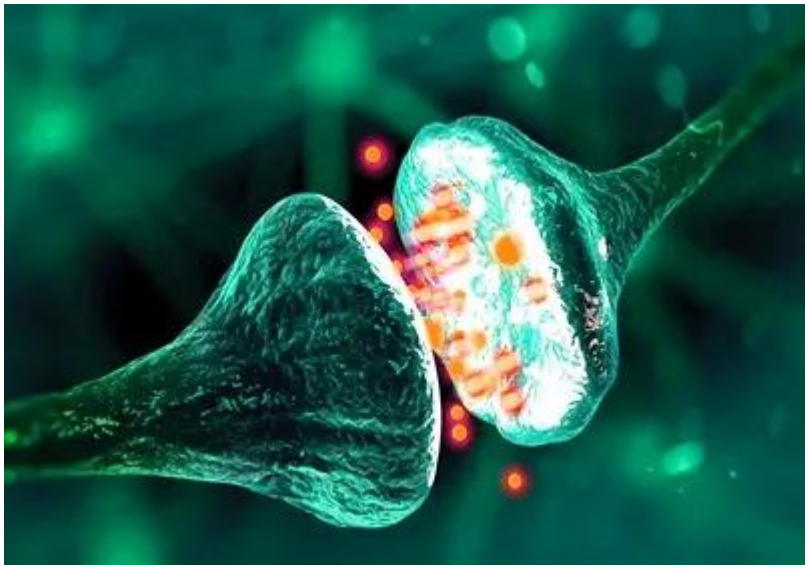
The researchers emphasized that GABA depletion caused by SARS-CoV-2 may explain the neuropsychiatric symptoms observed in patients with acute COVID-19 and neuro-long-COVID, such as anxiety, depression, sleep disorders, posttraumatic stress disorder, and cognitive disorders.



***About the Study and** Results*

The study included 18 right-handed patients diagnosed with neuro-long COVID syndrome and cognitive deficits. 12 were women, and the mean age was 50 ± 11 years. During the acute phase of SARS-CoV-2 infection, the patients were not hospitalized. The study also included 16 healthy controls.

All participants were examined for the presence of symptoms lasting for more than 12 weeks following the acute SARS-CoV-2 infection, such as fatigue, respiratory symptoms, palpitations, gastrointestinal tract symptoms, myalgia, joint pain, tinnitus, vertigo, visual disturbances, and fever. The participants were especially examined for persistent neurological symptoms, including paraesthesia, anosmia/ageusia, cognitive deficits, mood disturbances, headache, hemiparesis, and insomnia.

The Montreal Cognitive Assessment (MoCA) test evaluated cognitive impairment, whereas

psychometrically validated tests evaluated attention and executive functions. The Fatigue Severity Scale (FSS) was used to assess fatigue in daily activities. In patients with neuro-long COVID syndrome and cognitive impairments, median MoCA corrected scores were significantly lower than in healthy controls. Also, most of them performed sub-optimally on the neuropsychological and executive function assessment and displayed a high level of fatigue on the FSS.

The ppTMS protocols were used to evaluate the inhibitory and excitatory intracortical networks, and to investigate the resting motor threshold (RMT), the amplitude of the motor evoked potential (MEP), short intracortical inhibition (SICI), intracortical facilitation (ICF), long-interval intracortical inhibition (LICI), and short-afferent inhibition (SAI) over the motor cortex. The results showed that RMT, mean MEP, and SICI did not differ significantly between patients diagnosed with long COVID and cognitive deterioration and healthy controls.

However, individuals with neuro-long COVID syndrome had significantly reduced LICI, as well as an abnormal pattern of ICF (also found to be abnormal in dementia patients). As LICI depends on slow inhibitory post-synaptic potentials mediated through $GABA_B$ receptors, and ICF reflects glutamatergic signaling, the main finding of this study is altered GABAergic and glutamatergic regulation of the motor cortex excitability in patients with long COVID syndrome and cognitive deterioration.

The authors stated that abnormal GABAergic and glutamatergic regulation, but normal cholinergic regulation of the motor cortex excitability, may reflect more widespread changes in the regulatory crosstalk between frontal and prefrontal cortical hubs.

Conclusion

According to these findings, TMS can be a useful non-invasive electrophysiological tool for assessing cortical excitability in patients diagnosed with neuro-long COVID syndrome.

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Journal Reference

Manganotti P et al. Deficient GABABergic and glutamatergic excitability in the motor cortex of patients with long-COVID and cognitive impairment. Clinical Neurophysiology 151 (2023) 83–91. https://doi.org/10.1016/j.clinph.2023.04.010


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