White matter changes and cognitive impairment in Long-COVID patients with fatigue

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Introduction

Neurological long-term complications of COVID19 are increasingly recognized and characterized [1]. Indeed, COVID19 can be associated with CNS pathologies, such as cerebrovascular events and neuroinflammation [2]. First reports have described neuropsychological deficits [3,4] and structural brain damage [4,5]. Here, we present first results of the CAMINO study on neurocognitive and diffusion imaging changes in patients with persistent new onset neurological symptoms after COVID19.

Methods

We recruited 50 patients (39f/11m, age 44.9±10.2 years) from the post-COVID outpatient clinic at the Department of Neurology at Charité–Universitätsmedizin Berlin between April-December 2021. Inclusion criteria were new onset neuropsychiatric symptoms for at least 3 months after a confirmed infection with SARS-CoV-2 and no history of neurological or psychiatric diseases. A control group of 46 healthy participants was matched regarding age, sex & education.

The CAMINO study protocol included a structured neuropsychological assessment of memory, attention, executive functions, and spatial navigation, and a 3T MRI acquisition. The diffusion-weighted scan (multiband EPI, 1.5x1.5x1.5mm, 98 diffusion directions, 1.5mm slice thickness, bvalue=3000s/mm²) was analysed using the FSL FDT Diffusion Toolbox [2]. Preprocessing included correcting for eddy currents, brain extraction, and fitting of diffusion tensor models. Diffusion maps were processed using tract-based spatial statistics (TBSS)[3] and Randomise with FDR correction [4]. Additionally, we segmented high-resolution T1-weighted scans (MPRAGE, 1x1x1mm³) using FSL FIRST [5] to obtain volume estimates and extract microstructural integrity scores for subcortical structures. The study was approved by the ethics committee of Charité–Universitätsmedizin Berlin.

Results

At a median of 8.4 (3.2-19.8) months after acute SARS-CoV-2 infection, we observed neuropsychological impairments of higher attentional functions *(80%, 40/50 of the patients affected)),* processing speed *(64%, 32/50),* executive functions *(46%, 23/50),* working memory *(36%, 18/50),* and verbal episodic memory *(30%, 15/50).* Severe motor *(86%, 43/50)* and cognitive fatigue *(82%, 41/50)* were the most prevalent neuropsychiatric features *(FSMC: 74.5±11.2).* Moreover, we observed increased levels of depressive *(BDI-II: 16.6±6.1)* and anxiety symptoms *(BAI: 14.7±6.9).*

Diffusion imaging revealed significantly reduced axial diffusivity (AD) of the left amygdala *(7.33*10^{-4} (±0.59*10^{-4}, patients) vs. 7.67*10^{-4} (±0.59*10^{-4}, controls), F(1,93)=4.37, p=.039)* and right putamen *(6.22*10^{-4} (±0.36*10^{-4}) vs. 6.53*10^{-4} (±0.33*10^{-4}), F(1,93)=6.76, p=.011)*. There was no evidence for damage to major white matter tracts on whole brain imaging, including the corpus callosum and association fibres such as the superior longitudinal fasciculus, uncinate, fornix, and cingulum.

Clinical scores were significantly associated with white matter and subcortical integrity in patients. Higher anxiety scores correlated with aberrant radial diffusivity (RD) of the amygdala *(left: r=-.38, p=.008; right: r=-.43, p=.002)* and hippocampus *(left: r=-.36, p=.011; right: r=-.40, p=.004)*. Additionally, increased fatigue was related to altered RD of the caudate nucleus *(left: r=-.44, p=.002; right: r=-.04; p=.042 (n.s. after Benjamini-Hochberg correction))* and amygdala *(left: r=-.56, p<.001; right: r=-.50, p<.001)*. Lower attention and executive functioning were associated with integrity of the right uncinate fasciculus *(Trail Making Test B, FA: r=-.45, p=.001; Stroop test errors, RD: r=-.40, p=.005)*. Lastly, impaired spatial navigation performance was accompanied by lower hippocampal volumes *(left: r=.49, p<.001; right: r=.38, p=.008)* and decreased integrity of hippocampal white matter tracts, including fornix *(FA: r=.37, p=.009)* and cingulum *(MD, left: r=-.42, p=.002; right: r=-.41, p=.003)*.

Conclusions

Impairment of higher attentional and executive functions, affective symptoms, and severe fatigue are frequent presentations of Long-COVID patients with neurological complaints. Our analyses show that, in the absence of global white matter damage, compromised microstructural integrity of subcortical hubs contributes to cognitive and neuropsychiatric symptoms in these patients. Future research will determine whether these neuronal correlates represent transient or persistent changes and shed light on their neuroimmunological mechanisms.

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