

Abnormal Brain Diffusivity in Participants with Persistent Neuropsychiatric Post COVID-19 Syndrome



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Introduction

- ❖ Neuropsychiatric symptoms are common symptoms in post-COVID syndrome, even in non-hospitalized recoverees (Taquet M et al 2021).
- ❖ Typical post-COVID neuropsychiatric symptoms: fatigue, concentration problems (“brain fog”), headache, anosmia, hypogeusia, anxiety, and emotional stress.
- ❖ The causes of these symptoms are unclear:
 - ✓ Postmortem studies: glial cell activation and immune cell infiltration (Pröbstel AK et al. 2021).
 - ✓ Plasma and CSF during acute infection: ↑glial fibrillary acidic protein (GFAP, glial activation marker) and ↑ neurofilament light (NfL, axonal damage marker) (Kanberg N et al 2020).
 - ✓ However, no evidence of persistent neuroinflammation.
- ❖ Prior studies using diffusion tensor imaging (DTI) found conflicting results and were not focused on the post-COVID syndrome.
- ❖ DTI: visualized tissue microstructure by measuring water molecular movement and was used in this study

Aims and Hypotheses

- ❖ Is chronic neuroinflammation the cause?

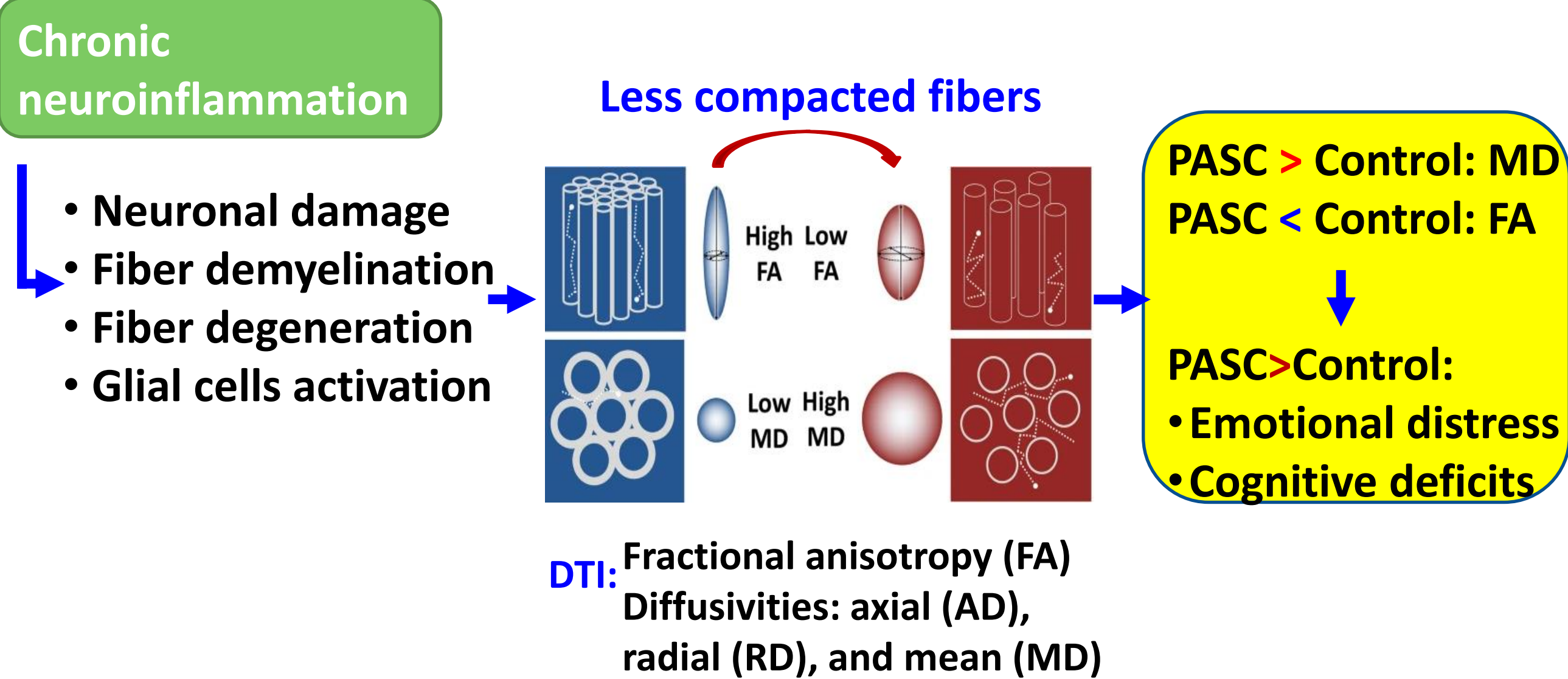


Table 1. Participants Features

	Control n=24	P-COVID n=23	p-value
Age (years, mean±SD)	44.3±12.5	44.1±12.2	0.726 ^a
Gender (# woman, %)	13 (54.2%)	15 (65.2%)	0.635 ^b
Race (#White / #Non-White)	9/15	14/9	0.190 ^b
Index of social position, (mean±SD)	29.3±14.8	30.3±14.7	0.208 ^a
Education level			0.134 ^b
High School or below (#, %)	6 (25%)	11 (47.8%)	
College (#, %)	8 (33.3%)	8 (24.8%)	
Above college (#, %)	10 (41.7%)	4 (17.4%)	
Vascular Disease Risk Factors			
Body Mass Index, (mean±SD)	27.7±6.6	32.0±8.3	0.056 ^a
Hypertension (#, %)	1 (4.2%)	6 (26.1%)	0.09 ^b
Diabetes (#, %)	0	4 (17.4%)	0.107 ^c
White matter lesion (#, %)	15 (62.5%)	15 (65.2%)	0.846 ^b
History of Substance use			
Lifetime tobacco use (#, %)	9 (37.5%)	9 (39.1%)	1 ^b
Past month tobacco use (#, %)	1 (4.2%)	1 (4.3%)	1 ^c
Lifetime marijuana use (#, %)	6 (25%)	10 (43.5%)	0.304 ^b
Past month marijuana use (#, %)	1 (4.2%)	1 (4.3%)	1 ^c
Lifetime alcohol use (#, %)	20 (83.3%)	19 (82.6%)	1 ^b
Past month alcohol use (#, %)	17 (70.8%)	15 (60%)	0.920 ^b

P-COVID=participant group with post-COVID syndrome. a: T test, b: Chi-Square test, c: Fisher's Exact test.

Figure 2. Percentage of self-report symptoms

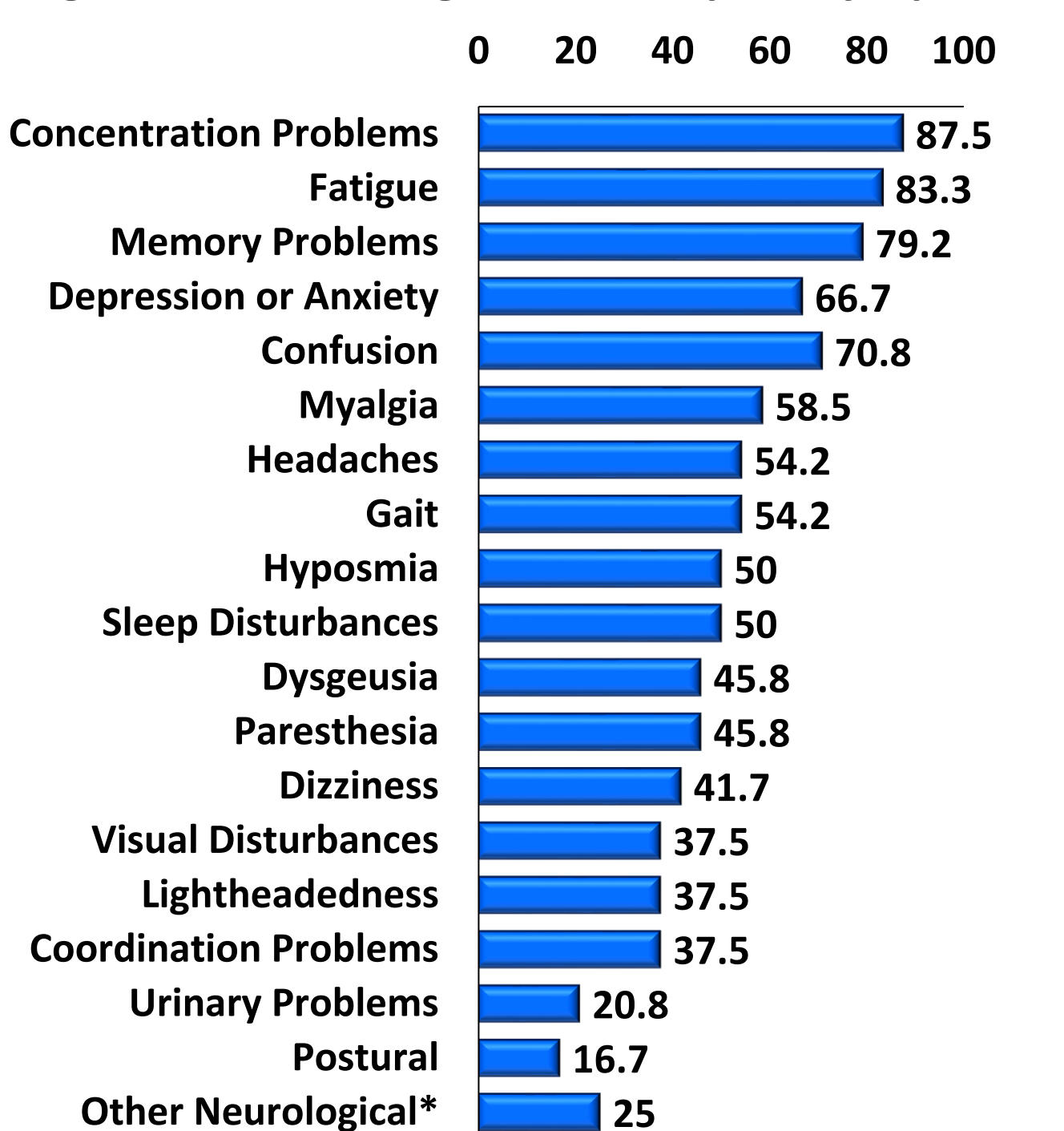
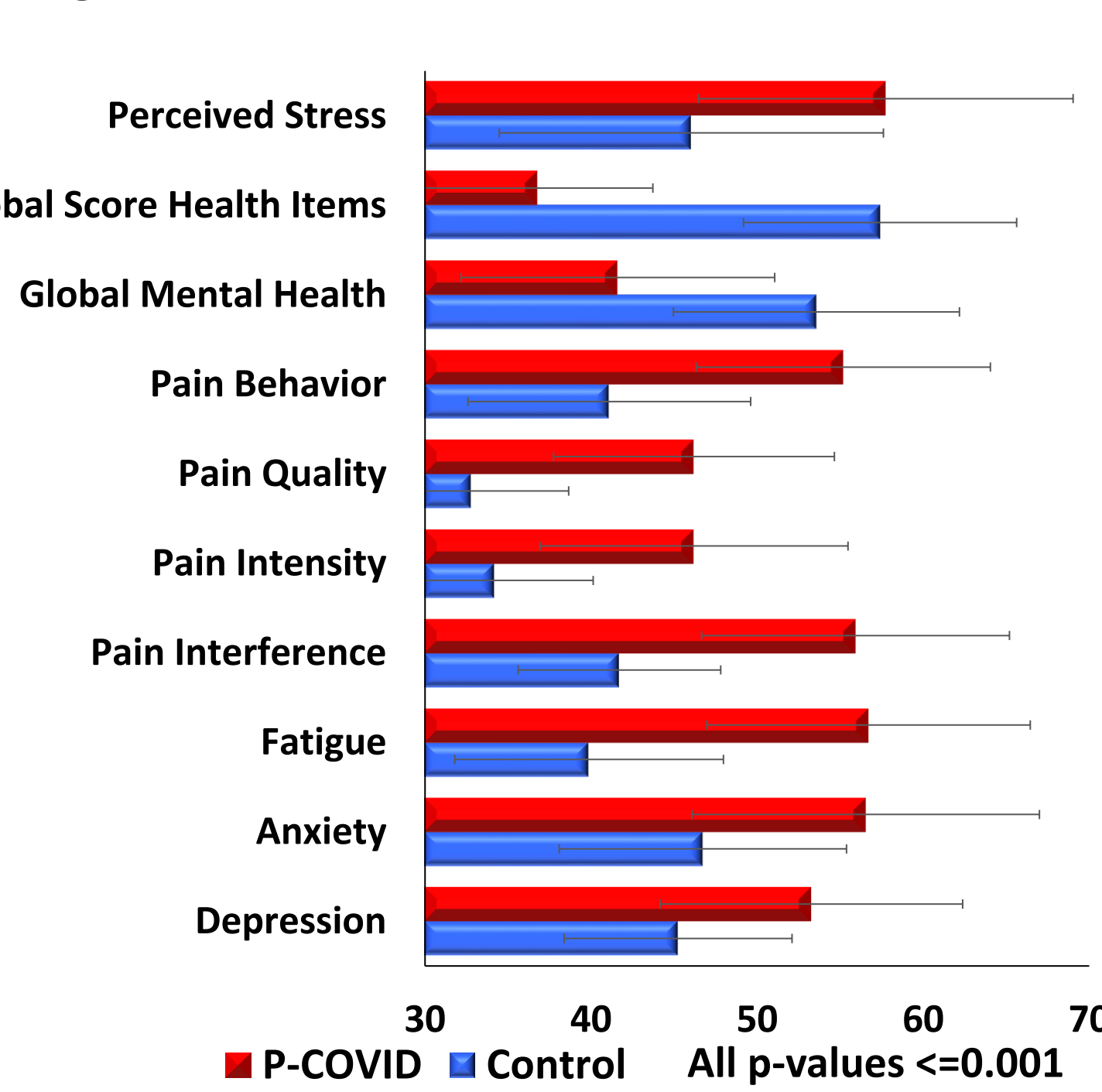


Figure 3. T scores on PROMIS emotional distress



Methods and Materials

- ❖ Clinical Measures:
 - ✓ Cognitive performance (NIH Toolbox®): fully corrected T scores for 6 domains: Attention, Episodic Memory, Working Memory, Language, Executive Function, and Processing Speed; and three composite scores: fluid cognition crystallized cognition, total cognition
 - ✓ Neuropsychiatric symptoms (PROMIS): fatigue, stress, depression, anxiety, pain, etc.
- ❖ DTI Measures: FA, MD, AD, RD
- ✓ ROIs: 9 major white matter tracts (WM) and 6 subcortical brain regions.
- ✓ 3 T Scanner, (axial, TR/TE=3700/88mm, FOV=220mm, 128*128 matrix, thickness=4mm, four b=0 scans, 12 diffusion directions with b=1000s/mm²).
- ✓ Image process: MRICloud (<http://www.MRICloud.org>)
- ❖ Statistic Model: Linear Mix model, with hemisphere and sub-region as repeated factors, subject ID as a random factor, and age and sex as covariates.

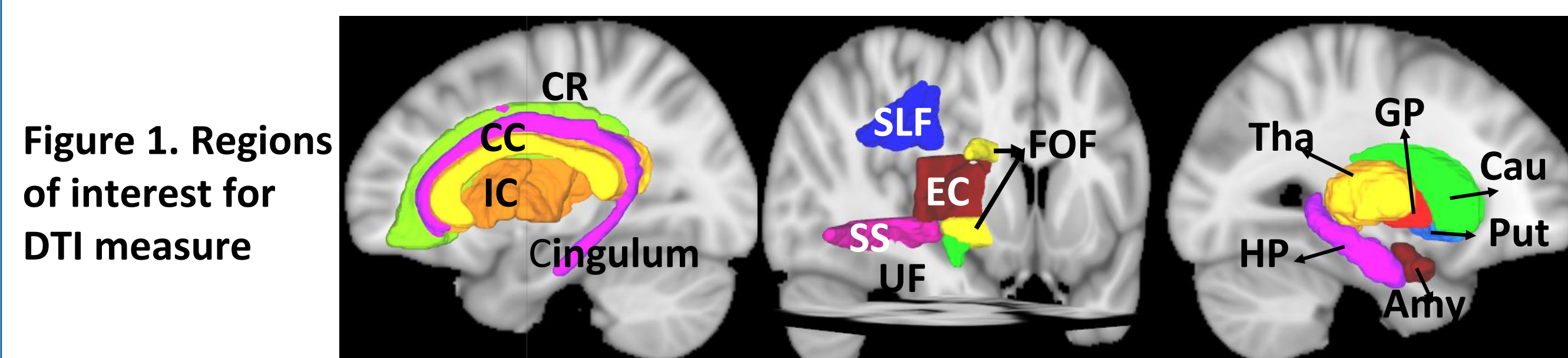


Figure 1. Regions of interest for DTI measure. CC=corpus callosum (genu, body, Splenium), CR=corona radiata (anterior, posterior, superior), IC=internal capsule (anterior posterior, retrolenticular), EC=external capsule, cingulum (cingulum cingulat, cingulum hippocampal), SS=sagittal stratum, FOF=frontal-occipital fasciculus (superior, inferior), SLF=superior longitudinal fasciculus, UF=uncinated fasciculus, Amy=amygdala, HP=hippocampus, Cau=caudate nucleus, Put=putamen, GB=globus pallidus, Tha=thalamus.

Figure 4. Participants with PASC had higher FA and lower MD than control participants.

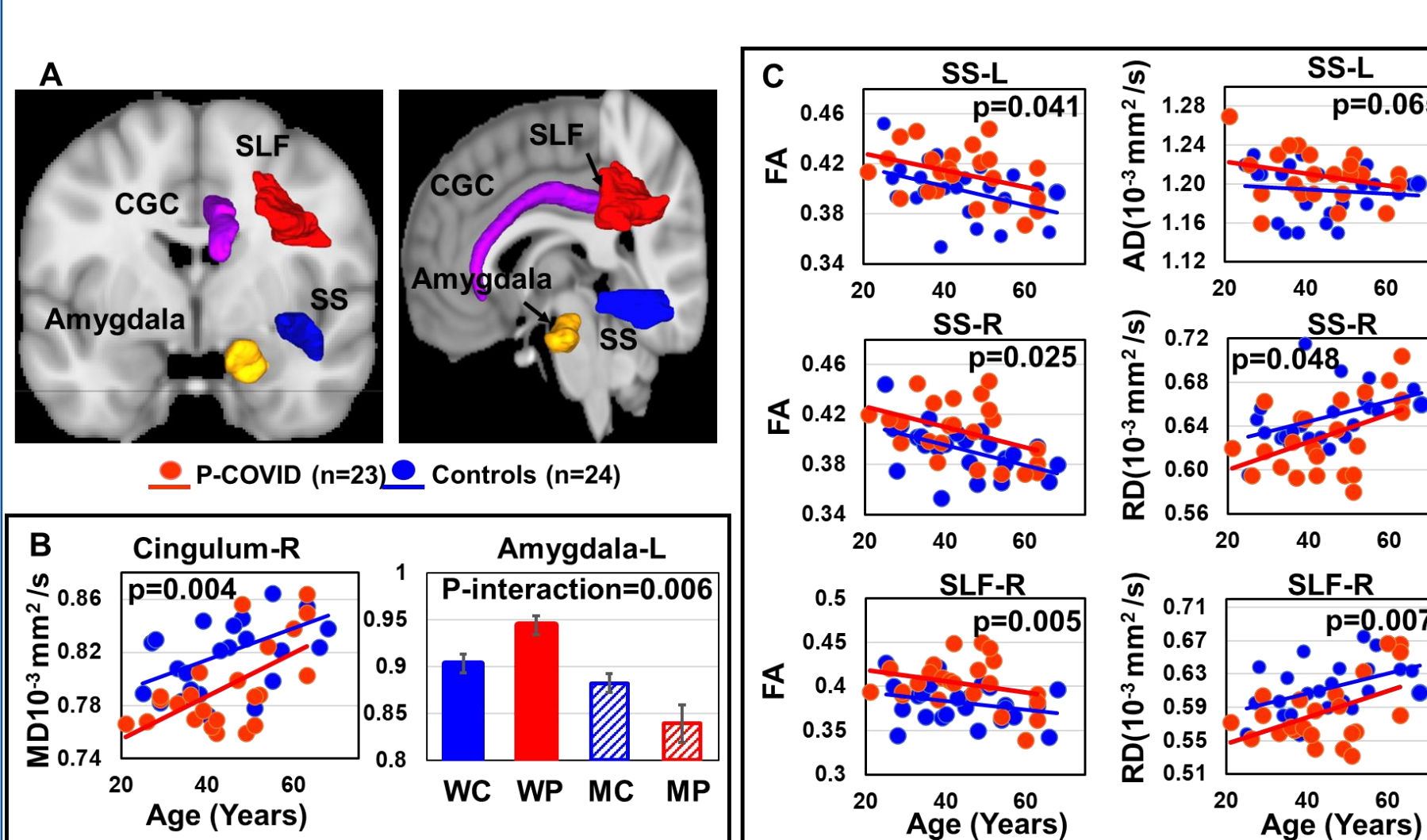
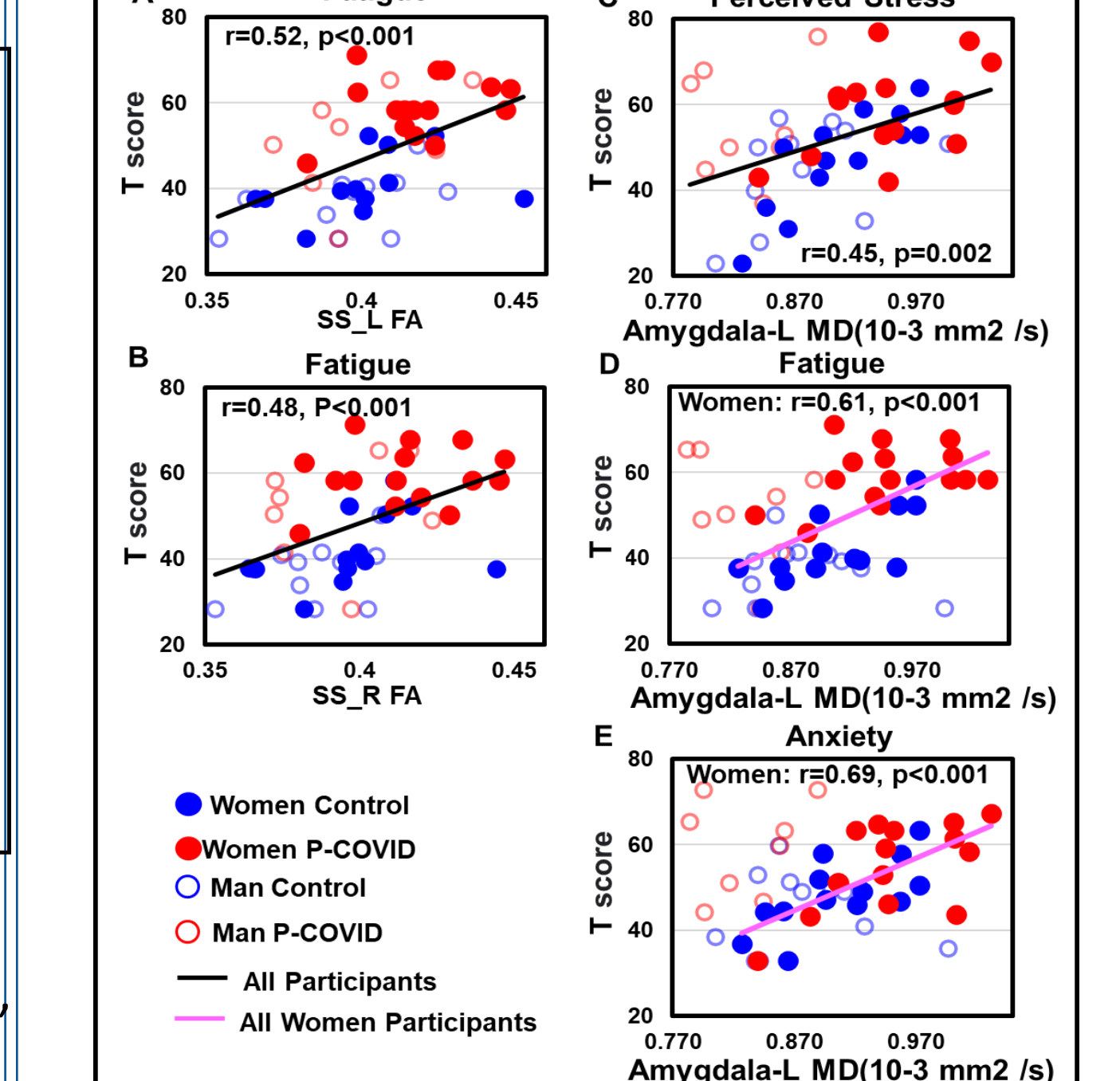


Figure 5. DTI Measures Predict Psychological Function.



WC=woman control, WP=women with the post-COVID syndrome, MC=man control, MP= men with the post-COVID syndrome. L-left, R=right.

Discussion

- ❖ P-COVID group had normal cognitive performance despite their complaints about ‘brain fog’ and memory problems.
 - ✓ Different from hypothesis but consistent with Dressing et al. 2021.
 - ✓ Future studies should use objective methods to evaluate cognitive function.
- ❖ P-COVID had higher T scores than Controls on stress and emotional distress
 - ✓ Consistent with the hypothesis and almost all previous studies, such as Premraj L, et al. J Neurol Sci. 2022, Taquet M, et al. PLoS Med. 2021.
- ❖ P-COVID had higher FA and lower MD than Controls
 - ✓ Indicating a more coherent and compact white matter fiber structure.
 - ✓ Does not support the chronic neuroinflammation hypothesis.
- ❖ Our study suggests a possible role of stress in the brain of COVID-19 recoverees
 - ✓ Stress causes neuron activation and glucocorticoids release, both trigger oligodendrogenesis to enhance myelination (Breton JM et al. 2021, Jak AJ et al. 2020), which leads to more compact and coherent fiber.
 - ✓ Stress causes enhanced neuronal dendritic branching in amygdala, which is critical for rodents to develop anxiety-like behavior after being exposed to stressor (Chattarji Set al. 2015).
 - ✓ Higher WM FA predicted greater fatigue in our study, and greater stress, and depression/anxiety in COVID-19 recoverees previously (Benedetti et al. 2021, Yang et al 2021).
 - ✓ COVID-19 related lockdown is stressful→ led to enlarged volume and decreased glucose metabolism in the left amygdala (Salomon et al 2021, Guedj et al 2022).
 - ✓ Trauma exposure ↑ FA and ↓ diffusivities (Sekiguchi et al 2014, Chen et al 2021).

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Acknowledgments

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