CORRESPONDENCE

Reply to "Predominance of visuoconstructive impairment after mild COVID-19?" by Díez-Cirarda et al. 2022

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TO THE EDITOR:

We read with great attention the correspondence by Díez-Cirarda et al. 2022 [1], regarding our recent published study on selective visuoconstructional impairment following mild COVID-19 with inflammatory and neuroimaging findings [2]. We thank the authors for recognizing the relevance of our work and to give us the opportunity to further discuss some of our findings.

The results at the copy component of the Rey–Osterrieth Complex Figure Test (ROCFT) were surprising for our research team, which initially expected deficits in attention, memory and executive functions due to patients' subjective cognitive complaints and initial findings in other COVID-19 studies. While assessing our patients the impairment observed in copy trials immediately called our attention due to its frequency and intensity (examples can be seen in the supplementary files of our manuscript), and were published as a preprint before being submitted as the current study. At that stage, other researchers not directly involved in the study were invited to analyze the drawings, including certified neuropsychologists from the Brazilian Neuropsychological Society, which were equally surprised by those unexpected results.

Performance in the ROCFT-copy trial shows a ceiling effect in typical development adults, while the recall trials usually show a more symmetric distribution [3]. The larger range of possible recall scores might minimize the prevalence of memory deficits. The deficit observed in the copy trial remained significant both using normative data for scoring and when we compared the raw data of a subsample of our patients to an age, sex and education matched sample. In addition, an ANCOVA analysis suggested a more specific deficit in the copy trial since, when it was controlled, the group differences in the recall trials were not significant. Impairment in the ROCF-copy with subsequent normal recall performance had been previously reported, for example, in association with HTLV-1 infection [4] and in patients with cerebellar ataxia [5], suggesting compensation from initial organization and copying strategies.

Thanks to the correspondence, an error came to our attention. The column titles were swapped (*controls* and *patients*): ROCF (copy) was 34.14 ± 2.95 for the control group and 29.22 ± 4.41 for the COVID-19 group. We are submitting an erratum to the journal. In addition, the number of correct pairs in switching fluency for controls should be read 8.76 ± 1.85. We used the Brazilian manual —commercially available from Pearson Clinic in Brazil—for its application, scoring and interpretation [6]. Normative data is available as mean ± standard-deviation for the following age-ranges: 16–20 years - 33.73 ± 2.94 (copy) and 20.31 ± 6.62 (recall), 21–40 years - 32.82 ± 3.19 (copy) and 18.70 ± 6.64 (recall, and 41–60 years - 32.25 ± 3.80 - for copy and 15.98 ± 5.56 for recall). Alternatively, percentiles could also be used for scoring, although it did not significantly change our results. These normative values are similar to those of international studies [3].

Indeed, the specific metrics for each neuropsychological test were not added in the published Table 1, which reports the following measures: *Trail Making Test* (time in seconds), *ROCFT* (total score based on the traditional 18 elements scoring system), verbal fluency (total words for animal and fruits and total number of pair in the switching condition; and 1 min for each condition), Digit Span (number of correct trials × maximum achieved span - Kessels et al. (2008) recommendations [7], Five Point Tests (total unique drawings) and Logical Memory (sum of correct answers).

In regard to the neuroimaging findings, the choice to inspect the statistical parametric maps with no correction for multiple comparisons was made due to the exploratory nature of the study, and we attempted to minimize false-positive findings by using a relatively strict threshold ($p < 0.0005$, two-tailed). We agree that it is important to reassess our findings with correction for multiple comparisons, and this is provided in the attached Table (applying family-wise error—FWE methods). The largest cluster of significant negative correlation between white matter volume and neuropsychological test performance retained statistical significance (FWE, cluster level), and so did one of the clusters of negative correlation between glucose metabolism and test performance (located in the right dorsal anterior cingulate cortex) (FWE, voxel-level).

While addressing the comments, we are urged to consider what awaits ahead in terms of recovery and possible interventions. The catching questions are how the virus promotes these changes and why not everyone recovers after a mild acute phase. The pandemic put the spotlight on the neuroinflammation that follows, not only SARS-Cov-2 infection, but also other systemic inflammatory conditions that compromises the whitte matter resulting in cognitive dysfunctions. We hope the comments were satisfactorily answered and make ourselves available for any further discussion about this very important and timely topic.

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Table 1. Significant correlations between performance on the Rey–Osterrieth Complex Figure Test and neuroimaging measurements of gray and white matter volumes (MRI) and glucose metabolism (FDG-PET).

Brain region[a]	Correlation	Cluster size[b]	Coordinates[c]			Peak Z score[d]	pFWE cluster level[e]	pFWE voxel level[f]
			x	y	z			
Gray matter volume								
No significant correlations.	–	–	–	–	–	–	–	–
White matter volume								
Left and right genu of the corpus callosum, extending to the cingulum bundle	Negative	1426	−6	26	−2	4.32	0.000	0.062
Right fusiform gyrus	Negative	93	32	−22	−26	4.01	0.262	0.186
Right lingual gyrus	Negative	127	30	−44	−8	3.84	0.180	0.307
Right inferior frontal gyrus	Negative	98	40	6	16	3.76	0.248	0.381
Left lingual gyrus	Negative	41	−18	−52	2	3.73	0.486	0.408
Left inferior frontal gyrus	Negative	20	−34	30	−2	3.48	0.633	0.685
Left inferior fronto-occipital fasciculus	Negative	15	−24	4	−8	3.47	0.676	0.691
Left inferior fronto-occipital fasciculus	Negative	15	−32	−10	−8	3.44	0.676	0.727
Right inferior fronto-occipital fasciculus	Negative	13	32	−10	−8	3.43	0.875	0.730
Glucose metabolism (FDG-PET)								
Left inferior temporal gyrus	Positive	34	−56	−46	−22	3.96	0.644	0.400
Left inferior occipital gyrus (superior portion)	Positive	53	−48	−68	−16	3.92	0.476	0.452
Right dorsal anterior cingulate gyrus	Negative	69	8	16	42	4.61	0.365	0.043
Right Rolandic operculum and opercular part of the inferior frontal gyrus	Negative	57	52	8	12	4.48	0.446	0.072
Right inferior occipital gyrus	Negative	62	38	−74	−6	4.15	0.410	0.234
Left calcarine and lingual gyri	Negative	66	−14	−92	−8	3.88	0.384	0.494
Left superior frontal gyrus	Negative	50	−16	60	−8	3.75	0.500	0.643
Left inferior occipital gyrus (inferior portion)	Negative	19	−30	−82	−8	3.46	0.798	0.918
Right medial frontal and orbital frontal gyri	Negative	20	18	54	−4	3.43	0.788	0.934

[a]For the analysis of white matter volumes, the brain regions where voxel clusters were located were identified according to the MRI Atlas of Human White Matter [8]. For the analysis of glucose metabolism, brain regions were identified according to the Automatic Anatomical Labeling Toolbox for SPM12 [9]).
[b]Number of contiguous voxels in each cluster that surpassed the initial cutoff of $p \leq 0.0005$ uncorrected for multiple comparisons.
[c]MNI coordinates of the voxel of maximal statistical significance within each cluster.
[d]*Z*-score for the voxel of maximal statistical significance in each region.
[e]Statistical significance after family-wise error correction for multiple comparisons (cluster level).
[f]Statistical significance after family-wise error correction for multiple comparisons (voxel level).

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AUTHOR CONTRIBUTIONS

Study conception and/or design: JJP, DMM, and MAR-S. Data analysis: JJP, FLSD, GB, DMM, MAR-S. Paper writing and/or revision: JJP, GB, DMM, MAR-S.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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