Association between cerebellum volumes and cognitive functioning

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To the Editor:

There has been an increase in interest towards understanding the implication of the cerebellum in cognition[1] and age-related pathologies affecting cognitive processes.[2,3] Recent publications suggest that cerebellar atrophy contributes to Alzheimer's disease (AD) clinical progression[2] and that higher synchronization of activity in cerebellar areas may be underlie the improved cognition in mild cognitive impairment (MCI) individuals with small-vessels disease following attention training.[3] Such an appreciation of the cerebellar functions contrasts with the traditional viewpoint of being mainly limited in motor control, for example in motor speech, timing, grip forces, and sensorimotor synchronization.[4]

We have very much appreciated the article entitled "The role of cerebellar volume in cognition in the general elderly population" by Hoogendam et al.[5] and the authors' efforts to control for multiple notable source of variance such as age and estimated total intracranial volume (eTIV). However, unlike other regions (e.g. the hippocampus), where atrophy becomes apparent around the fifth decade,[6] cerebellar volume starts to decrease in the second decade,[7] and thus, optimal age correction needs to be based on the lifetime appreciation of atrophy trajectories for the adult human brain.

We previously published morphometric normative data for multiple areas of the brain correcting for age, sex, eTIV, and scanner characteristics,[6,8,9] but not for the cerebellum. Hence, based on the same methodology and sample as previously published,[6,8,9] we have computed for this letter normative volumetric data for the cerebellum white and grey matter (WM; GM) using *FreeSurfer* 5.3 from data acquired on 2,713 healthy adults (aged 18 to 94 years old, 50% female). These norms correct for effects related to age, sex, intracranial volume, scanner type and scanner strength, and have been made publicly available (https://github.com/medicslab/mNormsFS53). Using these volumetric cerebellum normative values, we have replicated the findings of Hoogendam et al. by investigating the associations between cerebellum volumes and cognitive function in a community-based sample (Nathan Kline Institute Rockland sample (NKI) n=664, mean age±sd: 45.4±18.9, age range: 18-86, 64% female) and in a clinical sample of older adults representing the continuum from subjective cognitive decline to AD (*Consortium pour l'identification précoce de la maladie d'Alzheimer - Quebec* (CIMA-Q) study n=137; age:

73.3±5.6, range: 65-89, 55% female). We also assessed the association of the cerebellum volume with grip strength, which is expected to be notably linked with cerebellar functions.

In the community-based sample, GM (r=-.208 p<.0001) and WM (r=-.148 p=.0001) cerebellum raw volumes showed significant correlations with motor speed (Grooved Purdue Pegboard test - both hand), but not with executive function (Combined Trail Making Test (TMT) B and Stroop condition 4 - Inhibition/switching, GM: r=-.052 p=.1924, WM: r=-.030 p=.4460), information processing speed (TMT-A, GM: r=-.011 p=.7739, WM: r=-.049 p=.2111), and episodic memory (Rey Auditory Verbal Learning Test - Delayed recall score, GM: r=.084 p=.0957, WM: r=.068 p=.1774). However, volumes corrected using our normative model were no longer significantly correlated with motor speed: GM (r=.008 p=.8441) and WM (r=.002 p=.9517). On the other hand, grip strength remained significantly related to cerebellum volumes, (GM: r=.456 p<.0001, WM: r=.363 p<.0001), even when using corrected normative volumes (GM: r=.154 p=.0001, WM: r=.212 p<.0001).

In the clinical sample, no significant correlations were observed between raw or normed cerebellum GM/WM volumes (normed volumes results reported) and executive function (TMT-B, GM: r=.023 p=.7871, WM: r=.003 p=.9744), information processing speed (Digit Symbol Substitution test, GM: r=.083 p=.3356, WM: r=.014 p=.1028), and episodic memory (Rey Auditory Verbal Learning Test - Delayed recall score, GM: r=-.028 p=.7480, WM: r=.021 p=.8077). Moreover, while grip strength was significantly correlated with raw cerebellar volumes (GM: r=.264 p=.0019, WM r=.216 p=.0114), it was no longer the case for normed volumes (GM: r=-.117 p=.1756; WM: r=.031 p=.7160).

Thus, atrophy in the cerebellum reflected by GM and WM volumes does not seem linked to cognitive function; while using proper normative morphometric data seems imperative in order to rule out age effects and draw adequate conclusions.

Respectfully yours,

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