Validation of a Jacobian AI-based Method to Measure Cerebellar Volume Changes in Multiple System Atrophy

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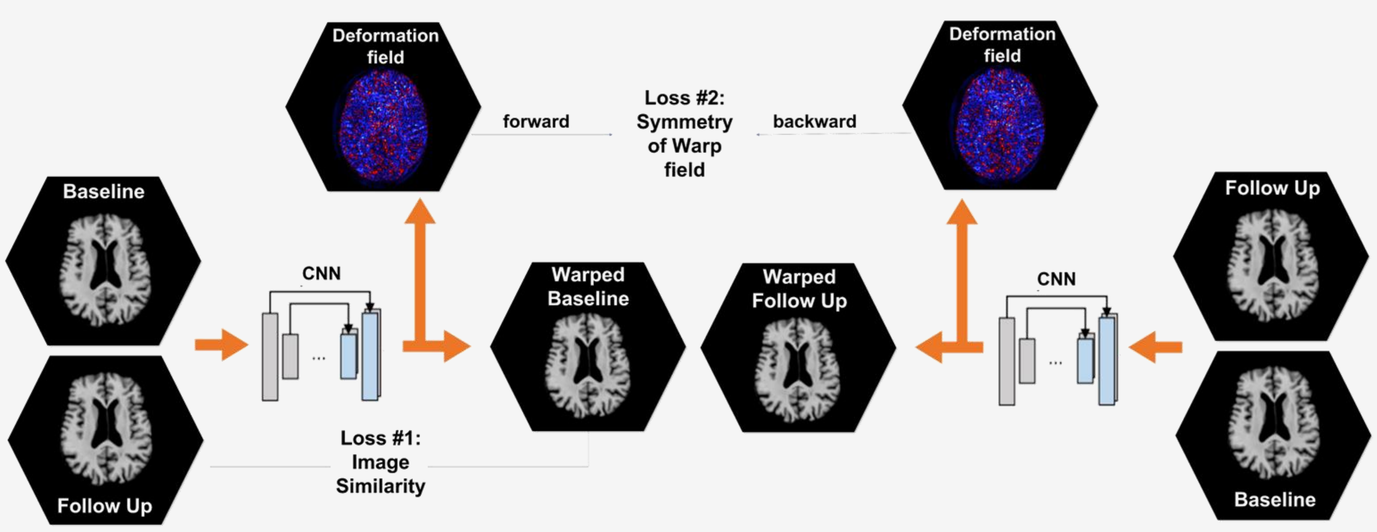
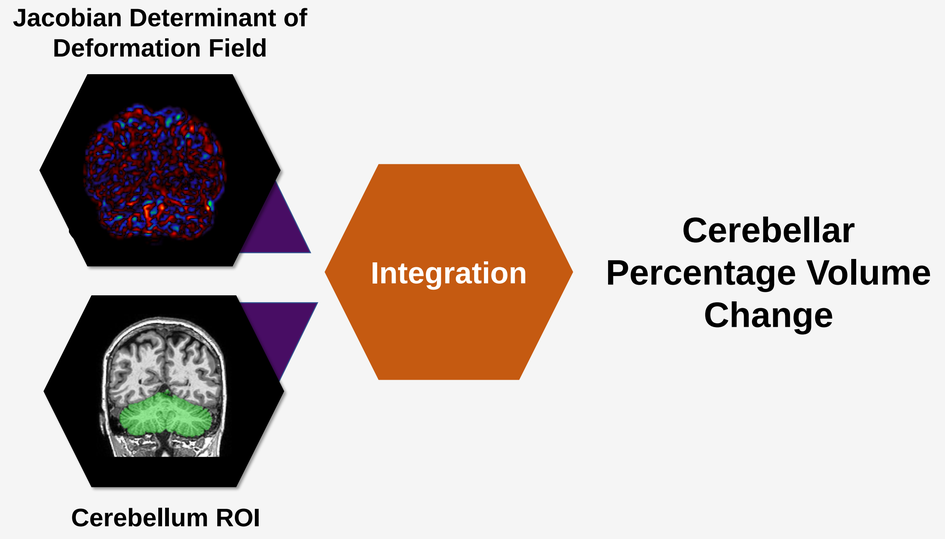
Cerebellar atrophy, seen in neurodegenerative diseases, such as multiple system atrophy (MSA), **can be quantified as cerebellar volume change on magnetic resonance imaging.** The estimation of cerebellar volume change, in an accurate, robust, consistent and scalable manner would be highly beneficial for clinical trials in multiple system atrophy (MSA) [1-3].

This work performs the **validation of a fully automatic volume change workflow in MSA using the Jacobian integration** from non-linear warp fields estimated with a convolutional neural network (CNN)-based 3D T1-weighed (T1W) image analysis workflow.

We analysed an MSA dataset (N=191, M-STAR clinical trial), consisting of individuals with predominant parkinsonism (MSA-P, N=76) or predominant cerebellar features (MSA-C, N=115). We did not differentiate between placebo and treatment groups. Each participant dataset comprised baseline and week 48 T1W scans, which were pre-processed cross-sectionally and pair-wise longitudinally. **Baseline images were segmented with a multi-atlas parcellation method to generate cerebellar ROIs [4].**





We **trained a CNN to perform non-linear registration of a serial, affinely aligned, pre-processed image pairs [5].** This provides a voxel-wise, high-resolution warp field in a fraction of the computed time taken by traditional methods [6].

Volume change measures were obtained through the **integration of Jacobian determinants from the deformation fields within the baseline cerebellum segmentations** (mean log Jacobian).

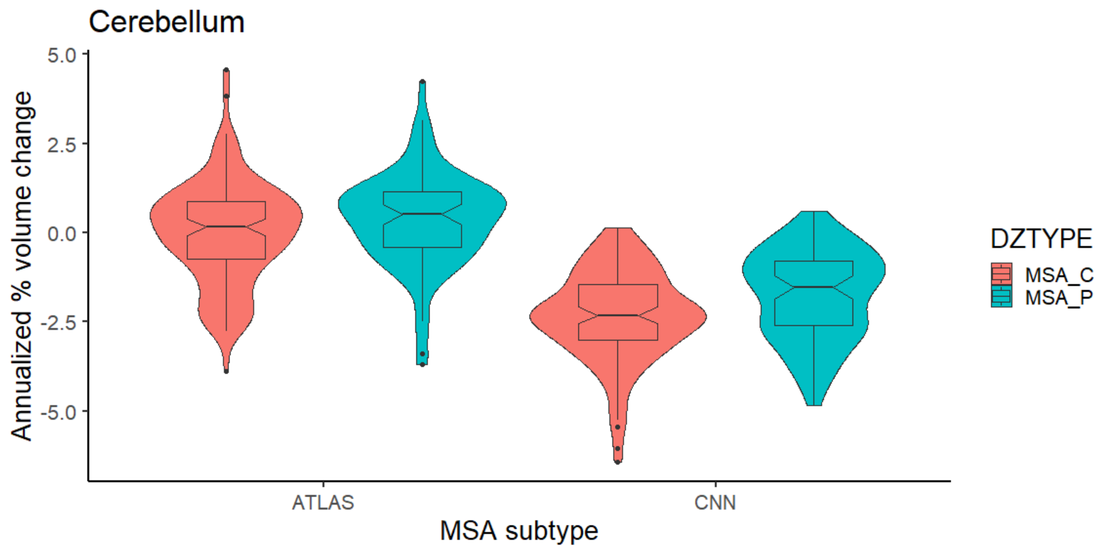
We compared cerebellar volume change from the proposed Jacobian **CNN** method and a temporally coupled segmentation-based method (**ATLAS**) [7].

Both methods used multi-ATLAS based cerebellum baseline segmentations [4].

The Jacobian **CNN method reported higher group differences based on annualised cerebellar volume change from baseline.** Of note, a negative (positive) sign indicates atrophy (growth).

Method	MSA-P Mean (SE)*	MSA-C Mean (SE)*	MSA-C vs MSA-P difference Mean (SE)*	P-value	Cohen's d Effect size
CNN	-1.75% (0.14)	-2.33% (0.11)	-0.57% (0.18)	0.001	-0.47
ATLAS	0.34% (0.16)	0.04% (0.13)	-0.30% (0.21)	0.151	-0.21

* Adjusted for age, gender, total UMSARS at Screening



Reduced sample sizes and increased effect size (for pooled MSA sub-types) were obtained with the proposed Jacobian CNN method when compared to both the ATLAS method and the PROMESA (Progression Rate Of MSA under EGCG Supplementation as Anti-Aggregation Approach) study, which used a widely used software, SPM12 [8].

Method	Mean (SD) Annualized % Change from Baseline	N	Cohen's d Effect Size	Sample size per arm*
CNN	-2.11% (1.29)	191	**-1.63**	**94**
ATLAS	0.16% (1.41)	191	0.11	20846.8
PROMESA (Placebo Group only)	-3.4% (3.70)	8	-0.92	297.4

* For hypothetical 2-arm clinical trial with 80% power, 25% treatment effect, 0.05 alpha

The developed framework provides a **fully automatic solution for estimating cerebellar volume change with increased sensitivity over comparable methods**. This framework is **flexible and highly scalable**, and as such has the potential to be advantageous for future clinical trials.

References:
[1] Hara D., Maki F., Tanaka S., Sasaki R., Hasegawa Y., "MRI-bases cerebellar volume measurements correlate with the Internal Cooperative Ataxia Rating Scale score in patients with spinocerebellar degeneration", *Cerebellum & Ataxias*, 2016, 14, doi:10.1186/s40673-016-0052-4
[2] Faber J., Schaprian T., Berkan K., Reetz K., Franca M.C., de Rezende T.J.R., Hong J., et al., "Regional Brain and Spinal Cord Volume Loss in Spinocerebellar Ataxia Type 3", *Movement Disorders*, 2021, 36(10), 2273-2281, doi:10.1002/mds.28610
[3] Paviour D.C., Price S.L., Jahanshahi M., Lees A.J., Fox N.C., "Longitudinal MRI in progressive supranuclear palsy and multiple system atrophy: rates and regions of atrophy", *Brain*, 2006, 129(4), 1040-1049, doi:10.1093/brain/awl021
[4] Wolz R., Aljabar P., Hajnal J.V., Hammers A., Rueckert D., et al., "LEAP: learning embeddings for atlas propagation", *NeuroImage*, 2010, 49(4), 1316-1325, doi:10.1016/j.neuroimage.2009.09.069
[5] Reinwald M., Joules R., Papoutsi M., Weatheritt J., Wolz R., "Towards a fully automatic AI framework to calculate voxel-wise atrophy in the human brain", *Alzheimer's & Dementia*, 2021, 17(Suppl. 5), doi:10.1002/alz.050068
[6] Avants B.B., Tustison N.J., Song G., Cook P.A., Klein A., Gee J.C., "A reproducible evaluation of ANTs similarity metric performance in brain image registration", *NeuroImage*, 2011, 54(3), 2033-2044, doi:10.1016/j.neuroimage.2010.09.025
[7] Wolz R., Heckmann R.A., Aljabar P., Hajnal J.V., Hammers A., Lotjonen J., Rueckert D., et al., "Measurement of hippocampal atrophy using 4D graph-cut segmentation: Application to ADNI", *NeuroImage*, 2010, 52(1), 109-118, doi:10.1016/j.neuroimage.2010.04.006
[8] Levin J., Maab S., Schuberth M., Giese A., Oertel W.H., Poewe W., Trenkwalder C., "Safety and efficacy of epigallocatechin gallate in multiple system atrophy (PROMESA): a randomised, double-blind, placebo-controlled trial", *The Lancet Neurology*, 2019, 18(8), 724-735, doi:10.1016/ S1474-4422(19)30141-3