Mapping Human Proprioceptive Projections of the Upper Limb Muscles through Spinal Cord fMRI

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Scientific context : Muscle proprioceptive projections in the human spinal cord have sparsely been studied despite their essential role in self-motion perception. Nevertheless, **recent advancements in technology and methodology have facilitated the exploration of the spinal cord using functional magnetic resonance imaging (fMRI),** overcoming inherent technical challenges. In this study, we investigated proprioceptive neural circuits by combining spinal fMRI and amagnetic mechanical vibration of wrist, biceps and deltoid muscle tendons. The protocol allowed exploration of both lateralization and top-down / rostrocaudal organization of the spinal cord in a single fMRI session through stimulation of six different sites across both arms.

Use of cluster : Analysis of cervical fMRI images atmultiple steps. Mainly useful to parallelize computation across images (25 participants x 4 runs each = **100x faster parallelizing, and way less demanding for my computer**).

- Preprocessing of images : data registration to template space, data cleaning and data smoothing with the Spinal Cord Toolbox (SCT, De Leener et al., 2014), or nilearn.
- Modelization of acquired images to study BOLD signal and observe spinal activations :
  - Univariate analysis : Using FEAT by FSL (Jenkinson et al., 2012) - 1h30 instead of several days
  - Multivariate analysis (MVPA) : nilearn tools tested and parallelized here.

Excerpt of obtained results :

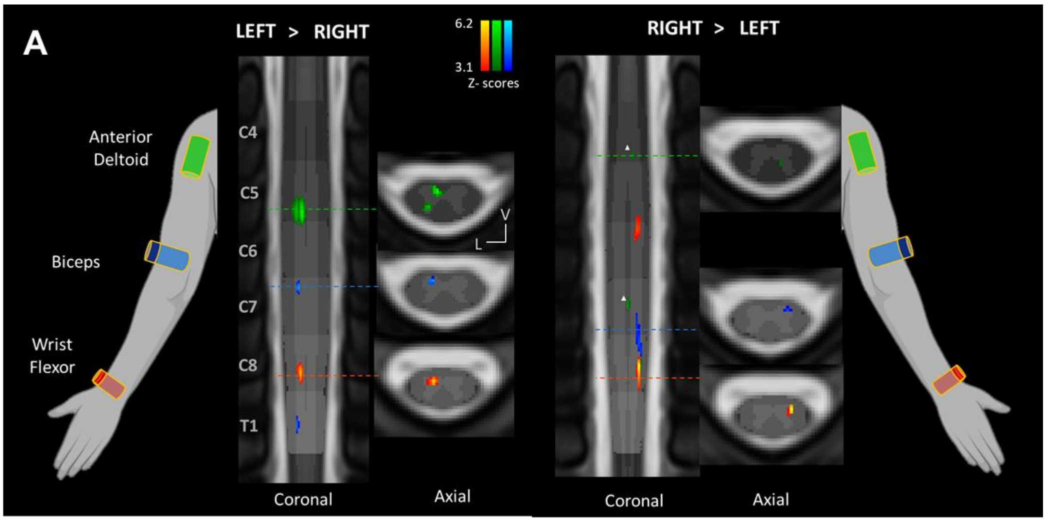

Figure 6. *A,* Group-level activation maps overlaid on the normalized probabilistic map (PAM50 template space), in coronal (max intensity projection) and axial (activation peak slice) views. The image on the left represents Left vs Right contrast of each stimulated arm level with a color code : Anterior Deltoid in green, Biceps in blue, and Wrist Flexor in red. The image on the right represents Right > Left contrasts with same color code. T-statistics are cluster-corrected (T>3.1, p < .05, cluster-corrected), except Right > Left Anterior Deltoid contrast map shown in T>3.1, p<0.001 uncorrected, indicated by a white triangle symbol. D : dorsal, V : ventral, L : Left, R : Right, C : Coronal, R : Rostral.

We found robust task-specific activations, primarily ipsilateral to the stimulated arm and concentrated in the ventral horn, consistent with the known connection of Ia afferents to motoneurons via a monosynaptic loop.

Considering the three arm levels stimulated, activations displayed a rostral-caudal distribution corresponding to the proximo-distal location of muscles, ranging from the shoulders (C5-C6) to the wrists (C8) [Figure 6A]. These observations were validated through cluster-corrected subject-level analyses within the probabilistic map. Furthermore, the innovative identification of individual spinal levels has unveiled new avenues for exploring participant spinal-level specific activity, through mesuring lateralization with a rigourous bootstrap/histogram method [Wilke et al., 2006] and **deciphering left-versus-right pattern decoding.** These advancements underscore the promising clinical implications of functional imaging in unraveling the complexities of spinal circuits.

Description of attached scripts :

- For Preprocessings :

the script of interest is invoked within `submit_job_xxx.sh`, which in turn calls `submit_job_xxx_split_runs.sh`. This process is designed to parallelize processes across all participants and runs.

- To run General Linear Model (GLM) with FSL's FEAT in fMRI analyses :

In both uni- and multivariate analyses, the script `run_feat.sh` is invoked within `submit_job_feat.sh`, which in turn calls `submit_job_feat_split_runs.sh`. This process is designed to parallelize the computation of the FEAT model across both participants and runs. Each participant and run has its configuration file, which is utilized as input in `run_feat.sh`. These configuration files are generated based on a template file (`cluster_template_design_MVPA_ses-02.fsf`) through a rapid Python script.

References :

1. Landelle, Caroline, Ovidiu Lungu, Shahabeddin Vahdat, Anne Kavounoudias, Véronique Marchand-Pauvert, Benjamin De Leener, et Julien Doyon. 2021. « Investigating the Human Spinal Sensorimotor Pathways through Functional Magnetic Resonance Imaging ». *NeuroImage* 245 (décembre): 118684. https://doi.org/10.1016/j.neuroimage.2021.118684.
2. Rowald, Andreas, Salif Komi, Robin Demesmaeker, Edeny Baaklini, Sergio Daniel Hernandez-Charpak, Edoardo Paoles, Hazael Montanaro, et al. 2022. « Activity-Dependent Spinal Cord Neuromodulation Rapidly Restores Trunk and Leg Motor Functions after Complete Paralysis ». *Nature Medicine* 28 (2): 260-71. https://doi.org/10.1038/s41591-021-01663-5.
3. Kinany N, Pirondini E, Martuzzi R, Mattera L, Micera S, Van de Ville D. 2019. Functional imaging of rostrocaudal spinal activity during upper limb motor tasks. Neuroimage.200:590-600
4. Kavounoudias, A., J.P. Roll, J.L. Anton, B. Nazarian, M. Roth, et R. Roll. 2008. « Proprio-Tactile Integration for Kinesthetic Perception: An FMRI Study ». *Neuropsychologia* 46 (2): 567-75. https://doi.org/10.1016/j.neuropsychologia.2007.10.002.
5. **De Leener, Benjamin, Simon Lévy, Sara M. Dupont, Vladimir S. Fonov, Nikola Stikov, D. Louis Collins, Virginie Callot, et Julien Cohen-Adad. 2017. « SCT: Spinal Cord Toolbox, an Open-Source Software for Processing Spinal Cord MRI Data ». *NeuroImage* 145 (janvier): 24-43. https://doi.org/10.1016/j.neuroimage.2016.10.009.**
6. **Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. Neuroimage. 2012 Aug 15;62(2):782-90. doi: 10.1016/j.neuroimage.2011.09.015. Epub 2011 Sep 16. PMID: 21979382.**
7. Frässle, Stefan, Eduardo A. Aponte, Saskia Bollmann, Kay H. Brodersen, Cao T. Do, Olivia K. Harrison, Samuel J. Harrison, et al. 2021. « TAPAS: An Open-Source Software Package for Translational Neuromodeling and Computational Psychiatry ». *Frontiers in Psychiatry* 12 (juin): 680811. https://doi.org/10.3389/fpsyt.2021.680811.
8. Abraham, Alexandre, Fabian Pedregosa, Michael Eickenberg, Philippe Gervais, Andreas Mueller, Jean Kossaifi, Alexandre Gramfort, Bertrand Thirion, et Gaël Varoquaux. 2014. « Machine learning for neuroimaging with scikit-learn ». *Frontiers in Neuroinformatics* 8. https://doi.org/10.3389/fninf.2014.00014.
9. De Leener, Benjamin, Vladimir S. Fonov, D. Louis Collins, Virginie Callot, Nikola Stikov, et Julien Cohen-Adad. 2018. « PAM50: Unbiased Multimodal Template of the Brainstem and Spinal Cord Aligned with the ICBM152 Space ». *NeuroImage* 165 (janvier): 170-79. https://doi.org/10.1016/j.neuroimage.2017.10.041.