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THE HEALTHY HUMAN CEREBELLUM ENGAGING IN COMPLEX PATTERNS: AN FMRI STUDY

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Target audience: Scientists and clinicians interested in functional magnetic resonance imaging (fMRI) of the cerebellum.

Purpose: To investigate the neurometric relationship between force and blood-oxygen-level dependent (BOLD) signal responses in the healthy human cerebellum.

Introduction: The human cerebellum has been implicated in the control of a wide variety of motor force parameters[1] and is engaged in cognitive and higher-level functions[2]. Previous fMRI studies have shown that the signal response from the human cerebellum correlates linearly with force amplitude when performing different motor tasks, including power and precision grip movements[3]. In the cortical and sub-cortical areas, on the other hand, there are studies of visuomotor tasks that have shown that the BOLD signal response tends to vary non-linearly in different motor and non-motor regions including M1, the supplementary motor area (SMA), insula, and several visual and associative areas[4,5]. The aim of this study was to explore the potential of fMRI to characterise linear and non-linear responses in the healthy human cerebellum to establish whether it demonstrates a complex response to grip force, generalising previous findings typical of cortical areas to the cerebellum.

Methods:

Subjects: 13 right-handed healthy volunteers with no history of neurological disease (5 female, 8 male; mean age 31 (± 4.64) years) participated in this study.

MRI protocol: A 3.0 T MRI scanner Philips Achieva system (Philips Healthcare, Best, The Netherlands) and a 32-channel head coil were used. The imaging protocol comprised: A BOLD sensitive T2*-weighted EPI: TE/TR = 35/2500 ms, voxel size = 3×3×2.7 mm^3, inter-slice gap of 0.3 mm, SENSE = 2, number of slices = 46 acquired with descending order, FOV = 192×192mm^2, number of volumes = 200, flip angle = 90° and a 3D anatomical T1-weighted reference scan.

FMRI paradigm: Subjects performed a dynamic power grip task with their right (dominant) hand, using an MR-compatible squeeze ball. Compression of the ball results in an air pressure measurement proportional to the force exerted. An event-related paradigm was used in this study comprising 75 active trials divided equally into 5 grip force targets (20, 30, 40, 50, and 60 % of each subject's maximum voluntary contraction) as well as 75 rest trials. Each active trial lasted 3 seconds and trials were specified in a randomized order. A visual cue presentation was used as an external instruction, showing live feedback on the subject's performance for each trial.

Image pre-processing and statistical analyses: The pre-processing steps for each subject followed an fMRI pipeline guided by the spatially unbiased infratentorial template (SUIT) software for the cerebellum, installed as part of the statistical parametric mapping software (SPM12)[6]. SUIT was used to optimize normalization procedures specific to the cerebellum. The pre-processing for the functional maps included slice timing, realignment, and co-registration to the T1-weighted volumes. Then, the within-subject first level analysis was performed for each subject. Each first level model included five regressors of interest optimized using polynomial functions of increasing orders (up to the 4^{th} order) [7]. The zero order term represents the main effect of hand gripping compared to the rest condition, irrespective of the applied force. The first positive order expansion models any BOLD linear change with force level; higher non-linear order effects induce subsequent regressors, modelling complex non-linear shapes (e.g. U-shaped captured by $+2^{nd}$ order or more complicated neurometric functions that can be approximated by the 3^{rd} and 4^{th} polynomial orders). At this level, t-statistics were used to test for the effects of each polynomial coefficient. Then, the following SUIT steps were performed: 1) Isolation of the cerebellum and brainstem from the rest of each subject's anatomical image; 2) Normalization of the anatomical images to the SUIT template using a nonlinear deformation; 3) Re-slicing the functional contrast images produced from the first level using the deformation produced from step 2) and masking out any activation outside the region of interest (i.e. the cerebellum). The normalized cerebellum functional contrast images (of each polynomial order) from each subject were then smoothed and submitted to a (between-subjects) standard second level random effects analysis, testing for increasingly higher order non-linear effects within the cerebellum with one sample t-test. Significance was set at a corrected (FWE) cluster level using a threshold of $P<0.001$ (uncorrected).

Results: In the main effect of movement (i.e. the zero order effect), activations were found in the ipsilateral (IL) lobules (I-VIII) as well as the contralateral (CL) lobule (VI) and part of the anterior and posterior vermis (Fig.1.A1). In the first order linear tests, activations were found in the IL I-V; as well as in the posterior cerebellum (lobule IX) (Fig.1.B1). Higher order positive non-linear effects were mostly found bilaterally, especially in the 4^{th} order form in lobules V-VI as well as Crus I, CL posterior cerebellum (VIIIa & b) and the posterior vermis (Fig.1.B1). A negative third order response was detected in the IL cerebellum (V-VII and Crus II) (Fig.1.B1).

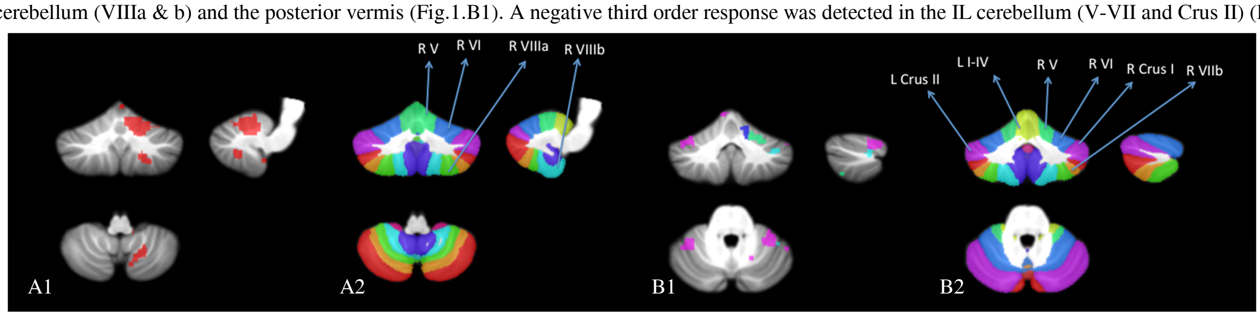

Fig.1: A1) Activations in the 0^{th} order (red). A2) Corresponding anatomical locations for A1. B1) Activations in the $+1^{st}$ (dark blue), $+2^{nd}$ (light blue), -3^{rd} (light green), and $+4^{th}$ (violet) order forms. B2) Corresponding anatomical locations for B1. In the maps, left is left (contralateral).

Discussion: The main observation of our analysis is the extensive involvement of the anterior as well as the posterior cerebellum in controlling dynamic power grip movement, confirming results from previous visuomotor studies[4]. Positive linear responses were mainly located in those cerebellar areas thought to play a key role in motor control - and to be linked with primary motor areas. Non-linear responses were observed both in bilateral motor and cognitive cerebellar areas suggesting that both cerebellar hemispheres play a role in higher-order motor control. It is interesting to note that our findings when focusing on the cerebellum reflect the linear and non-linear effects previously observed in cortical areas[4,5] (e.g. the response in the anterior parietal lobule matches that in the posterior cerebellum that neuroimaging studies implicate in executive and sensory functions). In short, previous studies have shown that the cerebellum is involved in different non-motor functions[2]. Our results have confirmed these findings from a different angle, illustrating that there is a cerebellar local organisation where each lobule is contributing to complex motor tasks with specific responses, in a similar manner as previously reported in the cortex.

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