DIFFERENTIAL INVOLVEMENT OF CORTICAL AND CEREBELLAR AREAS USING DOMINANT AND NON DOMINANT HANDS

Adnan Alahmadi[1,2], Rebecca Samson[1], David Gasston[3], Egidio D'Angelo[4,5], Ahmed Toosy[1,6], and Claudia A.M. Wheeler-Kingshott[1]

[1]NMR Research Unit, Department of Neuroinflammation, Queen Square MS Centre, UCL Institute of Neurology, London, United Kingdom, [2]Department of Diagnostic Radiology, Faculty of Applied Medical Science, KAU, Jeddah, Saudi Arabia, [3]Department of Neuroimaging, Institute of Psychiatry, King's College London, London, United Kingdom, [4]Department of Brain and Behavioral Sciences, Neurophysiology Unit, University of Pavia, Pavia, Italy, [5]Brain Connectivity Center, IRCCS C.Mondino, Pavia, Italy, [6]NMR Research Unit, Department of Brain Repair and Rehabilitation, Queen Square MS Centre, UCL Institute of Neurology, London, United Kingdom

TARGET AUDIENCE: Scientists and clinicians interested in motor functional magnetic resonance imaging (fMRI).

PURPOSE: The functional recruitment of cortical areas and the cerebellum during complex motor tasks remains unclear. The purpose of the present work is to: i) investigate brain activations in right (R) and left (L) hemispheres using dominant (DH) and non-dominant (NDH) hands in right-handed (RH) healthy volunteers using a complex motor task; ii) investigate whether different contra-lateral (CL) and ipsi-lateral (IL) brain areas are recruited under different task conditions.

BACKGROUND: fMRI studies have compared cortical activations using DH and NDH, with mixed findings [1], although most studies found motor cortex activations in RH subjects to be prominent in the L hemisphere [2]. To our knowledge, no study has directly compared DH and NDH using an event-related dynamic handgrip fMRI paradigm with different target grip force (GF) levels in healthy subjects. We investigated whether i) task-related activations in the R or L hemispheres depend on the use of the DH or NDH and ii) the relationship between CL and IL activations with the applied GF.

METHODS: ***<u>Participants:</u>*** We studied 14 (5F, 9M; mean age 31.0 (±4.48) yrs) RH volunteers. ***<u>Paradigm:</u>*** Subjects performed a power grip task with an MR-compatible squeezeball using both hands unimanually. Two fMRI scanning sessions comprised 75 3s visually cued trials interspersed with 75 null events in randomized and counter-balanced orders. The 75 task trials were divided into 25 trials at GF levels of 20, 40 and 60 % of the subject's Maximum Voluntary Contraction (MVC). Four inter-trial intervals were used: 2, 4, 7.5 and 9s. ***<u>MRI acquisition:</u>*** A 3T Philips Achieva MR scanner (Philips Healthcare, Best, The Netherlands) with a 32-channel head coil was used to perform a 3DT1-weighted anatomical scan and two T2*-weighted EPI fMRI scans. The fMRI acquisition parameters were: TR/TE=2500/35ms, 46 3mm slices positioned to include the cerebellum, with $3mm^2$ in-plane resolution, FOV=192 mm^2 and 200 functional volumes. ***<u>Data pre-processing:</u>*** Image analysis was performed with SPM8 [3] using conventional pre-processing steps: slice timing, realignment, co-registration, normalization (using a symmetrical MNI template [4]) and smoothing. ***<u>Statistical analysis:</u>*** <u>Within-subject</u>: A categorical design was used by defining the 3 GF as separate conditions. T-statistics were used to reveal individual effects of forces vs baseline as a result of using DH and NDH, independently. Linear contrasts across the 3 GF levels were also specified. Next, the resulting contrast images (CIs) for each subject and for the DH and NDH at each GF were flipped about the mid-sagittal line and re-sliced with respect to the un-flipped original contrasts [5] to generate flipped (fDH and fNDH) CIs. <u>Between subjects</u>: The CIs from the "within-subject" analysis were entered into random effects analyses (RFXs). For all tests the significance level was set at a corrected P<0.05 (FWE) at cluster level with a minimum extent of 10 voxels (initial uncorrected threshold of P<0.0001; T=5.11). Cluster peaks were labelled using the AAL atlas [6] as implemented in Peak_nii [7]. Figures were visualized using FIVE [8]. Three types of RFX analysis were performed:

1) <u>Linear effects</u> to reveal increased activations at the highest force using a one-sample t-test on the linear CIs.

2) <u>Conjunction analysis</u> to investigate common regions of activation. Firstly, Group CIs were created using a one-sample t-test performed on CIs obtained from the "within-subject" analysis at each GF level for DH/NDH/fNDH. Then, each of the group CIs was thresholded, binarized, and multiplied in pairs to define common regions. Conjunction analysis assessed common regions in terms of **a)** R and L hemisphere activations independently of handedness by testing DH and NDH group CIs; **b)** CL and IL hemisphere activations with respect to performing the task with the DH or NDH by testing group DH and fNDH CIs (i.e. regions in the L and R hemispheres correspond to the CL and IL sides, respectively).

3) <u>Paired t-tests</u> to assess **a)** specificity, and **b)** lateralisation of activations when using the DH or NDH. For detecting **a)** regions specific to the DH or NDH we performed a paired t-test between DH and NDH CIs; for **b)** the lateralisation analysis CIs were compared with corresponding flipped data (i.e. DH with fDH; NDH with fNDH).

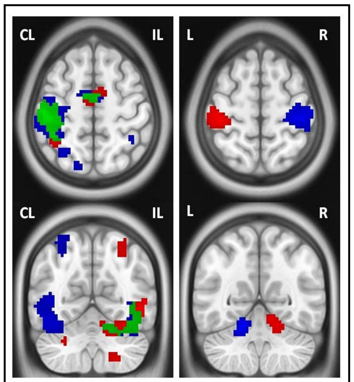

Fig1: Activation areas (green) from conjunction analysis b) of DH (red) vs. fNDH (blue) to show CL and IL involvement.

Fig2: Categorical comparison using paired t-test (a) to show R and L hemisphere regions specific to DH and NDH tasks.

Table.1 Common activation regions as a result of the conjunction analysis a)			
Brain regions	**20**	**40**	**60**
L Hemisphere			
Cerebellum		✔(6)	
Inf /Sup parietal L			✔
Inf Occipital G	✔	✔	✔
Inf Temporal G	✔	✔	✔
Mid Cingulate C		✔	✔
Mid Occipital G	✔	✔	✔
Mid Temporal G			✔
SMA			✔
SupraMarginal G			✔
R Hemisphere			
Angular G		✔	
Cerebellum	✔(8)	✔(6,7)	✔(6,8)
Fusiform G	✔	✔	✔
Inf Frontal G	✔	✔	
Inf Frontal oper	✔	✔	
Inf Parietal L			✔
Inf/Mid Occiptal G	✔	✔	✔
Inf/Mid Temporal G	✔	✔	✔
Insula			✔
Pre/Post Central G	✔	✔	✔
Rolandic Oper			✔
SMA	✔	✔	✔
Sup Parietal L	✔	✔	✔
SupraMarginal G	✔	✔	✔

Table.2 Common activation regions as a result of the conjunction analysis b)			
CL regions to each hand			
Cerebellum		✔(6)	
Fusiform G		✔	
Inf Occipital G	✔	✔	✔
Inf Parietal L	✔	✔	✔
Inf Temporal G	✔	✔	✔
Mid Cingulate C		✔	✔
Mid Occiptal G	✔	✔	✔
Mid Temporal G	✔	✔	✔
Pre/Post Central G	✔	✔	✔
Rolandic Oper			✔
SMA	✔	✔	✔
Sup Parietal L			✔
SupraMarginal G		✔	✔
IL regions to each hand			
Cerebellum	✔ (8)	✔(8,6)	✔(8,6)
Fusiform G	✔	✔	✔
Inf Occipital G	✔	✔	
Inf Temporal G		✔	
Mid Occipital G	✔	✔	
Mid Temporal G	✔	✔	✔
SMA			✔
SupraMarginal G			✔

RESULTS & DISCUSSION: The linear response group analysis revealed increased activations in the CL pre/post central gyri and IL anterior cerebellum, in agreement with previous studies of the DH [9]. Here we show that performing the task with the NDH revealed the same pattern, with additional CL areas indicating increased neuronal recruitment at the highest GF, namely the posterior cingulate cortex, thalamus, and hippocampus. Table 1 shows the results of the conjunction analysis **a)**, indicating that there are common areas of activation in both hemispheres when performing a task with the DH and NDH. More common activations in R hemisphere regions were also seen independently of the hand or GF level. This may be due to the role of cortical regions in controlling and processing complex movement. Conjunction analysis **b)** indicates that there are areas of activation in the CL and IL hemispheres common to motor tasks performed with either hand such as the well known CL pre/post central gyri, SMA and the IL cerebellum (Table 2 and Fig1, e.g. green areas). Moreover, the findings of the conjunction analysis **a)** & **b)** show that the NDH task activates bilateral regions such as SMA and cerebellum (VI), which are common to areas activated by the DH at the highest and middle forces, respectively. It has been hypothesized that the SMA controls sequential movements [10], hence its involvement in this task that requires following the randomisation of the task. In line with our results, bilateral cerebellum (VI) involvement has recently been reported using a different task [11] and interpreted as an engagement with tracking error [12]. Paired t-tests **a)** & **b)** confirmed the findings of the conjunction analysis showing that the specificities were in CL pre/post central gyri and IL anterior cerebellum (Fig 2) and lateralisations were more in the R hemisphere regions (e.g. Insula and inferior frontal gyrus), respectively.

Conclusion: We showed the patterns of activations using a complex fMRI task performed using DH and NDH. The role of the R hemisphere suggests the presence of subconscious data elaboration, which could be related to geometrical representation of the task. Also the consistent bilateral involvement of the cerebellum when the NDH task is performed suggests its involvement in error tracking or could suggest the presence of synkinetic processes between DH and NDH that warrant further investigation.

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