

BA 4p BOLD response profile distinguishes low and high MS morbidity

Adnan A.S. Alahmadi^{1,2}, Matteo Pardini^{1,3}, Rebecca Samson Egidio D'Angelo⁶, Karl J Friston⁵, Ahmed T Toosy^{1,7}, Claudia A.M. Wheeler-Kingshott¹

This study investigates how multiple sclerosis (MS) selectively affects regional BOLD response to variable grip forces (GF). It is known that the anterior and posterior BA4 areas are anatomically and functionally distinguishable – and that in healthy subjects there are linear and non-linear BOLD response components. After modelling BOLD responses with a polynomial expansion of the applied GF during task, we showed that in BA4a MS subjects respond like healthy subjects. BOLD response in BA4p, instead, was altered in MS, with those with greatest disability showing the greatest deviations from the non-linear profile of the healthy response.

Purpose: To investigate, specifically, how the relationship between blood-oxygen-level-dependent (BOLD) response and different applied grip forces (GF) behaves in the presence of multiple sclerosis (MS) pathology within the cytoarchitectonic divisions of BA4.

Background:

The BOLD response to a complex motor task, involving different GF, is complex and characterised by different response profiles [1]. While the impact of MS on motor function and on regional BOLD pattern changes is well described in MS, how these signal responses may be altered by pathology has not yet been investigated. In this study, we focus on Brodmann area 4 (BA4), corresponding to the primary motor cortex, M1, because of its role in motor function. BA4 is particularly interesting because it has two cytoarchitectonically distinct sub-regions: anterior (BA4a) and posterior (BA4p) (figure-1) [2,3]. Additionally, BA4p has been shown, using fMRI motor tasks, to be modulated, compared with BA4a, by attention [4], fine forces [5] and imagined forces [6]. In a recent visuomotor fMRI study in healthy subjects, we showed that the BOLD signal responded differently within BA4p with a non-linear (third order) relationship with GF [1], also indicating distinct responses to differing motor complexity [7]. These findings suggest that these two sub-areas have separate functional roles in executing motor complexity. Therefore, in this study we assessed whether, in MS, the BOLD-GF relationship is altered in BA4 and shows regional differences between BA4a and BA4p.

Methods: 14 right-handed (RH) healthy volunteers (HV) (9 female, 5 male; mean age 31 (\pm 4.64) years) and 14 RH relapsing remitting MS (RRMS) patients (10 female, 4 male; mean age 35 (\pm 5.36) years; median (range) expanded disability status (EDSS) score 3.5 (1.5-6.5)) were assessed with fMRI whilst performing a motor task using a squeezeball. A 3.0 T MRI scanner Philips Achieva system and a 32-channel head coil were used for MRI acquisition and the imaging protocol is provided in figure-2.

The experimental design was a *visually* guided event-related fMRI paradigm, where subjects used their right (dominant) hand to squeeze a rubber ball with varying GF levels. The design comprised 5 GF targets (20, 30, 40, 50 and 60% of subjects' maximum voluntary contraction) interleaved with rest, each repeated randomly 15 times. Pre-processing was performed using SPM12 (slice timing; realignment; co-registration; normalization and smoothing).

Statistical analysis: Within-subjects: Signal changes were modelled using a polynomial function. Between-subjects: Contrast images from the within-subjects analysis were entered into random effects analyses, testing for non-linear effects within and between groups, with the appropriate sample *t*-tests. Significant voxels were defined using $P < 0.0001$, corrected for multiple comparisons. BA4 was subdivided according to [3] as guided by [1]. In addition, to better understand the effect of disability, we divided the MS group based on their median EDSS score into two sub-groups of low (EDSS \leq 3) and high disability (EDSS $>$ 3).

Results: We report three major findings: 1) Main effect of movement: RRMS patients showed increased and greater activation extent compared with HV in both BA4a and BA4p sub-regions (figure-3) (p -value=0.0001). RRMS patients also showed increased activations as their EDSS increased within BA4p only (p -value=0.001; $r=0.68$); 2) Mean BOLD versus GF in BA4p (figure-4): in patients with low EDSS, the BOLD-GF function was very similar to HV (mainly negative 3rd order), whereas at higher EDSS, the plot of BOLD versus GF deviated from the HV pattern (figure-4, 3rd column). Mean BOLD versus GF in BA4a: no differences were detected between MS subjects and HVs (figure-5); 3). Response profile comparison at subject level: the profile was very similar across subjects, when comparing plots of subjects at similar stages of the disease (figure-4-5).

Discussion: We have shown altered relationships in BA4 between BOLD and GF in a motor fMRI task. The observation that the BOLD response to GF in patients with low EDSS was similar to that of HV, while it was consistently altered at higher EDSS (within BA4p but not BA4a) poses interesting mechanistic questions, suggesting differences not only in cytoarchitecture but also in myeloarchitecture of these two sub-regions, translating into differences in the susceptibility to MS pathology. Further investigations will aim at disentangling the role of an altered vascular response in MS as well as the involvement of preferential axonal-myelin damage within BA4p. Furthermore, the between-subject consistency in the patterns of BOLD-GF modulations suggests that not only the main effect of movement but also alterations of the BOLD response itself should be considered as potential biomarkers of disease.

References: [1]Alahmadi et al. Brain Struc Func, 2015. [2]Geyer S. et al. Nature, 1996.382:805–7. [3]Binkofski F et al . J Neurophysiol, 2002.88(1):514–519 [4]Kuhntz-Buschbeck et al. NI, 2008. 40(4):1469-81. [5]Sharma N et al. NI, 2008. 41(1):92–99. [6]Alahmadi et al. Hum Brain Map, 2015. [7]Eickhoff S et al. NI, 2005. 25(4):1325–1335.

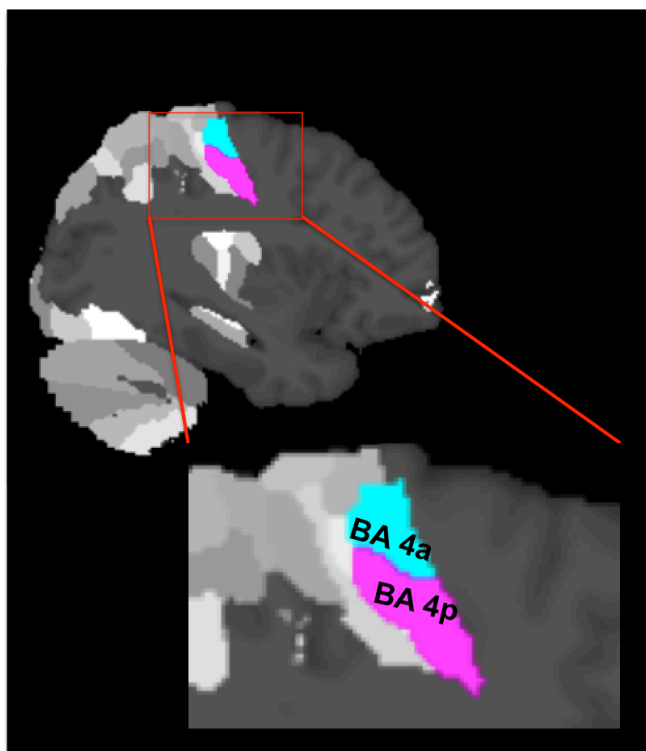


Figure.1: The cytoarchitectonic assignments of BA 4a and BA 4p projected onto the maximum probability map as provided by [7].

	Sequence	TR	TE	TI	FA	Slices	Voxel Size	gap	FOV	SENSE	Volumes
FMRI	GE - EPI	2.5s	35ms		90	46/Descending	3x3x2.7mm ³	0.3 mm	192mm ²	2	200
T1	3D- GE - FFE	6.9ms	3.1ms	824ms	8	72	1x1x1mm ³		192mm ²		
PD/T2	Dual echo -TSE	3500ms	19/85sm		90	50	1x1x3mm ³		240x180mm ²	1.7	

Figure.2: The imaging protocols and parameters.

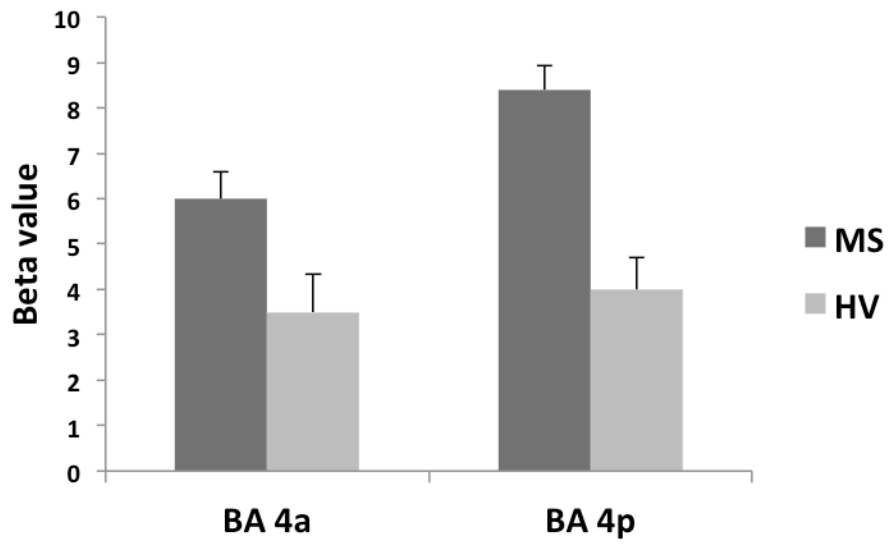
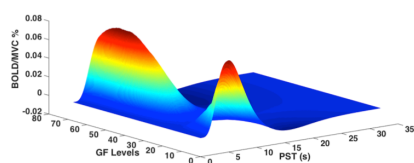
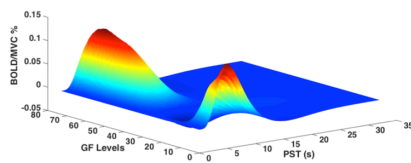


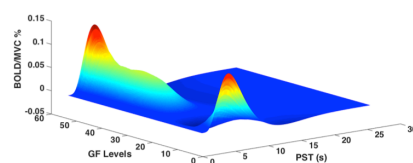
Figure 3: Mean of the beta values and their standard errors calculated at group level for the main effect of gripping for both groups and sub-regions. There are significant higher betas in the MS compared to the HV within the sub-regions.



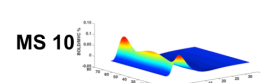
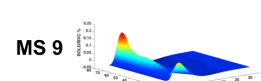
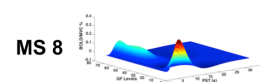
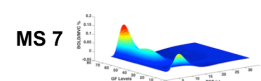
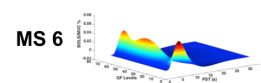
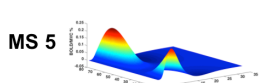
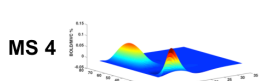
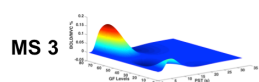
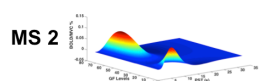
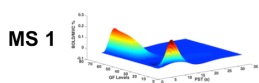
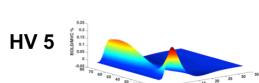
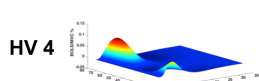
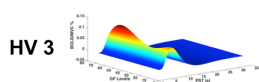
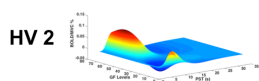
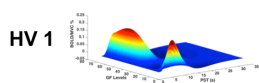
HV Average



MS Average (EDSS: 1.5-3)



MS Average (EDSS: 3.5 – 6.5)



BA 4p

Figure.4: BOLD responses (Z-axis) of the fitted polynomial-orders of GF (Y-axis) at the defined post-stimulus time (PST) (X-axis) within BA4p for HV, MS patients with low and high EDSS—representing an estimate of the mapping between GF and BOLD based on all components of the polynomial expansion. The top row shows the average group effect while underneath examples of individual subjects are plotted.

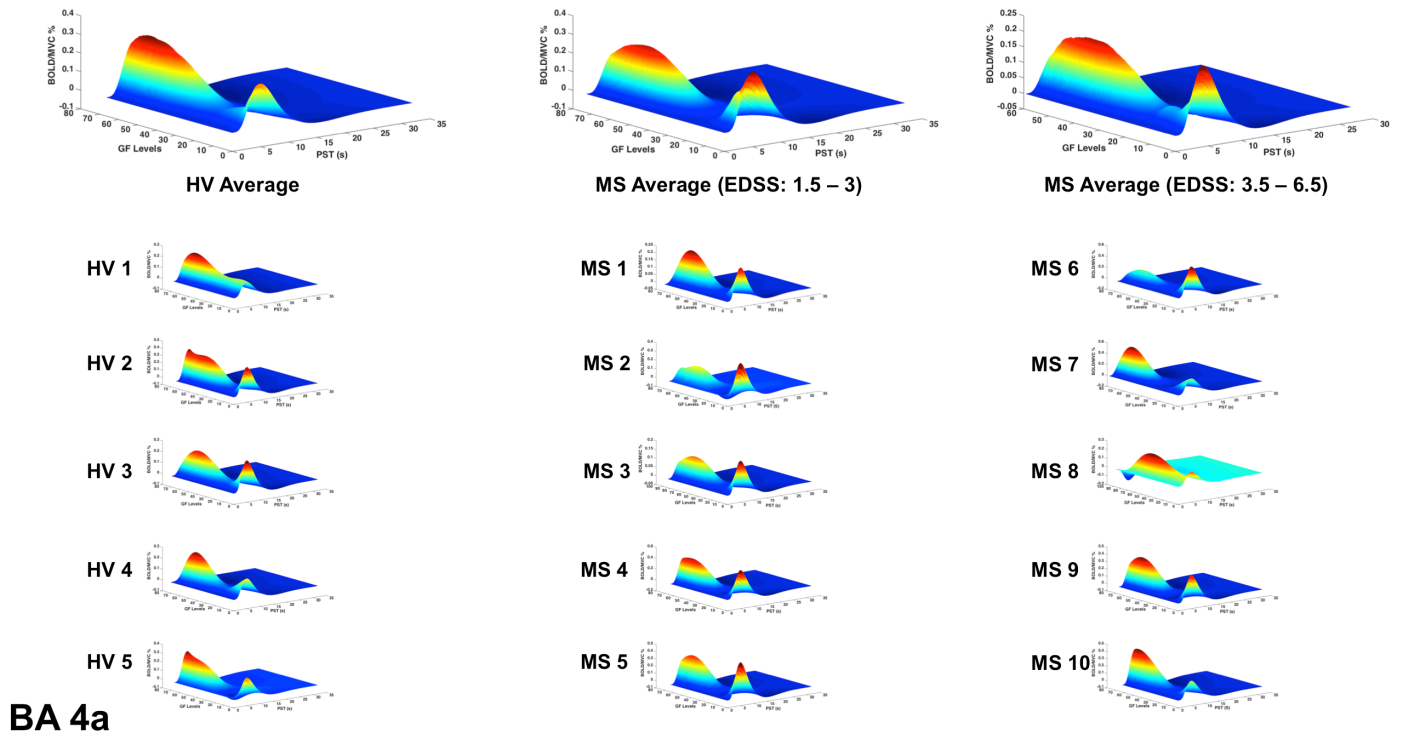


Figure.5: BOLD responses (Z-axis) of the fitted polynomial-orders of GF (Y-axis) at the defined post-stimulus time (PST) (X-axis) within BA4a for HV, MS patients with low and high EDSS—representing an estimate of the mapping between GF and BOLD based on all components of the polynomial expansion. The top row shows the average group effect while underneath examples of individual subjects are plotted.