PARAMETRIC EVENT RELATED FMRI TO INVESTIGATE NON-LINEAR BOLD EFFECTS IN MOTOR TASK

Adnan Alahmadi[1,2], Rebecca Samson[1], David Gasston[3], Matteo Pardini[1,4], Karl Friston[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 Neurosciences, Ophthalmology and Genetics, University of Genoa, Genoa, Italy,* [5]*Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, London, United Kingdom,* [6]*NMR Research Unit, Department of Brain Repair and Rehabilitation, Queen Square MS Centre, UCL, London, United Kingdom*

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

Purpose: To investigate non-linear correlates of BOLD fMRI to variable grip force (GF) by modelling higher order polynomial expansions using event-related design.

Background: Previous studies using fMRI with parametric block designs addressed the relationship between GF and BOLD signal using power grips [1-2]. Most of these studies reported linear responses in the contralateral primary motor cortex and ipsilateral cerebellum. These experiments, however, either used two levels of GF or did not investigate non-linear effects. Indeed, non-linear contributions to motor performance are rarely reported and poorly understood to date [3]. Their identification could be potentially instrumental in the development of more physiologically-sounded models of motor controls as suggested by neurophysiology experiments in animal studies which have shown that neuronal firing patterns have linear and non-linear components in response to different forces in primary motor regions, see [4] for review. The aim of the study is thus to explore the potential of fMRI to quantify the contribution of non-linear responses to motor control in healthy subjects.

Methods: *Subjects and MRI* - 13 right-handed healthy volunteers (5F, 8M; aged 25-41 (± 4.64) yrs) were scanned with a 3T MRI scanner (Philips Achieva, Best, The Netherlands) using a 32- channel head coil. The protocol included: 1) T1-weighted volume (3DT1): 3D inversion-recovery prepared gradient-echo (fast field echo) sequence with TI = 824ms, TE/TR = 3.1/6.9ms, voxel size = 1mm isotropic and flip angle = 8°. 2) T2*- weighted EPI sequence with: TE/TR = 35/2500ms, voxel size = 3mm isotropic, 46 contiguous slices with descending order, FOV=192x192mm^2 and 200 volumes. *fMRI paradigm* - Subjects performed a power grip task with their right hand, using an MR-compatible squeezeball. Compression of the ball resulted in a measured air pressure proportional to the force exerted. The force signal sampling rate was 20 Hz. An event-related fMRI paradigm was developed and optimized using OptSeq (*http://www.surfer.nmr.mgh.harvard.edu/optseq*). The design comprised 75 trials divided into 5 GF targets (20, 30, 40, 50, and 60 % of each subject's maximum voluntary contraction (MVC)). Each trial lasted 3s and trials were specified in a counter-balanced and randomized order. Rest time between squeezing trials was randomized with a minimum rest period of 2s and maximum rest period of 12s. The rest time was 51% of the whole session (500s). The cue for the paradigm execution was implemented using Visual Studio and projected on an MR-compatible screen inside the scanner room. The presentation consisted in alternating two slides: one with a horizontal line and one with a crosshair situated in the centre of the screen. Subjects were shown the line representing the GF target level to achieve. This was the cue to start squeezing. As soon as the subject started to squeeze the ball, a green bar gave a real time feedback indicating the applied force. Once the target was reached, the subjects had to hold it until the crosshair appeared on the screen (total time per trial 3s). *Image pre-processing and analyses* were performed using SPM12 (*www.fil.ion.ucl.ac.uk/spm)* and Matlab12b (Mathworks, Sheborn, MA). The pre-processing steps for each subject were: 1) slice timing correction, 2) Realignment of volumes and re-slicing the mean image only, 3) Co-registration of the re-sliced mean image with the 3DT1, 4) Estimation of normalization parameters between 3DT1 and the standard SPM12 template, 5) Application of the normalization parameters to the fMRI EPI volumes, 6) Smoothing EPI volumes with an 8mm isotropic Gaussian kernel. *Statistical analysis* was performed at two levels: 1) first level: a parametric specification was chosen to avoid categorical variability. All GF values were modelled as delta functions. Parametric covariates were modelled using a set of orthogonalized polynomial expansions up to the fourth order and specified by the integral of the grip responses. The movement parameters were included as regressors of no interest. At this level, t-statistics were used to test for the effects of each polynomial coefficient; 2) second level: the contrast images of five polynomial coefficients were entered into a between subject random effects analysis, testing for increasingly higher order non-linear effects with one sample t-tests. Significance was set at a corrected (FWE) cluster level after using a threshold of P<0.0001 (uncorrected) with a minimum voxel extent of 10 (corresponding to T= 5.26). Cluster peaks were identified with the SPM Anatomy toolbox [5].

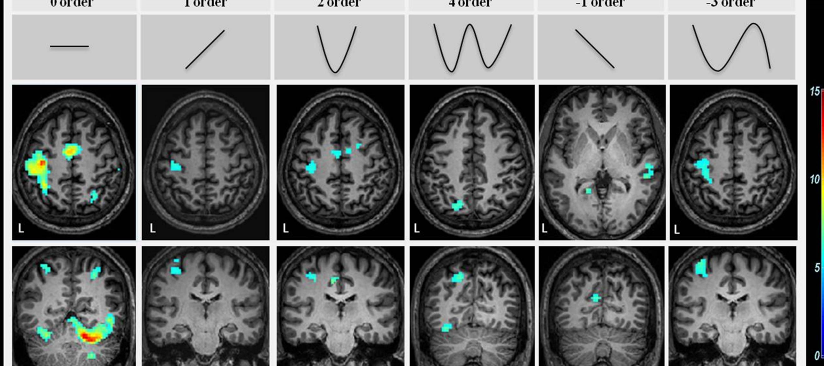
Results and discussion: All subjects were able to perform the task adequately (mean grip duration (± st dev) was 2.8 (±0.3). All trials reached the requested force within 10% of the target). There were two major findings in this study: 1) The rapid event-related design confirmed the presence of major activated motor areas irrespective of GF and consistent with previous GF block-design fMRI studies (i.e. zero order effects) [2]; 2) We have demonstrated the prevalence of high order (non-linear) BOLD responses to GF modulation that have a clear and distributed regional specificity (Figure.1). To our knowledge, this is the first study showing linear and non-linear BOLD responses to varying GF in the primary motor cortex. We also found non-linear relationships (up to 4th order) between GF and BOLD response in areas outside the primary motor cortex (e.g. premotor, sensory, parietal, and cerebellar) areas. A recent study, reported a linear response in the motor cortex and cerebellum, and non-linear components in other areas [6]. The partial agreement between these two studies may be due to differences in the design, where Keisker et al used a categorical design and three GF while we used a parametric design with 5 GF levels.

Conclusion: This study showed that it is possible to capture non-linear contributions to motor task performance using an optimized acquisition and analysis protocol. Indeed, our approach allowed quantifying area-specific activation patterns, which represent the anatomical underpinning of the complex interactions between motor performance, visuomotor tasks, attention, saturation, recruitment and fatigability. Future studies are warranted to explore their physiological roles.

Figure 1: Brain activations at group level corresponding to fitting polynomial of different orders to the BOLD response

The shape of the fitted polynomial function is shown for each order above the corresponding image displaying significant clusters. In the images, clusters are corrected at P<0.05. A T-value color bar is shown to the right of the images.

0 order	1 order	2 order	4 order	-1 order	-3 order



Anatomical labeling of clusters with the highest probability of being in the specified Brodmann Areas (Brodmann Areas)

0 order	1 order	2 order	4 order	-1 order	-3 order
L pre/post central G. (3,4a,p,6)	L precentral G. (6,4a)	L precentral G. (6)	L Sup Par Lob (7A)	L lingual G. (18)	L precentral G. (4a,p)
R/L SMA (6)		R/L SMA (6)	L fusiform G.	R Sup Temp G.	R Sup Occ G.
R/L cerebellum Lob 6, 8, 9		L Midd Cing G. (6)	L cerebellum Lob 6		
V4 and R putamen		L Sup Par Lob (1)			
Others (R/L 44, R 40)		R Infr Fron G. (44)			

References: [1] Ward NS, et al. EJN. 2007; 25(6):1965-73. [2] Kuhtz-Buschbeck JP, et al. NI. 2008; 40(4):1469-81. [3] Ward NS, et al. Brain. 2003; 126(6): 1430-48. [4] Ashe J. Behav Brain Res. 1997; 87(2): 255-69. [5] Eickhoff SB, et al. NI. 2005; 25(4):1325-35. [6] Keisker B, et al. HBM. 2009; 30(8):2453-65. ***Acknowledgements:*** MS Society of the UK; BRC UCL/UCLH; KAU, Jeddah, Saudi Arabia & UKSACB, London.