# Functional response to a complex visuo-motor task supports local compensatory mechanisms in Multiple Sclerosis

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## Synopsis

**We investigated simple and complex (non-linear) relationships between BOLD signals and different applied grip forces in multiple sclerosis (MS) patients and healthy volunteers (HV). Using a power grip event-related paradigm and modelling BOLD responses with a polynomial expansion of force, we show profound and distributed functional network reorganizations in sensorimotor, associative and cerebellar areas, probably indicating compensatory mechanisms in MS.**

## Purpose

To investigate the local reorganisation of motor function network in multiple sclerosis (MS) by studying the neurometric relationship between applied grip force (GF) and blood-oxygen-level dependent (BOLD) signal response.

## Background

Potentially, a better characterisation of the patterns of brain activation during an ecologically valid motor task could enhance understanding of the functional reorganisation processes observed in MS and possibly their functional significance [1,2]. Using a dynamic power grip event-related design, we characterised the relationship between BOLD and applied GF, expanding upon a study performed in healthy volunteers (HV) [3], which demonstrated specific polynomial relationships, common to regions with similar functional roles. Here, we aimed to assess how MS alters healthy (non-linear) brain BOLD responses to GF.

## Methods

Subjects: 16 right-handed (RH) HV (12 female; mean age 32 (± 4.75) years) and 16 RH relapsing-remitting MS patients (11 female; 36 (± 5.21) years; median expanded disability status (EDSS) 4 range (1.5-6.5)) were recruited.

MRI protocol: A 3.0T MRI scanner (Philips-Achieva) and a 32-channel head-coil were used to acquire fMRI data. Imaging protocol: T2*-weighted EPI (TE/TR=35/2500ms, voxel size=3×3×3mm$^3$, SENSE=2, Slices=46, FOV=192mm$^2$, volumes=200, FA=90°), a PD/T2-weighted, and 3D T1-weighted scans were acquired.

Paradigm: Subjects performed a dynamic power grip task with their right (dominant) hand, using a squeezeball. An event-related visually guided paradigm was used; comprising 75 active trials divided equally into 5 GF (20, 30, 40, 50, and 60% of each subject's maximum voluntary contraction), with 75 rest trials.

Image pre-processing: Using SPM12, standard fMRI pre-processing was performed.

Statistical analyses:

1) First (within-subject) level: Parametric covariates were modelled using (orthogonalised) polynomial expansions up to 4$^{th}$ order. The 0$^{th}$ order term represents the main effect of grip, irrespective of GF. The 1$^{st}$ order models linear BOLD changes with GF; higher non-linear orders induce subsequent regressors, modelling complex shapes (e.g. U-shaped captured by +2$^{nd}$ order or more complicated neurometric functions that can be captured by 3$^{rd}$ and 4$^{th}$ orders). *T*-statistics were used to test for the effects of each polynomial coefficient.

Figures

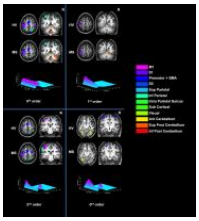

Fig.1 Illustrations of activations masked with different anatomical regions are projected onto axial and coronal views of T1-weighted maps in MNI space for HV and MS. Colour keys for anatomical regions are provided to the right. Typical representations of different polynomial orders are underneath brain images. These plots show examples of activations within each group, for the purpose of illustrations.

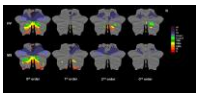

Fig.2 Illustrations of activation maps for each polynomial order for HV and MS, projected on the SUIT flattened cerebellum. Colour keys for cerebellar lobules are provided to the right.

2) Second (between-subject) level: Contrast images were entered into a random effects analysis, testing for within ($P$<0.05, FWE corrected) and between ($P$<0.0001, uncorrected) group effects with appropriate $t$-tests. Anatomical parcellation was performed [4].

In addition, the SUIT software [5] was used to optimize anatomical normalization procedures specific to the cerebellum and map activated volumes to the SUIT flattened map [6].

## Results

Fig.1 shows examples of activated regions, for each group, masked with different anatomical areas. Fig.2 shows activated regions projected onto the SUIT flattened map for each group.

For the main effect of grip, in both groups, activations in motor and visual areas irrespective of GF were detected. In MS patients, activated regions were mostly bilateral and characterised by stronger activations – with wider spatial extents.

Positive 1$^{st}$ order (linear) effects were found in the contralateral primary and secondary motor and sensory areas in both groups. A significant stronger and more extended positive linear increase in the ipsilateral anterior (lobule V) and superior posterior (lobule VI) cerebellum in MS patients compared to HV was observed.

Areas responding following a positive 2$^{nd}$ order term (U-shape) were localized within key motor and associative areas, and mostly lateralized in MS, showing a stronger and more extended local non-linear response in MS.

Negative 3$^{rd}$ order effects were observed mainly in visual areas in both groups but with a lesser extent and smaller effect size in MS.

## Conclusion

We investigated how MS affects non-linear BOLD response to a complex visuo-motor task. Results in HVs replicated previous findings [3]. Comparing the main effect of movement in MS versus HV we demonstrated increased recruitment of fronto-parietal areas and the cerebellum, possibly related to local compensatory attempts [2]. This is supported by the increased linear responses seen in M1 and the cerebellum.

Additionally, the 2$^{nd}$ order effect showed extensive cortical and sub-cortical re-organization in MS. This may reflect metabolically optimal energy consumption at intermediate forces, resulting in a reduced BOLD signal at mid force levels [3]. The increased 2$^{nd}$ order response in MS may suggest that associative areas are more engaged during low and high forces due to increased attention requirements, which could be indicating a compensatory mechanism.

A lower spatial extent of negative effects (i.e. lower BOLD response at higher GF) may indicate an increased focus on motor-related and associative areas, in line with previous findings of general increased activation in MS [1,2].

This work shows that altered patterns of activations in MS compared to HV involve sensorimotor, associative and cerebellar regions, all indicating local reorganization of a wide functional network that supports complex ecologically meaningful visuo-motor tasks.

## Acknowledgements

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## References

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