CoBeN

# Novel Network-Based Approaches for Studying Cognitive Dysfunction in Behavioural Neurology

*H2020-MSCA-RISE-2016-734718*

MARIE CURIE ACTIONS

# D22: MRI data acquisition for tasks 3, 4

| | |
|---|---|
| Work Package: | WP3 |
| Task: | - |
| Deliverable due date: | 31 .1. 2020 |
| Responsible partner: | MU |
| Deliverable number: | D3.4 |
| Deliverable type: | R/O |
| Dissemination level: | PU |

# 1 Introduction

*MRI data acquisition for tasks 3, 4: we will acquire data in healthy controls and patients with PD as described in the protocol and WP4.*

# 2 Methods

### Task design

We employed a modified random kinematogram paradigm, in which participants attend a circular aperture containing coherently moving dots of a single color [1]. At the start of each trial, a text message appeared for 0.5 seconds, warning participants to attend a specific attribute of consequent stimuli (shade of color or direction of motion). Afterwards, two consecutive random kinematograms were displayed for 0.8 seconds each, followed by a target stimulus after a rest period of 4 seconds. Participants had to decide whether the relevant attribute of the target was the same as it had been in one of the previous two kinematograms. Each trial lasted for 16.6 seconds, and there were 40 trials for each condition (80 altogether). In the pilot study, we reduced the number of trials to 20 per condition. For a depiction of the task, see Figure 1.

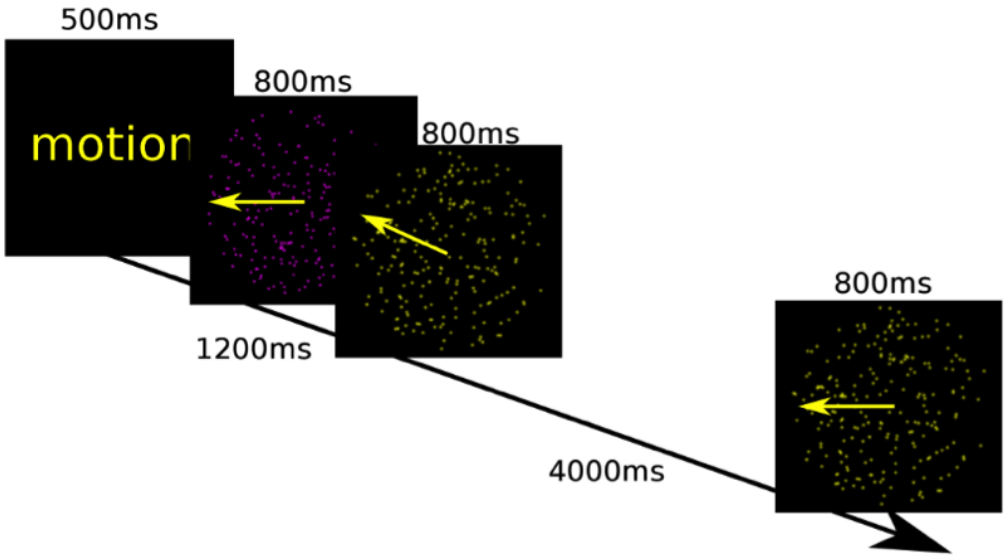



Figure 1. fMRI random kinematogram task design

### Participants

For this report, we analyzed the data of 18 patients with Parkinson's disease (PD) and 20 age- and sex-matched healthy controls. All participants had normal or corrected-to-normal eyesight, and healthy participants did not suffer from any neuropsychiatric conditions. Table 2 contains pertinent demographic and clinical data.

| **Study group** | **N** | **Age (mean±sd)** | **Sex (m/fm)** |
|---|---|---|---|
| HC | 20 | 63.03±8.88 | 11/9 |
| PD | 18 | 64.48±8.67 | 10/8 |

### Image acquisition

3D T1-weighted fast spoiled gradient echo images (FSPGR-IR, TR: 5.3 ms TE: 2.1 TI: 450 ms, slice thickness: 1 mm, matrix: 512x512, FOV: 256x256 mm, slice no. 312, whole brain coverage, flip angle: 12°) and T2*-weighted BOLD EPI images (TR: 2500 ms, TE: 27 ms, 44x3mm axial slices providing whole-brain coverage, FOV: 288x288mm; matrix: 96x96, flip-angle: 81°) were acquired on a 3T GE MR750W Discovery scanner (GE, Milwaukee, USA). The functional MRI protocol comprised the acquisition of 535 volumes, which took approximately 22 minutes (this was halved for the pilot study – 270 volumes, 12 minutes). Stimuli were displayed on a screen in the scanner room via a video projector. Participants saw the screen through a mirror applied to the head coil frame.

### Pre-processing

Pre-processing steps were performed via FEAT 6.0 as contained in the FMRIB Software Library (FSL[3]). The first 5 volumes were discarded to avoid saturation effects. Motion correction was applied using a rigid body (6 DOF) registration to the middle volume with MCFLIRT. Non-brain tissue was removed from the images via FSL's Brain Extraction Tool [4]. Following slice-timing correction and grand-mean intensity scaling, a high-pass temporal filter was applied (Gaussian-weighted least-squares straight line fitting, with $\sigma$ = 100.0s). Resulting volumes were normalized to standard 2mm MNI-space using a two-stage boundary-based registration process as implemented in FSL. For the multivariate analysis, volumes were resampled into 4mm standard space resolution to reduce computational load.

### Univariate analysis

We carried out the statistical analysis of time series using FILM with local autocorrelation correction [5]. The boxcar event plot of stimuli onset times was convolved with a canonical hemodynamic response function. Set in the general linear model framework, we employed an event-related design, which was specified by 7 explanatory variables encoding the following events:

- EV1: cue
- EV2: attend to color
- EV3: attend to motion
- EV4: test stimulus in the color condition – true
- EV5: test stimulus in the color condition – false
- EV6: test stimulus in the motion condition - true
- EV7: test stimulus in the motion condition – false

Contrasts coded the mean activation during the two conditions, and the two-sided difference of activation means during the two conditions. We excluded effects of stimulus/target congruency in the current analysis. We carried out higher-level analysis of group differences with FLAME, which is contained in FEAT version 6.0 [6]. Z (Gaussianised T) statistic images were thresholded using clusters determined by Z > 2.3 and a corrected cluster significance threshold of P=0.05.

### Multivariate analysis

We performed a multivariate analysis of the activation maps using tensorial independent component analysis (TICA [7]). TICA performs a trilinear decomposition of the data into independent component matrices, which describe spatial, temporal and subject-dependent dimensions as per the following equation:

$$X_{ijk} = \Sigma a_{ir} b_{jr} c_{kr} + \varepsilon_{ijk},\ r=1...R$$

Here, $X_{ijk}$ denotes the data of subject k at voxel location j and time point i. The matrices A= $[a_{ir}]$, B = $[b_{jr}]$ and C = $[c_{kr}]$ each contain R one-dimensional vectors which, for each estimated process r, characterize the temporal, spatial and subject-dependent signal variations, and epsilon is the confounding Gaussian noise. This trilinear combination is optimized via a least-squares approach so that different modes are maximally non-Gaussian. MELODIC thresholds spatial maps via an alternative hypothesis test based on fitting a Gaussian/Gamma mixture model to the distribution of voxel intensities within spatial maps and a posterior probability threshold of $p < 0.5$. In the pilot study, data dimensionality was estimated automatically using the Laplace-approximation to the Bayesian evidence of the model order. For the PD analysis, we constrained the decomposition to 60 independent components. We classified ICs as signal or noise via visual inspection following recent guidelines [8]

# 3 Results

### Univariate analysis

No significant differences were detected in any contrasts between HC-MS and HC-PD. Mean activations for each contrast from the PD analysis are depicted in Figures 2 and 3.

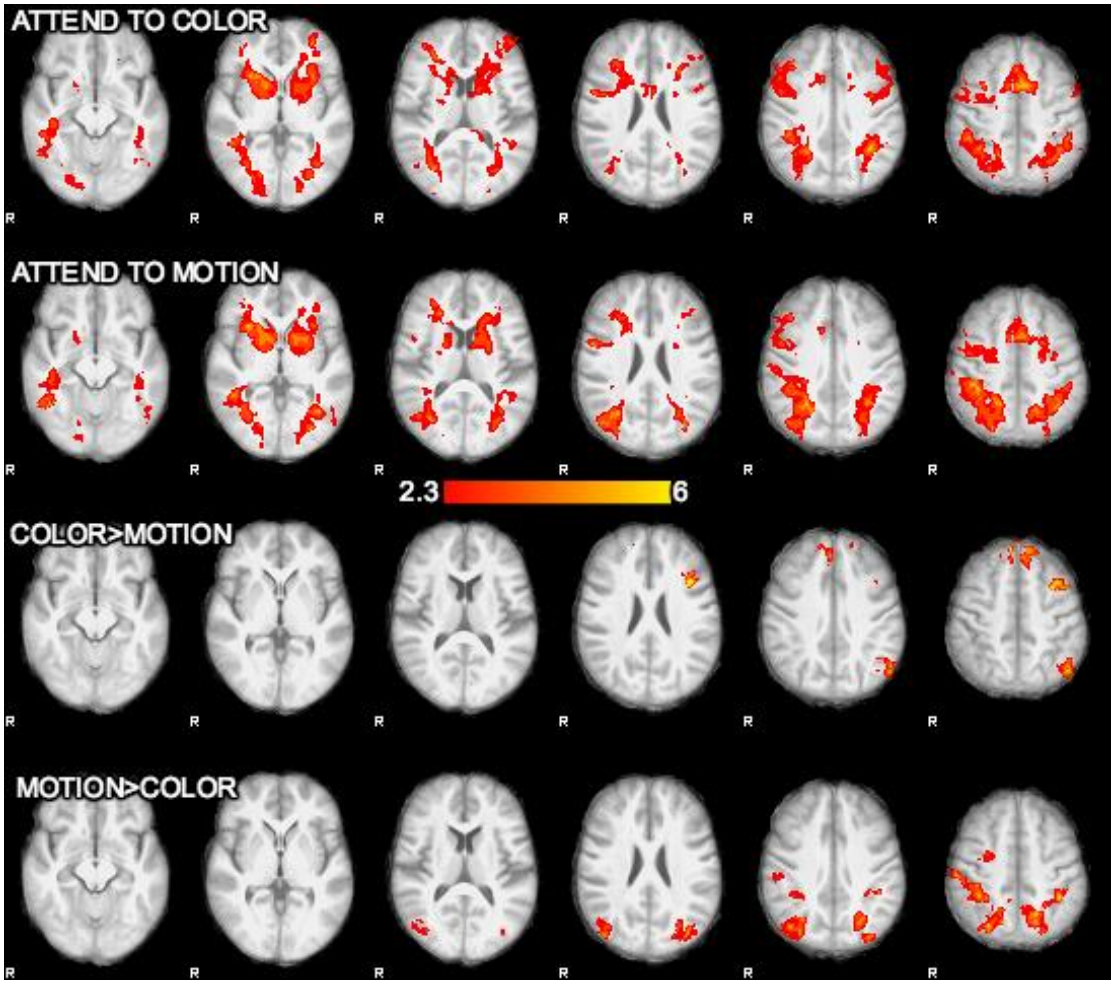



**Figure 2. Results of the univariate analysis for healthy participants. Z-maps are overlaid on the MNI152 standard template. The colorbar represents Z-values.**

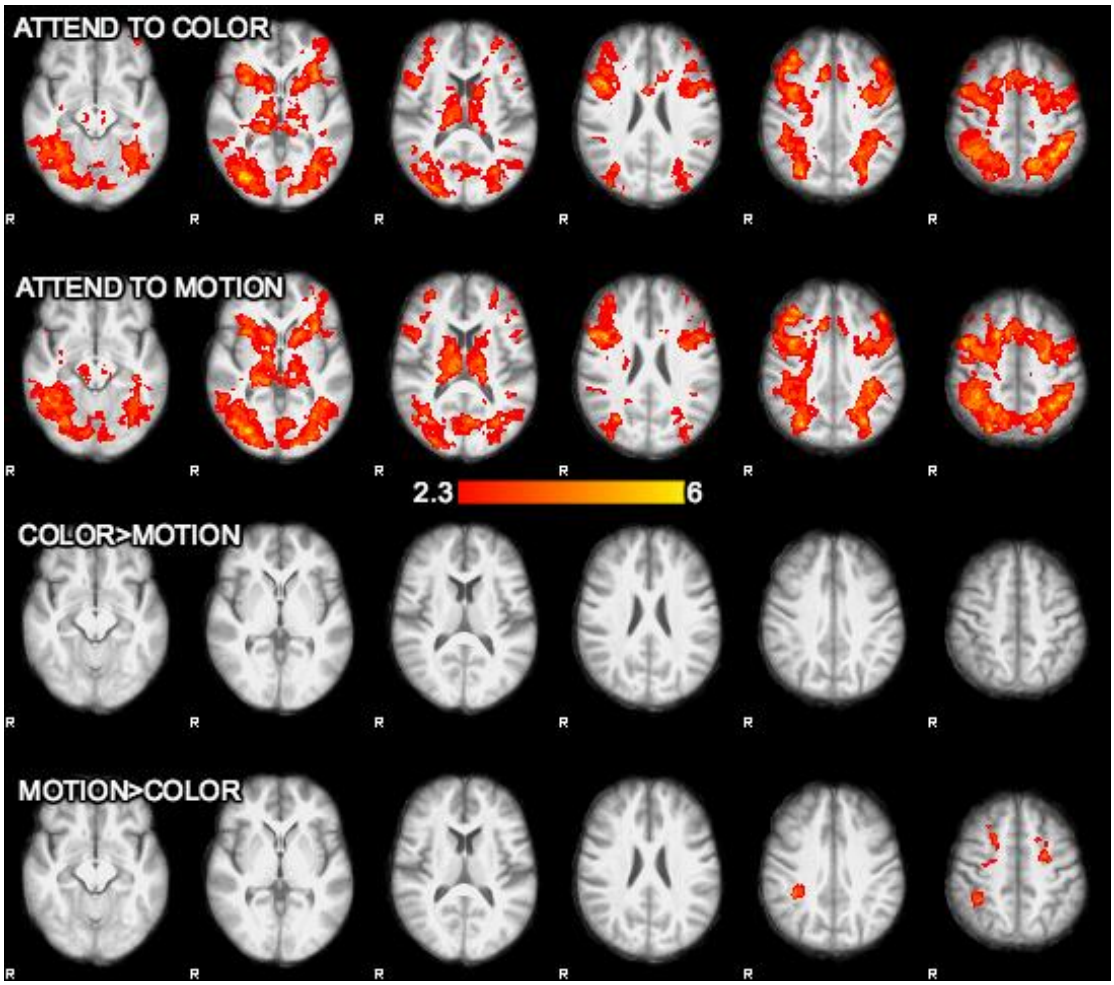



**Figure 3. Results of the univariate analysis in PD subjects. Z-maps are overlaid on the MNI152 standard template. The colorbar represents Z-values.**

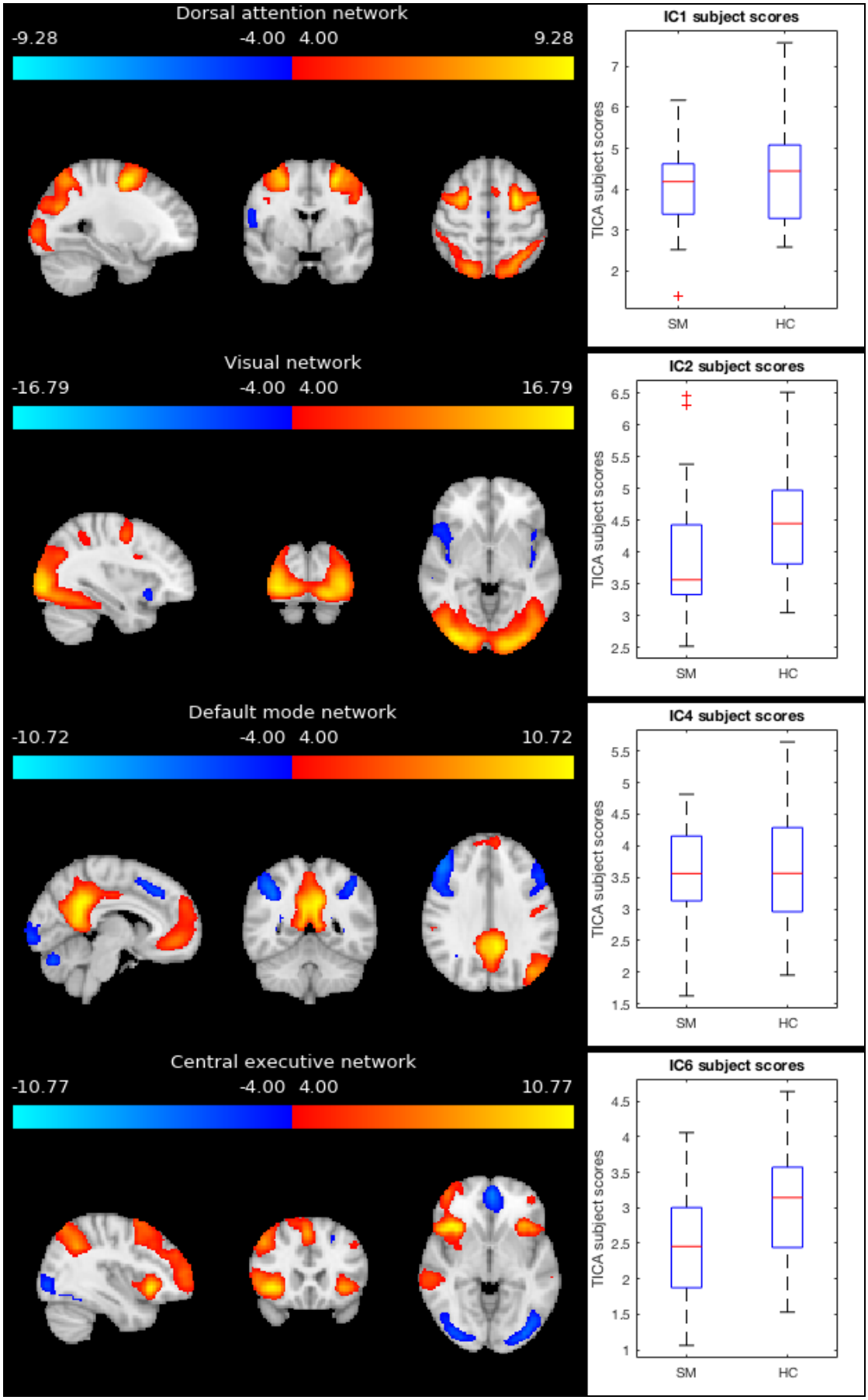
## Group ICA - RRMS

We selected ICs 1, 2, 4 and 6 as valid components, as they resembled known functional networks in spatial and temporal properties, and were consistent across subjects. The criteria for the latter meant the absence of outliers in the overall pool of individual subject modes.

IC1 comprised the bilateral extrastriate cortices, frontal eye fields, supplementary motor areas, intraparietal sulci and anterior caudate nuclei, IC2 contained bilateral lower-level visual cortices and, to a lesser extent, the bilateral intraparietal sulci and FEFs, IC4 consisted of areas that resemble the default-mode network (ventromedial prefrontal cortex, precuneus, bilateral angular gyri and superior temporal gyri), and IC6 comprised the anterior cingulate cortex, the ventral frontal cortex and superior parietal lobule on the right and the bilateral striate cortices. The spatial maps of ICs are depicted in Figure 4.

A post-hoc regression analysis was carried out by FSL's MELODIC on the estimated component time courses, using an event-related design that coded the onset of the cue, the color and motion conditions, and contained the target as nuisance regressor to exclude effects of task performance. IC1 and IC2 showed greater activation in the motion condition ($p<0.001$ and $p<0.036$), whereas IC6 was expressed more in the color condition ($p<0.011$). IC4, the default-mode network anticorrelated with the task design as expected.

Subject modes of IC2 and IC6 showed significant differences between healthy controls and patients, with lower scores in the MS group ($p<0.032$ and $p<0.004$, respectively).


Dorsal attention network
-9.28
-4.00 4.00
9.28
Visual network
-16.79
-4.00 4.00
16.79
Default mode network
-10.72
-4.00 4.00
10.72
Central executive network
-10.77
-4.00 4.00
10.77
IC1 subject scores
IC2 subject scores
IC4 subject scores
IC6 subject scores
TICA subject scores
SM
HC

### Group ICA – PD

IC1 was selected as a valid, task-related component because of its adherence to the task model in both groups (GLM OLS fit to time series: p<0.0001 in both conditions, with stronger expression in the motion condition: p<0.0001), its consistency in the subject domain (no outliers in the overall subject mode pool), and its spatial features, as it includes the bilateral intraparietal sulci, frontal eye fields and lateral visual cortices. IC1 was expressed to a significantly lesser degree in the PD cohort (GLM OLS fit to subject scores: p<0.018). The absence of other task-related components might be attributed to the lower number of subjects. IC1 is depicted in Figure 5.

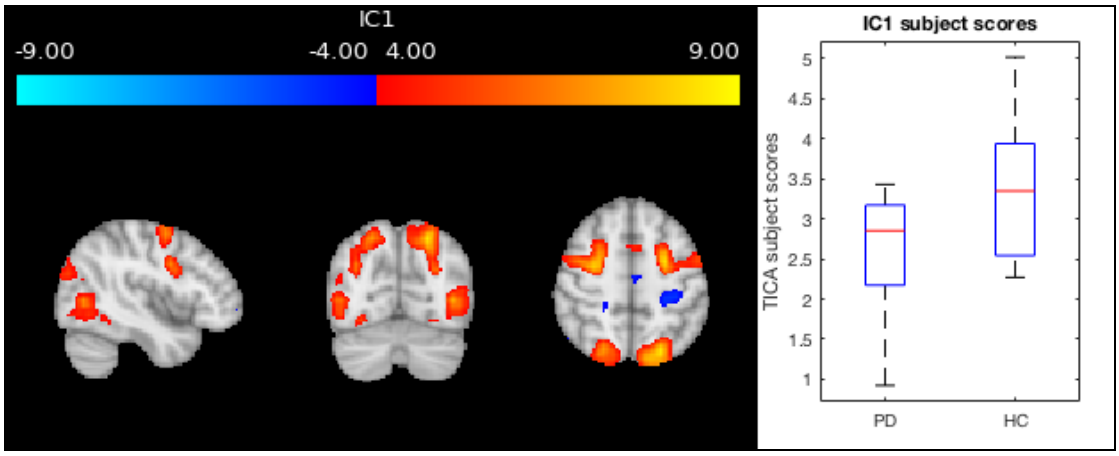



Figure 4. IC1 from the PD analysis.

# 4 Conclusions

Our analysis showed that:

1. The univariate analysis detected greater activation in the intraparietal sulcus and frontal eye fields during the motion condition compared to the color condition. There were no significant differences in any contrasts between HC-MS and HC-PD (presumably due to motion artefacts).
2. TICA in PD showed that the task-related component was expressed to a significantly lesser degree in PD patients.
3. In the RRMS study, task-related components IC1 and IC2 showed greater activation in the motion condition while IC6 was expressed more in the color condition. IC4, the default-mode network anticorrelated with the task design. IC2 and IC6 were expressed to a significantly lesser degree in RRMS patients.

## Multiple sclerosis and brain networks during attention task

Using the same fMRI task measured with PD patients, we have done an analysis with patients with multiple sclerosis. Our preliminary results shows that task-related networks manifest differently in relapsing-remitting multiple sclerosis patients, reflecting network-level functional adaptation that scales with cognitive disability.

# 5 References


1. Zanto, T.P. and A. Gazzaley, *Neural suppression of irrelevant information underlies optimal working memory performance.* J Neurosci, 2009. **29**(10): p. 3059-66.
2. Polman, C.H., et al., *Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria.* Ann Neurol, 2011. **69**(2): p. 292-302.
3. Smith, S.M., et al., *Advances in functional and structural MR image analysis and implementation as FSL.* Neuroimage, 2004. **23 Suppl 1**: p. S208-19.
4. Smith, S.M., *Fast robust automated brain extraction.* Hum Brain Mapp, 2002. **17**(3): p. 143-55.
5. Woolrich, M.W., et al., *Temporal autocorrelation in univariate linear modeling of FMRI data.* Neuroimage, 2001. **14**(6): p. 1370-86.
6. Woolrich, M.W., et al., *Multilevel linear modelling for FMRI group analysis using Bayesian inference.* Neuroimage, 2004. **21**(4): p. 1732-47.
7. Beckmann, C.F. and S.M. Smith, *Tensorial extensions of independent component analysis for multisubject FMRI analysis.* Neuroimage, 2005. **25**(1): p. 294-311.
8. Griffanti, L., et al., *Hand classification of fMRI ICA noise components.* Neuroimage, 2017. **154**: p. 188-205.