CoBeN

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

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MARIE CURIE ACTIONS

D4.6 Functional MRI identified changes associated with impaired AMWM and abnormal brain activation/connectivity in PD

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1 Introduction

One of the aims of work package 4 (WP4) is to use functional MRI imaging to investigate top-down regulation (enhancement and suppression) in patients with Parkinson's disease (PD) in comparison to healthy controls (HC).

2 Methods

We included clinically diagnosed PD patients (Postuma et al., 2015) who were well compensated on their stable dopaminergic medication without major motor fluctuations or dyskinesias. The patients were longitudinally followed at the First Department of Neurology, Faculty of Medicine and St. Anne's University Hospital, Masaryk University, Brno, Czech Republic. Age-matched healthy subjects were recruited from our database at the Central European Institute of Technology (CEITEC), Masaryk University in Brno. Exclusion criteria for all subjects included alcohol/drug abuse, hallucinations or visual misperceptions, and any diagnosed psychiatric disorder. PD patients were examined in the ON medication state without dyskinesias. The participants underwent clinical examination, cognitive testing using a detailed neuropsychological test battery and brain MRI examination using the 3T Siemens Prisma MR scanner (Siemens Corp., Erlangen, Germany). The MRI protocol included structural scans and visual task fMRI scans (according to (Gazzaley et al., 2005)). Each subject signed an informed consent form, and the study was approved by the local ethics committee.

The following MRI sequences were used: magnetization-prepared rapid gradient-echo (MPRAGE) high-resolution sequence (240 sagittal slices, slice thickness = 1 mm, TR = 2300 ms, TE = 2.33 ms, FA = 8°, FOV = 224 mm, matrix size 224×224) and gradient-echo echo-planar imaging sequence during a working memory task (575 scans, 44 transversal slices, slice thickness = 3 mm, TR = 2500 ms, TE = 33 ms, FA = 80°, FOV = 192 mm, matrix size 64×64).

The visual task was designed according to Gazzaley's paradigm (Gazzaley et al., 2005). It consisted of three different conditions in which the participants viewed a series of four sequentially presented stimuli: a) Remember Faces and Ignore Scenes, b) Remember Scenes and Ignore Faces, and c) Passively view. All trials were followed by a delay period (showing fixation cross) and 1) in memory trials a response period showing face/scene requiring subjects to report whether this stimulus matched one of the previously presented stimuli, 2) in passive trials a response period showing left/right arrow requiring subjects to report whether the arrow points left or right. Before next trial another delay period was incorporated. For task details, see Figure 1. Altogether, the protocol consisted of 9 blocks (3 blocks of each condition), each block contained 10 trials.

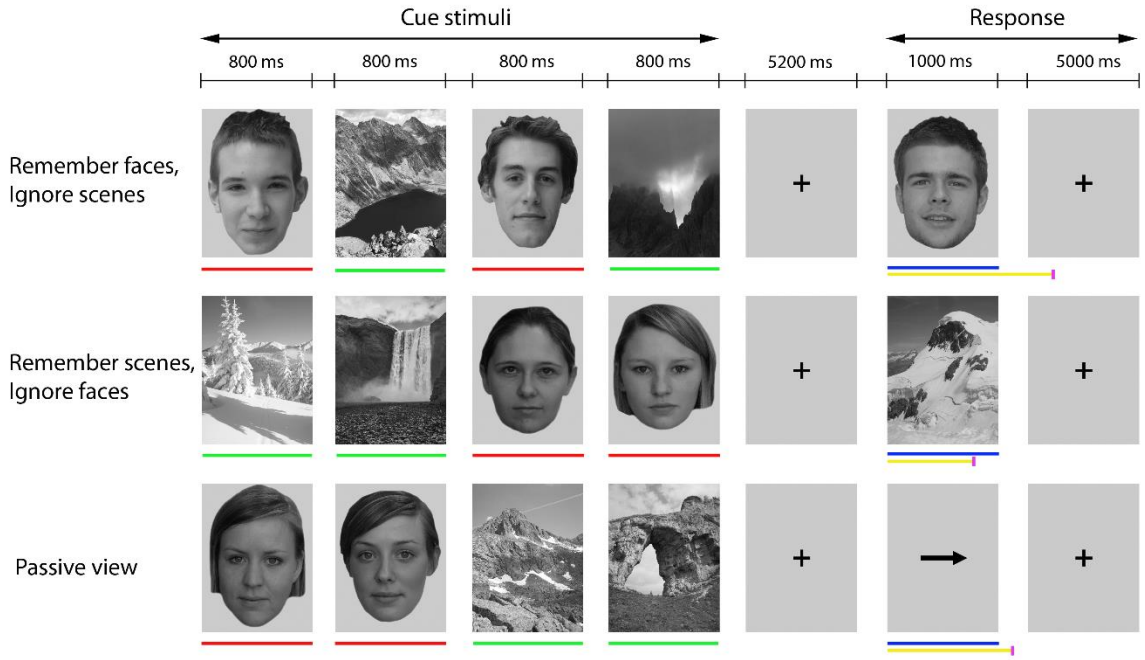

Figure 1: Final version of the working memory paradigm

The pre-processing of the functional data consisted of realignment and unwarping, normalization into standard anatomical space (MNI), and spatial smoothing using a Gaussian filter kernel with FWHM of 5 mm. Individual subject masks were calculated using Mask_explorer (Gajdoš et al., 2016) and checked for excessive signal dropouts.
The level of motion within task fMRI was evaluated using framewise displacement (FD) (Power et al., 2012). No subject from final cohort had more than 10% of scans with FD>0.75. The group mask was calculated and data inserted into a general linear model. We used a complex fMRI design in order to calculate mean group activations under different conditions, see Figure 1 and 2. The visual task time courses were convolved with a canonical haemodynamic response function and six movement parameters obtained during realignment and unwarping and response conditions were used as nuisance regressors, see Figure 2. Contrast files with the activation effects (Faces Remember/Passive/Ignore and Scenes Remember/Passive/Ignore) were calculated for HC and PD groups, see Figure 2. These data were then entered into Repeated Measures ANOVA with condition (Remember/Passive/Ignore) as a within-subject factor, and group (HC/PD) as between-subject factor, with age and gender as covariates of no interest.

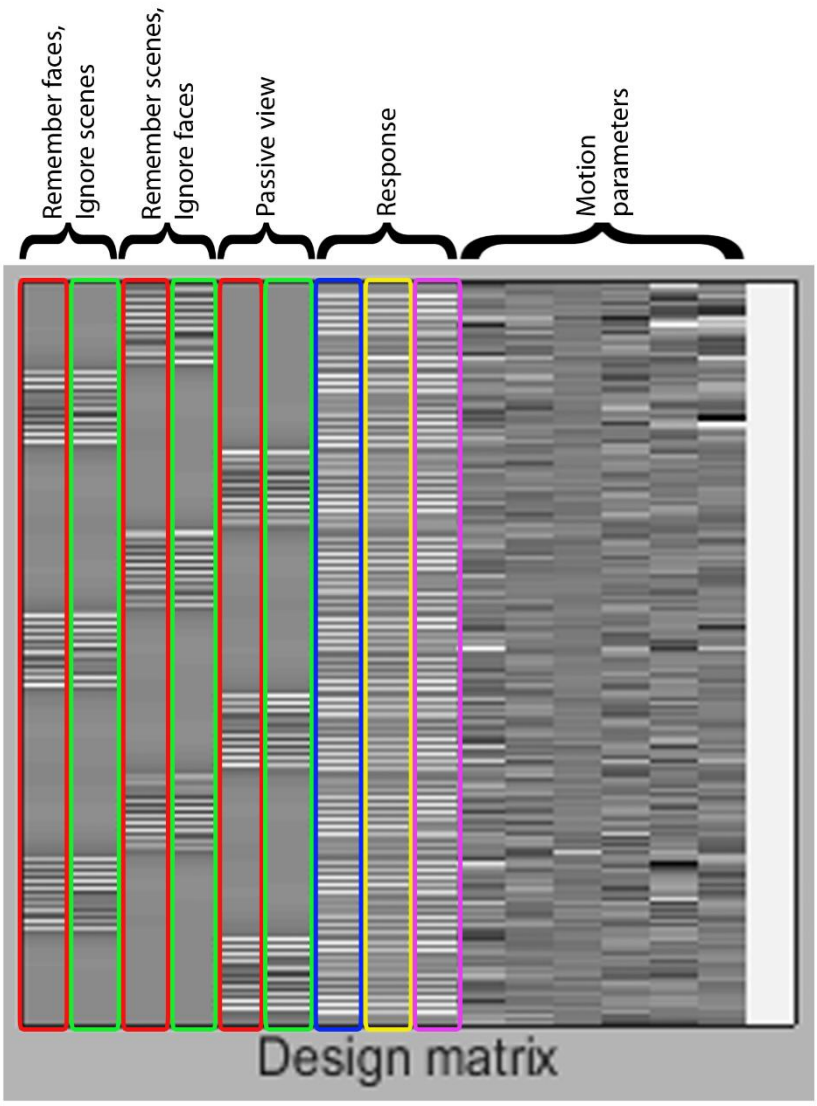

Figure 2: First level model in task activations analysis

Category-specific cortical regions of interest were identified in both hemispheres according to Julian et al. (Julian et al., 2012), including fusiform face area (FFA), occipital face area (OFA) and superior temporal sulcus (STS) as face-specific regions, and parahippocampal place area (PPA), transverse occipital sulcus (TOS) and retrosplenial cortex (RSC) as scene-specific regions. In addition, we were interested in multiple-demand system, where we isolated ten bilateral masks MDS 1 – MDS 10 (Fedorenko et al., 2013), for details see Table xy. These masks were intersected with group activation masks during the visual task, separately in HC and PD groups. The final masks then were used in the subsequent analyses.

Firstly, we compared reaction times and scores between HC and PD using Mann-Whitney U test. Data were adjusted for age and gender.

In order to assess differences between HC and PD in different task conditions, Repeated Measures ANOVA with condition (Remember/Ignore) as a within-subject factor, and group (HC/PD) as between-subject factor. In addition, in order to assess subjects' performance in

the task individual two-sample t-tests were performed between Remember/Passive/Ignore task conditions with FDR correction in each group separately. Age and gender were included as covariates of no interest and were regressed out.
Spearman's partial correlations (controlling for the effects of age, gender) of the activation effects in different task conditions within ROIs with scores and reaction times (both total and faces and scenes separately) were calculated for both HC and PD groups.

3 Results

Our final cohort consisted of 14 PD patients aged 66.89 ± 8.42 years (50% men) and 23 healthy controls (HC) aged 67.15 ± 4.97 years, 35% men. The groups significantly differed neither in age (Mann-Whitney U test, $p = 0.87$), nor in gender distribution (Pearson's Chi-Squared test, $\chi2 = 0.836$, $p = 0.36$).

Behavioral results

The direct comparison between the PD and HC groups revealed significant extension of both mean reaction times ($p = 0.03$) and "Remember faces" and "Remember scenes" reaction times ($p = 0.03$; $p = 0.02$) in the PD group. Moreover, PD displayed significantly lower mean score ($p = 0.002$) and "Remember faces" and "Remember scenes" reaction times ($p = 0.008$; $p = 0.001$) when compared to HC.

Task activation – ROIs for faces recognition

In the HC group we found significant differences between "Remember Faces" and "Passive view" condition in bilateral FFA, bilateral OFA and right STS. There were also significant differences between "Remember Faces" and "Ignore Faces" condition in left FFA and bilateral OFA. These results are FDR corrected. In the PD group, after FDR correction there were no significant differences.
Regarding differences in activations under Remember/Ignore conditions between groups, Repeated Measures ANOVA showed no significant results.

Task activation – ROIs for scenes recognition

In the HC group we found significant differences between "Remember Scenes" and "Passive view" condition in bilateral PPA, bilateral RSC and bilateral TOS. There were also significant differences between "Remember Scenes" and "Ignore Scenes" condition in bilateral RSC and bilateral TOS. These results are FDR corrected. In the PD group, after FDR correction there were no significant differences.
Regarding differences in activations under Remember/Ignore conditions between groups, Repeated Measures ANOVA showed significant differences in left TOS and right RSC.

Task activation – Multiple-demand system

In the HC group we found significant differences between "Remember Faces" and "Passive view" condition in MDS 1, MDS 3, MDS 5, MDS 6, MDS 7 and MDS 10 parcellations. There were also significant differences between "Remember Faces" and "Ignore Faces" condition in MDS 1- MDS 7 and MDS 10 parcellations. In addition we discovered significant differences between "Remember Scenes" and "Passive view" condition in MDS 1 – MDS 7 and MDS 9 – MDS 10 parcellations. There were also significant differences between "Remember Scenes" and "Ignore Scenes" condition in the same regions - MDS 1 – MDS 7 and MDS 9 – MDS. These results are FDR corrected. In the PD group, we found significant differences between

"Remember Faces" and "Passive view" condition in MDS 4 parcellation, and significant differences between "Ignore Faces" and "Passive view" condition in MDS 4 and MDS 10 parcellations. In the PD group, after FDR correction there were no significant differences between "Remember Scenes" and "Passive view" condition.
In the second part of analysis, Repeated Measures ANOVA showed significant differences in MDS 3 pascellation for Remember Faces/Ignore Faces conditions, and in MDS 1, MDS 3 and MDS 10 parcellations Remember Scenes/Ignore Scenes conditions.
We found high negative correlations between reaction times during visual task and activations (mostly in MDS 1, MDS 2, MDS 3 and MDS 4 parcellations) in the PD group in "Remember scenes" condition and high positive correlations between scores during visual task and activations in the PD group in "Remember scenes". In the HC group there were no significant correlations.

4 Conclusion

We performed fMRI data analysis to evaluate top-down regulation (enhancement and suppression) in patients with Parkinson's disease in comparison to healthy controls (HC). We found significant differences in enhancement and suppression between these two groups and strong correlations between behavioral scores and activations during the visual task. Currently we are in the process of publication preparing and writing.

5 References

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