Exploring the specificity of fatigue-related brain activity in early Multiple Sclerosis.

Camille Guillemin[1,2], Maëlle Charonitis[1,2], Nikita Beliy[1], Florence Requier[1,2], Jessica Gilsoul[1,2], Evelyne Balteau[1], Gaël Delrue[3,4], Emilie Lommers[1,3], Isabelle Hansen[1,3], Pierre Maquet[1,3], Christophe Phillips[1,5], Fabienne Collette[1,2].

[1]GIGA-CRC In Vivo Imaging, University of Liège, Liège, Belgium; [2]Psychology and Cognitive Neuroscience Research Unit, University of Liège, Liège, Belgium; [3]Department of Neurology, University Hospital of Liège, Liège, Belgium; [4]Neurocognitive and speech rehabilitation unit, Department of physical medicine and functional rehabilitation, University Hospital of Liège, Liège, Belgium; [5] GIGA In Silico Medicine, University of Liège, Liège, Belgium.

Contacts: Camille Guillemin: c.guillemin@uliege.be
Fabienne Collette: f.collette@uliege.be

Introduction. Fatigue is a predominant symptom in persons with multiple sclerosis (pwMS) with major repercussions on quality of life[1,2]. However, little is known about its brain substrates, especially in the earliest stages of the disease [3,4]. This study aims at exploring functional brain activity associated to fatigue during a working memory task in pwMS and matched healthy controls (HC).

Methods. Sixteen recently diagnosed pwMS and 17 HC performed a fatigue induction task (Time Load Dual Back task[5]) in conditions of High or Low Cognitive Load (HCL/LCL). The cognitive load differed regarding the time available to process stimuli. The two conditions were counterbalanced and administered in two separate sessions. Following fatigue induction, participants performed an N-Back task[6] with 3 levels of difficulty (1 to 3-Back) in a block-design fMRI experiment (6 blocks per working memory load). The Fatigue Scale for Motor and Cognitive Function (FSMC, trait fatigue) was administered before the experiment. State fatigue was assessed with Visual Analogous Scales (VAS) before fatigue induction, before and after the N-back task).

Behavioral data were analyzed with Bayesian statistics using JASP software, with Mann-Whitney tests for FSMC and repeated measures ANOVA for VAS and N-Back (sensitivity index d'). Functional MRI time series were acquired on a 3T head-only scanner (64 channels head coil, multi-band EPI 2D Bold, 36 slices, TR = 1170ms, acquisition time ≈ 16min). Structural images (T1w and FLAIR) were also acquired following the fMRI session. Preprocessing and statistical analyses were performed with SPM12. F-tests on whole brain were performed ($p < 0.001$ uncorrected) to detect (i) group differences in brain activity and (ii) correlation between brain activity and FSMC score, depending on fatigue induction (HCL vs LCL) and task difficulty in the high load condition (HCL 1vs2Back ; HCL 1vs3Back). Results maps from correlation analysis (ii) were extracted and used as small volumes correction for group comparisons (iii).

Results: The FSMC did not statistically differ between groups ($BF_{10} = 0.38$) while post-hoc analyses on VAS showed that subjective fatigue significantly increased after fatigue induction ($BF_{10} = 7.02$) and remained stable afterwards ($BF_{10} = 0.15$). Regarding the N-Back task (fig.1), we observed an effect of difficulty on d' ($BF_{incl} = 2.12e+43$). However d' was not influenced by the fatigue induction condition ($BF_{incl} = 0.17$) regardless of Group ($BF_{incl} = 0.27$) and Difficulty ($BF_{incl} = 0.10$).

fMRI results did not show group difference in brain activity during task performance, and no correlation with FSMC was observed in the HCL vs LCL contrast. However, we observed in the HCL condition that the FSMC is positively correlated in control and negatively in pwMS to activity in left cingulate, frontal and precentral regions, and positively correlated, in HC only, in temporal regions

and the cerebellum for the contrast 1vs2Back (fig. 2a). For the 1vs3Back contrast (fig.2b), the FSMC is positively correlated in control and negatively in pwMS to activity in left precentral, postcentral, paracentral, frontal and temporal regions, left thalamus, hippocampus, and cerebellum and right caudate, and positively correlated in HC only in the right cingulate.

Conclusion: Both high and low cognitive load conditions triggered subjective fatigue in our protocol, and we do not observe larger effect of fatigue induction on performance, subjective reports and brain activity in pwMS, likely due to the early stage of the disease. Yet, significant different correlations were observed between trait fatigue and brain activity during the N-Back task. This could indicate that the neural response to induced fatigue slightly vary according to presence of minor brain damage. The changes seems however independent of task-related brain areas and task performance.

Figures:

Figure 1. Performance (d' sensitivity index) at the N-Back task. A: performance following the High Cognitive Load Condition; B: performance following the Low Cognitive Load Condition. MS: Multiple Sclerosis patients; HC: Healthy Controls; 1B, 2B, 3B: 1-Back, 2-Back and 3-Back conditions of the N-back task. Horizontal bars represent means, dots represent single subjects.

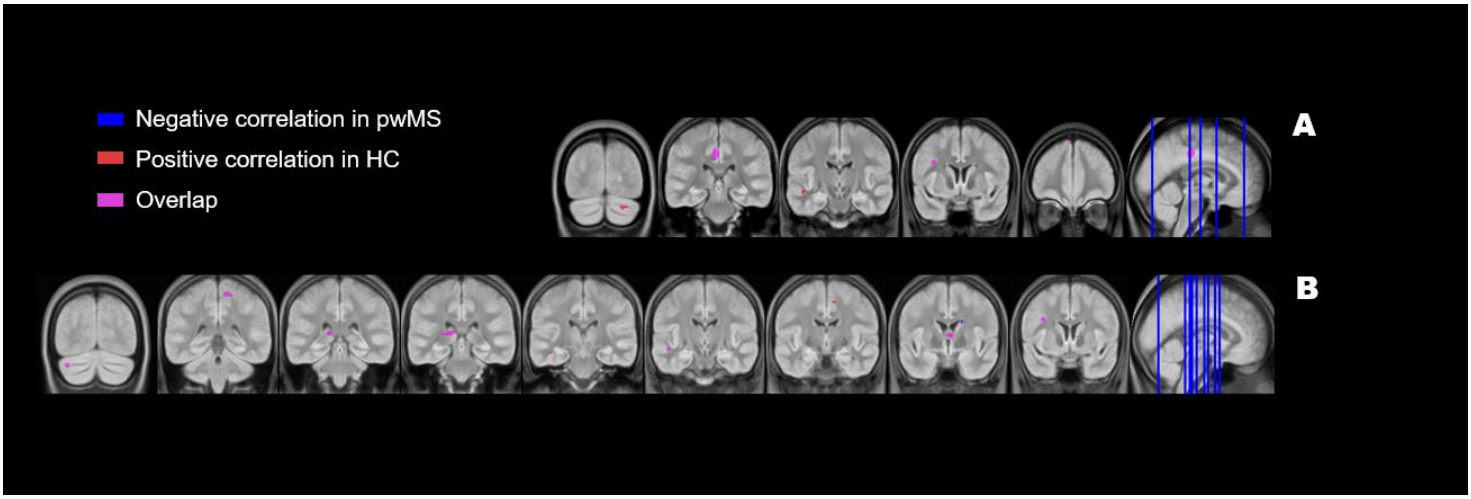

Figure 2. Coronal view of regions with group-specific correlations between brain activity and trait fatigue. A: Correlations in the 2-Back vs. 1-Back contrast; B: Correlations in the 3-Back vs. 1-Back contrast. Region with negative correlations in people with multiple sclerosis (pwMS) are displayed in blue, positive correlations in healthy controls (HC) in red, and regions of overlap in violet (negative correlation in pwMS and positive correlation in HC).

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