The Specificity of fatigue cerebral substrates in early Multiple Sclerosis: *An f-MRI study*

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#MT115

Introduction

Fatigue is highly prevalent and debilitating in people with **Multiple Sclerosis** (pwMS), at any stage of the disease[1]. Among fatigue hypotheses in pwMS, alterations within the s**triato-thalamo-cortical** (STC) loop have provided numerous support from MRI studies[2,3]. Despite its high incidence, the pathophysiology of MS-fatigue in the **early stages of the disease** had rarely been studied, and no cognitive-task fMRI study has been reported so far .

Aim of the study: Exploring disease-specific functional substrates of fatigue in early pwMS and matched Healthy Controls (HC) during a working memory task of varying difficulty (N-Back) [4].

Methods

Population:

- 16 pwMS/17 HC
- Age mean(SD) : 31,44 (4,62) / 31,42 (5,99)
- Women n(%):12 (75%) / 13 (76,47%)
- Education mean(SD) : 14,19 (2,17) / 14,41 (1,46)
- Diagnosis (years) mean(SD) : 1,80 (1,22)
- EDSS median(range) : 1,75 (1-2,5)

MRI Parameters:

- Field: 3T
- Coil: 64 channels head coil
- multi-band EPI 2D Bold
- TR = 1170ms
- acquisition time ≈ 16min
- Structural: T1w and FLAIR
- Processing: SPM12

Design:

Participants performed a **fatigue induction** task (the Time Load Dual Back[5]) in conditions of **High or Low Cognitive Load** (HCL/LCL). The two conditions were counterbalanced and administered in two separate sessions (results described elsewhere[6]). After fatigue induction, participants performed an N-Back task (**1 to 3-Back**) in a **block-design fMRI experiment** (18 blocks: 6 per working memory load). The **Fatigue Scale for Motor and Cognitive Function** (FSMC[7], trait fatigue) was administered before the experiment. State fatigue was assessed with Visual Analogous Scales (VAS) before and after fatigue induction, as well as after the N-back task (T0 to T2).

Analyses:

Behavioral:

Behavioral data were analyzed with **Bayesian** statistics using JASP software, with **Mann-Whitney** tests for FSMC and **rmANOVAs** for VAS and N-Back (sensitivity index d', Reaction Times: RTs). Results were interpreted according to Jeffreys's[8] grades of evidence (BF> 3: evidence for an effect; BF< 0,33: evidence for absence of effect).

fMRI:

fMRI data were analyzed using a two-steps procedure (Fig. 1) taking into account **intra-individual variance** T-Tests**, then inter-individual variance** F-tests.

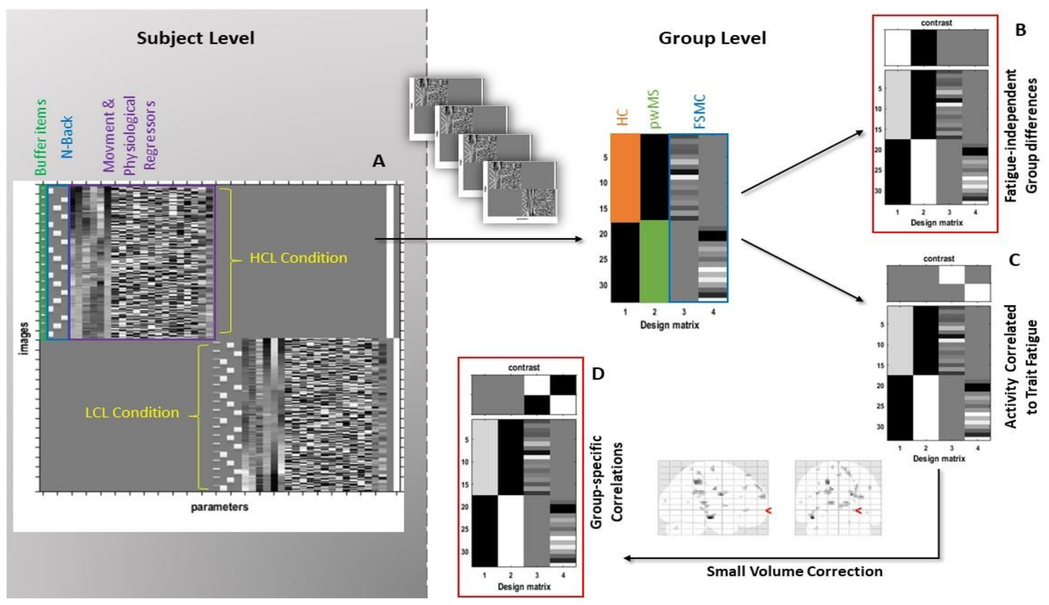

Figure 1. Statistical maps were first computed individually at the subject level **(A)**, with a GLM including the two fMRI sessions (yellow). 1B, 2B and 3B blocks (blue), and buffers items (green) were entered as individual regressors. Movement and physiological noise were added as regressors of no interest (purple). F-Test group level analyses were performed with FSMC added in covariable of interest (mean centered across all subjects). Group differences **(B)** were assessed in FSMC-independent brain activity**.** Trait fatigue-dependent activity (**C – D**) was next assessed. First, statistical activity maps were computed in all subjects **(C)** and used as small volume correction for analysis **(D)** which explored if correlations with FSMC score were group-specific. Results from **(B)** and **(C)** are reported and discussed here.

Results

Behavioral data:

Fatigue Scales:

- ***FSMC***: between group difference was inconclusive (BF_{10} = 0.38)
- ***VAS***: **Effect of time** was significant (Bf_{incl} > 3) with fatigue increasing following fatigue induction (T0 vs. T1, BF_{10} = 7.02) but remaining stable until the end of the N-Back (T1 vs. T2, BF_{10} = 0,15). Fatigue **load condition** (HCL vs LCL) did not influence subjective fatigue (BF_{incl} =0.169). Evolution of subjective state over time and across conditions followed a **similar pattern in pwMS and HC** (Condition*Time*Group interaction, all BF_{incl} = 0.256).

Performance:

	$BF_{inclusion}$ Mean RTs	$BF_{inclusion}$ d'
Difficulty (1-3 Back)	**2.12 e^{+27} *** **	**2.12 e^{+43} *** **
Condition (HCL v. LCL)	**0.261***	**0.173***
Group (pwMS vs. HC)	0.606	0.445
Difficulty*Condition	**0.107***	**0.102***
Difficulty*Group	**0.138***	0.972
Condition*Group	0.349	**0.286***
Difficulty*Condition*Group	**0.213***	**0.180***

Highlights:

- Performance decreased with task difficulty
- Fatigue induction load condition did not affect performance
- Effect of group was inconclusive

fMRI data:

Contrast assessing activity following HCL vs. LCL condition yield no significant result. Since fatigue load condition did not affect behavioral performance, analyses focused on the HCL session. The contrasts **1vs.2Back** and **1vs.3Back** were assessed.
fMRI results showed **no between-group difference regarding fatigue-independent** brain activity (Fig. 1B). However, FSMC **fatigue scale was correlated with cerebral activity** in a group specific manner (Fig. 2).

Cluster Size (voxels)	$p_{FWE\text{-}corrected}$ (Cluster)	Peak z	$p_{FWE\text{-}corrected}$ (Peak)	X Y Z	Regions	Correlation
Contrast 1 – 2-Back vs. HCL 1-Back						
1	**0.022***	3.44	**0.007****	-3 41 56	Left superior frontal gyrus	Pos in HC Neg in MS
6	**0.018***	3.75	**0.002****	-33 2 29	Left precentral sulcus	Pos in HC Neg in MS
8	**0.017***	3.92	**0.001****	-48 -13 -13	Left inferior temporal sulcus	Pos in HC
16	**0.012***	3.93	**0.001****	-6 -31 35	Left mid cingulate	Pos in HC Neg in MS
1	**0.022***	3.36	**0.010***	27 -79 -31	Right cerebellum	Pos in HC
Contrast 2 – 3-Back vs. HCL 1-Back						
8	**0.026***	3.86	**0.005****	15 -37 59	Right postcentral gyrus	Pos in HC Neg in MS
4	**0.040***	3.64	**0.012***	-36 2 26	Left precentral sulcus	Pos in HC Neg in MS
4	**0.040***	3.52	**0.018***	-48 -16 -13	Left inferior temporal sulcus	Pos in HC Neg in MS
1	0.059	3.25	**0.047***	9 -10 50	Cingulate motor area	Pos in HC
12	**0.019***	3.56	**0.017***	-15 -13 8	Left pulvinar thalamus	Pos in HC Neg in MS
3	**0.044***	3.44	**0.025***	0 -1 8	Right anterior thalamus	Pos in HC Neg in MS
4	**0.040***	3.30	**0.040***	18 -4 23	Right caudate	Neg in MS
5	**0.035***	3.37	**0.031***	-36 -76 -34	Left cerebellum	Pos in HC Neg in MS

Highlights:

- While fatigue is associated to increased cerebral recruitment in HC, the opposite pattern is observed in pwMS
- Fatigue is associated with regions from the STC loop, early in the disease
- Parietal and temporal regions associated to fatigue may relate to perception of effort and attention processes
- Early structural alterations of the brain connectome in pwMS may lead to alternative fatigue-related functional networks

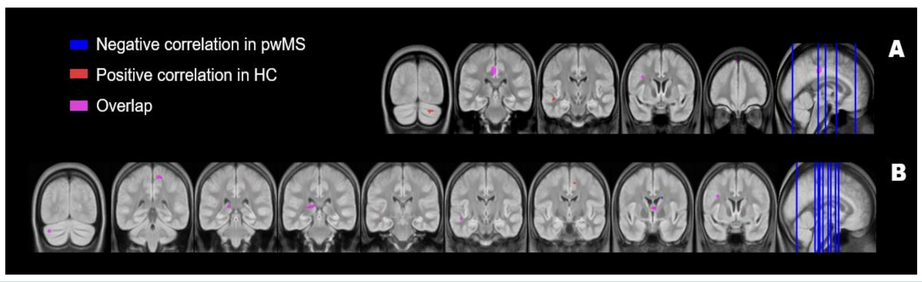

Figure 2. Group-specific correlation with the FMSC score for the 1vs.2Back **(A)** and the 1vs.3Back **(B)** contrasts.
Overlap: Negative correlation in pwMS & Positive in HC

Conclusion

- **Specific activation patterns** relating to fatigue in pwMS and HC, despite **similar behavioral performance and subjective fatigue**.
- **Implication of the STC and effort perception** (precentral sulcus) **networks** in fatigue pathophysiology, form the very early stages of the disease.
- **Activity of these areas** during a cognitive task is **negatively associated** to subjective feeling of fatigue in every-day life (trait scale) in pwMS.

SCAN ME

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