No volumetric and metabolic differences in the brain between severely fatigued and non-fatigued disease-free cancer survivors

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Purpose Postcancer fatigue (PCF) is a frequently occurring, severe, and invalidating problem, impairing quality of life. Cognitive behavior therapy (CBT) addresses the perpetuating factors of PCF and has a clinically relevant effect in reducing fatigue in severely fatigued cancer survivors.[1] However, until now, little is known about (neuro)physiological factors determining PCF. For non-cancer patients with chronic fatigue syndrome (CFS), certain characteristics of brain morphology and metabolism were already identified.[2-4] In CFS patients, significantly reduced gray matter volumes,[2] significantly reduced levels of N-acetylaspartate in the hippocampus,[3] and significantly increased ratios of choline to creatine in the occipital cortex were observed.[4] It may be hypothesized that these volumetric and metabolic traits are a reflection of fatigue in general and may also be of importance for PCF. **Aim:** to assess if N-acetylaspartate levels in the hippocampus, ratios of choline:creatine in the occipital cortex, subcortical brain volumes, and global volumes of gray and white matter are different between non-fatigued and severely fatigued disease-free cancer survivors, and to examine the effect of CBT on these volumetric and metabolic parameters in severely fatigued disease-free cancer survivors.

Methods Thirty-six severely fatigued cancer survivors were included in the randomized controlled trial, of which 22 patients were randomly assigned to the intervention condition (CBT) and 14 patients to the waiting list condition (WL). Both patient groups were assessed twice, at baseline and at six months follow-up. Baseline measurements of 20 severely fatigued cancer survivors were compared with 20 age- and sex-matched non-fatigued cancer survivors. Non-fatigued patients were assessed once. Fatigue severity was measured by the fatigue severity subscale of the Checklist Individual Strength. All participants had completed treatment of a malignant, solid tumor minimal one year earlier and had no evidence of disease recurrence. Patients with a brain tumor in the past or with a co-morbidity that could explain fatigue were excluded. MR measurements were performed on a 3T Siemens MR system using the standard head coil. High-resolution T1-weighted images (voxel size 1mm^3, TR=2300ms, TE=3.16ms) of the whole brain were acquired using an MPRAGE sequence. Segmenting gray and white matter was performed using the voxel-based morphometry toolbox in the SPM5 package.[5] Segmentation of subcortical brain structures was performed using the FIRST module of FSL 4.1.4.[6] Subcortical brain volumes were expressed as a percentage of total brain volume, defined as the sum of white matter volume and gray matter volume. T1-weighted images were used to position one 2D-magnetic resonance spectroscopic imaging (MRSI) slice through the hippocampus and a second 2D-MRSI slice through the occipital cortex. ^{1}H-spectra were acquired using the semiLASER pulse sequence (voxel size 10mm^3, TR=1500ms, TE=30ms for N-acetylaspartate levels in the hippocampus and TE=136ms for ratios of choline:creatine in the occipital cortex) and were analyzed using LCModel. Data of the CBT and WL group are presented as the percentage change from baseline to follow-up.

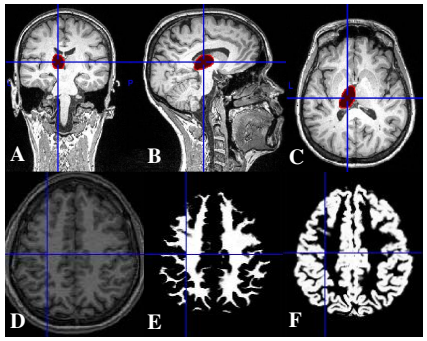

Figure 1. Example of subcortical brain segmentation (thalamus) in coronal (A), sagittal (B), and transversal plane (C), and an example of voxel-based segmentation, an anatomical (D), a white matter (E), and a gray matter image (F).

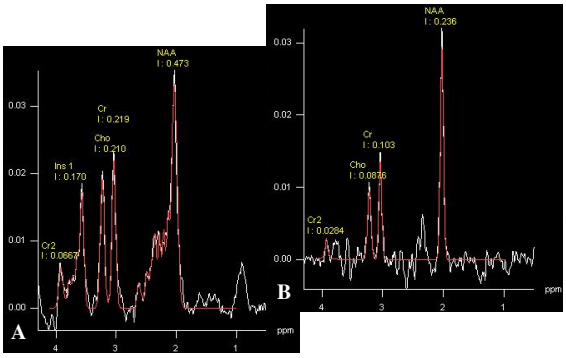

Figure 2. Example of a spectrum in the hippocampus (A) and in the occipital cortex (B).

Table 1. Comparison of non-fatigued and fatigued patients and of the CBT and WL condition

Parameter	Non-fatigued	Fatigued	CBT	WL
Gray matter	661.6±60.4 ml	689.1±76.8 ml	-0.66±1.39%	-0.41±1.10%
White matter	501.3±62.4 ml	530.8±94.3 ml	-0.20±0.76%	-0.21±0.86%
Accumbens	0.097±0.018%	0.090±0.013%	-1.50±8.18%	0.23±6.21%
Amygdala	0.299±0.040%	0.280±0.043%	1.60±6.28%	2.47±3.35%
Caudate nucleus	0.596±0.053%	0.606±0.054%	0.26±1.78%	0.50±2.00%
Hippocampus	0.679±0.065%	0.647±0.063%	-0.25±2.45%	-0.22±2.63%
Globus pallidus	0.319±0.031%	0.321±0.024%	0.28±2.71%	-0.89±2.23%
Putamen	0.891±0.065%	0.873±0.062%	0.24±1.93%	-0.91±2.07%
Thalamus	1.357±0.073%	1.318±0.077%	0.10±1.79%	0.79±1.33%
Brainstem	1.957±0.139%	1.911±0.130%	0.37±3.00%	-0.97±2.45%
Choline:Creatine	0.35±0.07	0.34±0.09	2.64±42.17%	8.11±32.26%
N-acetylaspartate	8.80±0.90 mmol/l	8.63±0.72 mmol/l	2.24±10.60%	0.32±7.72%

Results Global brain volumes (Figure 1), subcortical brain volumes (Figure 1), and metabolite concentrations and ratios (Figure 2) were not significantly different between non-fatigued and fatigued patients (all p>0.05, Table 1). Change scores of global brain volumes, subcortical brain volumes, and metabolite concentrations and ratios were not significantly different between patients in the CBT condition and patients in the WL condition (all p>0.05, Table 1). Patients in the CBT condition reported a significantly larger decrease in fatigue severity than patients in the WL condition (p<0.001, change scores respectively -45.5±22.7% and -16.4±25.0%).

Discussion In contrast to the results of uncontrolled trials in mostly small numbers of CFS patients, there are no significant volumetric and metabolic differences between non-fatigued and fatigued cancer survivors in the present study. The randomized controlled trial showed that CBT resulted in a significantly larger decrease in fatigue severity compared to a period of waiting for therapy, but had no significant effect on the studied parameters. This may suggest that, although PCF and CFS show strong resemblances as a clinical syndrome, the underlying physiology is different. It should be noted that in the MR spectroscopy part, we studied much larger group sizes in the present study than in the CFS studies, which thus may have suffered from too low statistical power.

Conclusion No relation was found between PCF and the studied volumetric and metabolic markers. Additional investigation is needed to explore biomarkers for PCF and to establish which are the essential elements of CBT for PCF.

References [1]Gielissen MF *et al* J Clin Oncol 2006, [2]de Lange FP *et al* Neuroimage 2005, [3]Brooks JC *et al* Br J Radiol 2000, [4]Puri BK *et al* Acta Psychiatr Scand 2002, [5]Ashburner J *et al* Neuroimage 2000, [6]Patenaude B *et al* Neuroimage 2011.