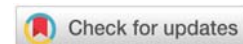




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## Research Article

# Alteration of brain structural organization after sepsis with Fatigue - a structural brain network analysis

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## Abstract

In our recent cross-sectional investigation, we found in sepsis survivors with persistent cognitive impairment a high number of patients who still suffer from Fatigue. This finding is of importance because Fatigue is highlighted as an associated long-term sequela after sepsis and therefore these patients require an appropriate rehabilitation therapy.

The aim of this study was to verify whether sepsis survivors with both cognitive impairment and Fatigue show any alteration in brain structure.

19 survivors of severe sepsis (longer than 2 years post sepsis) with persistent cognitive deficits ascertained with a battery of neuropsychological tests with cognitive and motor Fatigue symptoms (according to two German Fatigue scales) were investigated with a high-resolution.

T1 weighted image of the brain at a 3.0 Tesla MRI scanner. The Voxel-based morphometry (VBM) was performed using VBM8 toolbox. 19 age- and sex-matched healthy control subjects were also scanned with MRI.

VBM analysis revealed significant gray matter volume reduction in sepsis survivors particularly in the lateral frontal operculum and anterior cingulate cortex. These regions are part of the cingulo-opercular network which maintains alertness. Gray matter volume loss of the orbitofrontal cortex is functionally associated with Fatigue.

These findings emphasize that networks of structural brain organization can be altered with corresponding clinical symptoms and neuropsychological deficits after sepsis.

## Introduction

Sepsis is an immunologically-guided inflammatory system disease which frequently causes complications in both the central and peripheral nervous system [1-3]. In the last two decades, persistent cognitive impairment after sepsis critical illness has been described. These impairments affect different cognitive domains, e.g., attention, memory or executive function [4-11]. Several studies demonstrated a relation

between cognitive impairment after sepsis and structural damage of the brain [5,12-14].

In a recent study of sepsis survivors with cognitive impairments we also found a high number of patients with motor and cognitive Fatigue [14]. The underlying neurophysiological processes of persistent cognitive deterioration and Fatigue symptoms in sepsis survivors are still not fully understood. Therefore, in the current study we search for alteration of

structural (gray matter and white matter) organization of the brain in sepsis survivors with persistent cognitive decline and Fatigue that can explain any relationship between cognitive impairment and Fatigue. The Voxel-based morphometry analysis [15] is used as an objective method that does not require an *a priori* hypothesis about localization of possible structural changes.

## Patients and Methods

### Subjects

19 sepsis survivors (mean age 53.7 years, range 38 to 69 years, n = 8 female) were recruited from a former study [14]. They were included because they had a severe sepsis or a septic shock (with an ICU stay of at least 48h) longer than one year before inclusion. They presented in one domain out of a battery of neuropsychological tests a T-value less than 40 to represent a “below average” value of a cognitive test and in two German Fatigue questionnaires a corresponding cut-off value for Fatigue.

19 sex- and age-matched control subjects were included with no neuropsychological deficit in all tests and without Fatigue according to two German Fatigue questionnaires.

Exclusion criteria for all subjects were contraindication against MRI (e.g. metals, etc.) and former affection of central and peripheral nervous system (like stroke, brain injury, symptoms of Parkinson’s disease, history of MS, meningitis, psychiatric symptoms, etc).

This study was approved by the local ethics committee (Ethics Committee of the Friedrich Schiller University Jena, Faculty of Medicine, Nr. 3305-11/11).

### Neuropsychological assessment

The following battery of tests were evaluated with the Test of Attentional Performance (TAP - “Testbatterie zur Aufmerksamkeitsprüfung”, Zimmermann & Fimm, 2012):

1. Alertness. Alertness is distinguished according to TAP in tonic alertness (intrinsic maintenance of attention in order to provide higher cognitive function) and phasic attention (rapid change in attention due to a brief warning i.e. audio event) [16].
2. Divided attention. A simultaneous execution of an auditory and visual task is performed.
3. Selective attention was tested with a go/no-go paradigm.
4. For working memory an n-back (2-back) paradigm is applied.

The following five domains of verbal memory were tested with the use of the German version of the Auditory Verbal Learning Test (VLMT, Helmstaedter, Lendt und Lux, Beltz Test GmbH, Göttingen, 2001). Test includes 15 aurally presented

words with five immediate recall trials, an interference word list, short and long recall trials and a word recognition task. They present the following domains:

1. Memory span, 2. learning capacity, 3. delayed retrieval, 4. rate of decay and recognition. All test results are adjusted to age, sex and education. For all tests standardized values in terms of T-values are available. T-values less than 40 (= mean minus one standard deviation) are considered to represent a deficit result that is “below average” range.

### Fatigue

Two German Fatigue questionnaires are used (“Würzburger Erschöpfungsinventar” WEIMuS [17,18] and “Fatigue Skala für Motorik und Kognition” FSMK [19]. Both contain items for cognitive and motor Fatigue symptoms and corresponding cut-off values. For both scales the obtained scores were transformed into z-values and separately averaged for a Fatigue total, a Fatigue cognitive and a Fatigue motor score.

### MRI data acquisition

For each subject (sepsis survivors and controls) a high-resolution T1 weighted image of the brain was acquired at a 3.0 Tesla scanner (Magnetom TrioTim system, Siemens, Erlangen, Germany) using a standard receiving 12 channel head coil (TR=2300ms, TE=3.03ms, flip angle=9°, 192 slices, slice thickness 1mm, matrix 256×256, in-plane voxel size 1mm×1mm, and total acquisition time 5:20min).

### Voxel-based morphometry and statistical analysis

Data were processed and analyzed using the SPM8 software (Wellcome Department of Imaging Neuroscience Group, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>), where we applied VBM implemented in the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm.html>) with default parameters (for details see e. g [20]. After VBM was performed the modulated volumes were smoothed with a Gaussian kernel of 10 mm full width at half maximum (FWHM). Voxel-wise gray matter (GM) and white matter (WM) differences between sepsis survivors and controls were examined using independent-sample t-tests. In order to avoid possible edge effects between different tissue types, we excluded all voxels with GM or WM values of less than 0.1 (absolute threshold masking). A threshold of  $p < 0.001$  (corrected for multiple comparisons) with an extent of 200 voxels across the whole brain was applied. Age was used as nuisance effect, which means that all effect that can be explained by age was removed from the data.

We were interested in VBM difference between sepsis survivors and control group. We also correlated individual T-value of tonic alertness tests and Fatigue scores of each sepsis survivor with individual gray matter intensity of regions of interest, respectively. Regions of interest (voxel wise) were selected based on significant VBM difference



between the comparison of sepsis survivors and control group. Additionally, these regions must be selected from networks that are anatomically related to tonic alertness and Fatigue. These networks were the Cingulo-Opercular (CO) network that is related to alertness [21,22] and the orbito-frontal cortex that is associated to Fatigue [23].

Anatomical description is based on probabilistic cytoarchitectonic maps as implemented in the SPM anatomy toolbox ([http://www.fz-juelich.de/inm/inm-1/DE/Forschung/\\_docs/SPMANatomyToolbox/SPMANatomyToolbox\\_node.html](http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMANatomyToolbox/SPMANatomyToolbox_node.html)) [24].

## Results

### Neuropsychological assessment

All sepsis survivors showed in one and more tests deficits (10 patients with deficits in two or more domains). Tonic alertness was most frequently affected (in 12 patients, 63%), followed by working memory (in 10 patients).

### Fatigue

All patients exceeded the cut-off value of Fatigue total scores (in WEIMuS or FSMK). For WEIMuS (mean value of Fatigue total score = 44.1 ( $\pm 17.2$  SD)), Fatigue cognitive was 22.6 ( $\pm 10.6$  SD) and Fatigue motor was 21.6 ( $\pm 8$  SD).

For FSMK, the mean value of Fatigue total score of 75.8 ( $\pm 17.3$  SD) was evident, Fatigue cognitive was 37 ( $\pm 9.7$  SD) and Fatigue motor value was 38.8 ( $\pm 8.2$  SD).

### VBM

In sepsis survivors, the VBM analysis revealed reduced gray matter volume in the right temporal gyrus (in particular, middle temporal gyrus, medial temporal pole and inferior temporal gyrus) compared to healthy control subjects. Also reduced gray matter volume in sepsis survivors was evident in the right lateral operculum, in the right anterior cingulate cortex and in the left anterior and middle cingulate cortex as well as in the left orbitofrontal gyrus with extension to the left inferior frontal gyrus (Table 1, Figure 1).

In VBM analysis of white matter no difference between groups was found.

A significant correlation was found between individual T-value of tonic alertness and gray matter intensity within the anterior cingulate cortex (peak voxel with Montreal Neurological Institute coordinates, MNI x-, y-, z-coordinate: 15, 41, 18;  $r = 0.5$ ;  $p = 0.01$ ) as a part of the CO network. Voxel with the maximum intensity difference within the lateral frontal operculum was not correlated with the individual T-value of tonic alertness. A negative significant correlation was also found between individual Fatigue score and gray matter intensity of the orbitofrontal cortex (peak voxel MNI -30, 42, 3;  $r = -0.5$ ;  $p = 0.02$ ). Higher Fatigue score is associated

**Table 1:** Peak voxels (MNI coordinates) of VMB analysis between sepsis survivors and control group.

control > sepsis survivors	z-score	Peak voxel (MNI coordinates, mm)		
		x	y	z
superior temporal gyrus	4.1	56	-3	1
middle temporal gyrus	4.5	60	-11	-12
medial temporal pole	3.7	60	8	-20
inferior temporal gyrus	3.6	62	-51	-6
lateral operculum	3.9	50	-7	11
anterior cingulate cortex	4.6	15	41	18
	4.0	-8	44	1
middle cingulate cortex	3.7	15	20	36
orbitofrontal gyrus	4.4	-30	42	3
inferior frontal gyrus	3.4	-47	30	4

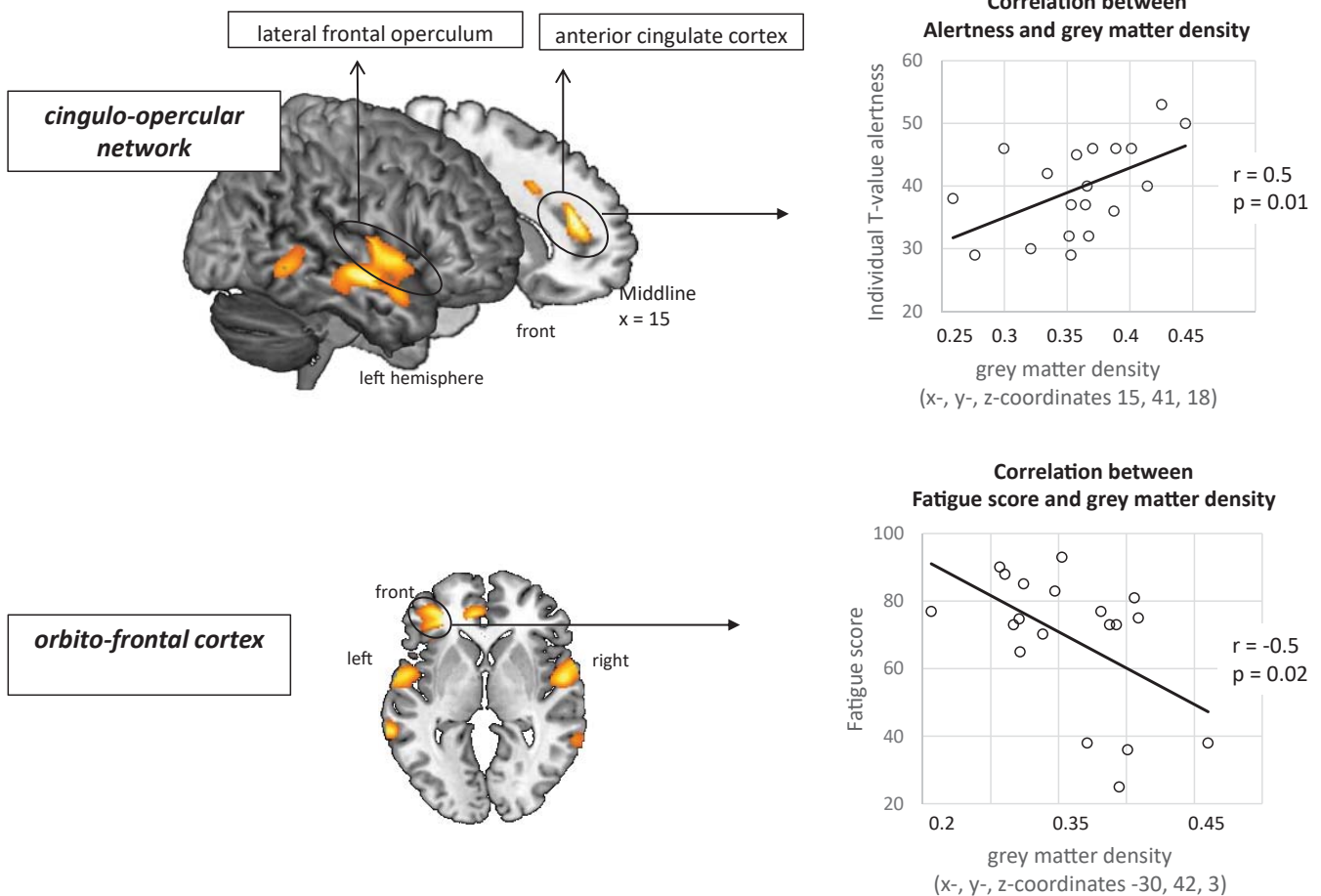
with less gray matter density.

## Discussion

While white matter integrity was not different between groups, sepsis survivors with cognitive impairment and Fatigue showed a reduced gray matter volume in the anterior cingulate cortex, lateral frontal operculum and orbitofrontal cortex (OFC) in comparison to the control group.

The anterior cingulate cortex and the lateral frontal operculum are part of the cinguloopercular (CO) network. The CO network is suggested to underlie intrinsically maintained tonic alertness [20,21] and is clearly distinguishable from other attention networks (i.e. dorsal attention network, fronto-parietal control network) at functional level [21,22,25]. Tonic alertness denotes mentally effortful, endogenously increased responsiveness [16,26] which is considered as precondition for higher attention functions as well as higher cognitive demands [26-28]. Affected basic attention function is therefore associated with higher cognitive deficits. This might explain the decline of higher cognitive functions like memory or executive functions in sepsis survivors.

Recent studies also represented structural damage in sepsis survivors with cognitive deficits in different regions, e.g. hippocampus, insula, cingulate cortex, precuneus, thalamus, cerebellum and frontal lobe [5,13,14], also in white matter regions [29]. The use of different methods explains diversity of findings. Studies used electroencephalography, or calculated volume of specific regions, applied diffusion tensor imaging or analyzed VBM but immediately after the onset of initial neurological deficit. These structural changes even with different methodological approaches emphasizes the idea, that sepsis as a systemic disease induces individually different finger prints of cognitive impairment in relation to affected brain structure and function. The affected CO-network in the current study could be the "tip of the iceberg",



**Figure 1:** Gray matter changes in different cortical regions. The lateral frontal operculum and anterior cingulate cortex are part of the cingulo-opercular (CO) network that is related to alertness. Sepsis survivors with cognitive deficits (mostly with alertness deficits) and Fatigue demonstrate gray matter alteration in specific network of CO and orbitofrontal cortex that is associated to Fatigue. Individual T-values of tonic alertness are close correlated with gray matter intensity of the anterior cingulate cortex (peak voxel with the maximum intensity difference with MNI coordinates x, y, z: 15, 41, 18). Individual Fatigue score are closely negative associated with the gray matter intensity of the orbitofrontal cortex. Higher Fatigue score is associated with less gray matter density (peak voxel with the maximum intensity difference with MNI coordinates x, y, z: -30, 41, 3).

since most included sepsis survivors had alertness deficits and Fatigue was an inclusion criterion. Therefore, further investigations are necessary with higher number of patients to analyze whether patients with Fatigue and deficits in other neuropsychological domains would also show a decline of CO network or alternatively other functional networks are affected.

Gray matter volume loss of left OFC with a maximum at the medial part is functionally associated with (task-related) Fatigue sensation [23]. The orbitofrontal cortex is generally affected by chronic stress [30-32]; for animals see [33-35] which is closely associated with Fatigue [36-38]. Moreover, alterations of the OFC are also associated with depression [39-41] which is often in co-occurrence with Fatigue [42-44]. Consequently, patients with clinical symptoms of Fatigue and alertness deficits after sepsis have altered networks of structural brain organization.

In the current descriptive study, we did not investigate the exact way how gray matter is declined in sepsis survivors

and which variables are closely associated with these changes. Clinical variables during acute stage of ICU stay e. g. occurrence of delirium, duration of delirium [4,5,8,9,12,10,45,46] and further specific risk factors like age, premorbid status of cognitive functioning or comorbidity of the sepsis patients [7] are risk factors for long-lasting cognitive impairment. Longitudinal serial data collection beginning from acute stage are necessary to understand the association between different clinical symptoms, laboratory-chemical tests, and other variables with brain structure changes.

## Conclusion

In the current study we compared sepsis survivors with cognitive deficits and Fatigue with a healthy sex- and age-matched control group. We found reduced gray matter volume in sepsis survivors in specific networks (CO-network, OFC) that are related to specific cognitive impairment and Fatigue. The use of another control group, for example sepsis survivors without cognitive deficits would probably present less alteration



in gray matter than a comparison with a healthy control group. Therefore, this circumstance warrants further investigation.

However, affection of the alertness network in Fatigue sufferers after sepsis renders the fact that physicians should be aware of Fatigue in sepsis survivors to provide patients with an appropriate therapy regime and to consider neuropsychological deficits for an adequate therapy [14].

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