Multiple Sclerosis and Related Disorders 6 (2016) 81–86

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Different cortical underpinnings for fatigue and depression in MS?

Katrin Hanken [a,b], Paul Eling [c], Jan Klein [d], Esther Klaene [e], Helmut Hildebrandt [a,b,*]

[a] University of Oldenburg, Department of Psychology, 26111 Oldenburg, Germany
[b] Klinikum Bremen-Ost, Department of Neurology, Züricher Str. 40, 28325 Bremen, Germany
[c] Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands
[d] Fraunhofer MEVIS Institute for Medical Image Computing, Universitätsallee 29, 28359 Bremen, Germany
[e] Neurological Rehabilitation Unit Oldenburg, Brandenburger Straße 31, 26133 Oldenburg, Germany

ARTICLE INFO

Article history:
Received 21 November 2015
Received in revised form
1 February 2016
Accepted 6 February 2016

Keywords:
Multiple sclerosis
Fatigue
Depressive mood
Brain atrophy
Cortical thickness measures

ABSTRACT

Background: Fatigue is a common complaint in MS patients but its origins are still not fully understood. A major difficulty is that fatigue seems strongly correlated with depression.
Methods: 95 MS patients and 15 healthy control subjects were included. The Fatigue Severity Scale and Beck's Depression Inventory were used to assess symptom-severity and to determine group membership for five groups: MS patients with and without fatigue, and with or without depressive mood, healthy controls. Participants were scanned using high-resolution structural 3D T1-weighted imaging. Cortical thickness for 84 areas was calculated using the NeuroQLab software in combination with the atlas for the Automated Anatomical Labeling software. A stepwise forward regression analysis was performed to predict group membership of the MS patients by thickness of cortical areas. We also performed a series of post-hoc ANOVAs to explore differences between the four patients groups and the healthy controls.
Results: About 20% of the patients suffered only from fatigue or only from depressive mood. Regression analysis explained 17.3% of the variance and thickness of the right inferior parietal cortex, middle temporal pole and parahippocampus contributed significantly to the model. Patients with pure fatigue showed a specific decrease in cortical thickness in the inferior parietal lobe, patients with both depressive mood and fatigue in the right middle temporal pole. Additional ANOVAs revealed cortical thinning in the right middle cingulate cortex in the group with pure fatigue as well as the groups with depression.
Conclusion: Fatigue and depression can be dissociated in larger MS-patient groups using questionnaires and cortical thickness measures, but the cortical thickness measures only explain a small portion of variance of these neuropsychiatric symptoms.

1. Introduction

Fatigue is a common and disabling symptom for MS patients and the origins of fatigue are still not fully understood (Kos et al., 2008). A major difficulty is the fact that fatigue is strongly correlated with depression. This strong correlation is also noticeable at a conceptual level: depression presumably encompasses emotional, cognitive and somatic aspects of which fatigue is arguably the most significant. Some authors have argued that it is impossible to distinguish between these two symptoms on the phenomenological-behavioral level and the somatic level (Feinstein, 2015).

However several findings indicate that some features can be distinguished that are associated with either fatigue or depression. In a clinical sample there will be patients experiencing only fatigue without being depressed and vice versa. Moreover, fatigue and depression can be distinguished, at least partly, according to some underlying biological characteristics and consequences. We (Hildebrandt and Eling, 2014) and others (Christodoulou et al., 2009) showed that MS patients with depression tend to develop cognitive impairments in the course of the disease, which is not true for patients with fatigue. Concerning the underlying biological features, Gold and Irwin (2009) showed that fatigue was related to an increased number of CD8+ T-cells, whereas depression in MS was related to an elevated evening salivary cortisol level. This suggests that fatigue and depression are elicited by different somatic dysfunctions. There are also studies showing that fatigue and depression in MS may be related to changes in different brain areas. Studies focusing on fatigue show that it is often accompanied by atrophy in the frontal, cingulate and especially the parietal cortex (for a review Hanken et al. (2015)). Studies focusing on depression,

* Corresponding author at: Klinikum Bremen-Ost, Department of Neurology, Züricher Str. 40, 28325 Bremen, Germany.
E-mail address: helmut-hildebrandt@uni-oldenburg.de (H. Hildebrandt).

http://dx.doi.org/10.1016/j.msard.2016.02.005
2211-0348/

reveal a correlation with atrophy in the left prefrontal cortex (for a review Bonavita et al. (2013)) and the frontotemporal white matter (Feinstein et al., 2010).

Recently, we proposed that experiencing fatigue may be related to increased levels of cytokines signaling inflammation to hypothalamic structures and thus inducing sickness behavior (Hanken and Hildebrandt, 2014) (for a similar explanation, see Hanken and Hildebrandt (2014)). The feeling of fatigue would then be evoked by a reduction of a neurotransmitter (for example, noradrenaline or histamine) and a lack of neuronal modulation in frontal or parietal cortices. Focal atrophy in these areas, due to demyelination and neurodegeneration, may additionally enhance the feeling of fatigue and objective signs of fatigue, i.e., an impairment on vigilance tasks. In our model, fatigue is independent of depression (but may often be associated with depression, due to overlap of affected brain areas, for example the hypothalamus). If this model is correct, it can be postulated that fatigue and depression can occur separately if only brain areas, associated with just one of these symptoms, are atrophied. More specifically, our model predicts that fatigue is related to brain atrophy in the (right) frontal und parietal cortices and the cingulate gyrus (Hanken and Hildebrandt, 2014), whereas other research has shown that depression may be associated with changes in the paralimbic lobes (van Eijndhoven et al., 2013) and the left frontal cortex.

Previous studies examining the relation between brain atrophy and fatigue used regression analyses and often excluded patients with clinically relevant depression. This may lead to misleading results if subclinical depression plays a role in the experiencing of fatigue. To test our predictions we therefore analyzed MRI brain scans by dividing the patients into four groups: those with fatigue but without depression, those with depressive mood, but without fatigue, those with depression (incl. fatigue) and those with neither fatigue nor depression.

2. Methods

2.1. Patients

Ninety-five patients with MS according to the criteria of McDonald et al., (2001) participated: 69 relapsing remitting patients, 17 secondary and 9 primary chronic patients. Additional inclusion criteria were: at least 4 weeks after the last cycle of immunosuppressive treatment and no other prior psychiatric and neurological disorders. We also included 15 healthy controls (Table 1). All participants gave their informed consent and permission for the study was granted by the ethical board of the Bremer Physician Society.

2.2. Clinical investigation

An experienced neurologist assessed patients with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Moreover, patients performed the Multiple Sclerosis Functional Composite (Fischer et al., 1999), which is composed of the timed walk test (TWT), the nine hole peg test (NHPT) and the paced auditory serial addition test (PASAT). The Alertness test of the "Testbatterie zur Aufmerksamkeitsprüfung"(Zimmermann and Fimm, 1992) was used to measure simple reaction time, both for a non-cued and a cued (an auditory warning signal) condition, each presented twice, and with 20 trials per series. The participant has to press a key as soon as a cross appears at the center of the screen.

To assess fatigue status, we used the Fatigue Severity Scale (FSS) (Krupp et al., 1989). Patients with a score equal to, or higher than 5 were regarded as patients with fatigue. For depression, we used the German version of the Beck Depression Inventory (BDI) (Beck et al., 1985). We used the items A–O, the psychic items, to calculate the score for mood impairment and the items P–U (sleep, tiredness, body weight, loss of sexual interest and somatic

Table 1
Demographic data and mean scores on neuropsychological test for the various groups.

	Groups				
	Healthy controls	No fatigue, no depressive mood	Pure fatigue	Pure depressive mood	Depressive mood and fatigue
Male/female	M: 6/F: 9	M:18/F: 24	M: 4/F: 14	M: 4/F: 17	M: 2/F: 12
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	37.0 ± 10.5	42.9 ± 11.7	43.1 ± 6.3	38.7 ± 9.7	42.1 ± 7.5
Education (years)	11.5 ± 1.5	11.5 ± 1.6	11.1 ± 1.5	11.1 ± 1.4	11.3 ± 1.7
Duration since diagnosis (months)	Not applicable	94 ± 103	82 ± 72	46 ± 57	85 ± 81
Expanded disability status scale	Not done	3.1 ± 1.8	3.4 ± 2.2	2.9 ± 1.8	3.1 ± 2.3
Brain Parenchymal fraction	81.8 ± 2.6	81.0 ± 4.3	80.8 ± 4.8	82.6 ± 5.2	80.1 ± 4.5
Fatigue Severity Scale [a, b, c, d, e]	24 ± 6	30 ± 12	56 ± 3	35 ± 12	56 ± 6
Beck's Depression Inventory: psychological items[a, b, f, c, d, g, e]	2.80 ± 1.9	2.18 ± 1.5	3.4 ± 1.3	8.9 ± 2.7	11.5 ± 3.3
Beck's Depression Inventory: cognitive_somatic Items[a, b, c, h, i]	1.63 ± 1.8	3.1 ± 2.1	6.5 ± 2.7	5.2 ± 2.6	8.5 ± 3.1
Beck's Depression Inventory: Total Score[a, b, f, c, d, g, e]	4.4 ± 1.9	5.3 ± 1.8	9.9 ± 2.0	14.1 ± 2.7	20.0 ± 3.2
Alertness without cueing[a]	236.1 ± 37.7	246.6 ± 46.2	261.1 ± 39.9	277.9 ± 82.8	314.2 ± 142.5
Alertness with cueing[a]	224.6 ± 31.5	242.1 ± 43.5	248.9 ± 38.6	267.0 ± 90.5	296.3 ± 114.7
Timed walk test	Not done	5.8 ± 2.3	7.3 ± 3.3	5.2 ± 1.5	7.9 ± 6.4
Nine hole peg test	Not done	25.4 ± 8.1	26.5 ± 11.0	27.2 ± 16.5	26.1 ± 8.3
Paced auditory serial addition test	50.8 ± 9.4	45.4 ± 11.2	39.0 ± 12.3	41.1 ± 12.6	39.1 ± 14.4

Significant differences in post-hoc Bonferroni corrected *T*-tests:

[a] Depressive mood and fatigue/healthy controls.
[b] Depressive mood and fatigue/no fatigue no depressive mood.
[c] Depressive mood and fatigue/pure depressive mood.
[d] Pure depressive mood/healthy controls.
[e] Pure depressive mood/pure fatigue.
[f] Depressive mood and fatigue/pure fatigue.
[g] Pure depressive mood/no fatigue no mood.
[h] Pure fatigue/healthy controls.
[i] Pure fatigue/no fatigue no depressive mood.