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Integrity of hypothalamic fibers and cognitive fatigue in multiple sclerosis

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Abstract
Cognitive fatigue is a common and disabling symptom of multiple sclerosis (MS), but little is known about its pathophysiology. The present study investigated whether the posterior hypothalamus, which is considered as the waking center, is associated with MS-related cognitive fatigue. We analyzed the integrity of posterior hypothalamic fibers in 49 patients with relapsing-remitting MS and 14 healthy controls. Diffusion tensor imaging (DTI) parameters were calculated for fibers between the posterior hypothalamus and, respectively, the mesencephalon, pons and prefrontal cortex. In addition, DTI parameters were computed for fibers between the anterior hypothalamus and these regions and for the corpus callosum. Cognitive fatigue was assessed using the Fatigue Scale for Motor and Cognitive Functions. Analyses of variance with repeated measures were performed to investigate the impact of cognitive fatigue on diffusion parameters. Cognitively fatigued patients (75.5%) showed a significantly *lower* mean axial and radial diffusivity for fibers between the posterior hypothalamus and the mesencephalon than cognitively non-fatigued patients (Group*Target area*Diffusion orientation: $F=4.047$; $p=0.023$). For fibers of the corpus callosum, MS patients presented significantly *higher* axial and radial diffusivity than healthy controls (Group*Diffusion orientation: $F=9.904$; $p<0.001$). Depressive mood, used as covariate, revealed significant interaction effects for anterior hypothalamic fibers (Target area*Diffusion orientation*Depression: $F=5.882$; $p=0.021$; Hemisphere*Diffusion orientation* Depression: $F=8.744$; $p=0.008$). Changes in integrity of fibers between the posterior hypothalamus and the mesencephalon appear to be associated with MS-related cognitive fatigue. These changes might cause an

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altered modulation of hypothalamic centers responsible for wakefulness. Furthermore, integrity of anterior hypothalamic fibers might be related to depression in MS.

1. Introduction

In multiple sclerosis (MS) patients, fatigue is rated as one of the most common and most disabling symptoms. Its prevalence ranges from 65% to 97% and it tends to seriously impair approximately one third of all MS patients (Bakshi et al., 2000; Fisk et al., 1994; Ford et al., 1998; Krupp et al., 1988; Murray, 1985; van der Werf et al., 1998). MS-related fatigue seems to be multifactorial in nature, including both cognitive and physical components (Krupp et al., 1988). Even though it has been subject of numerous studies (Bakshi, 2003; Kos et al., 2008; Schwid et al., 2002), the exact pathology of MS-related fatigue remains poorly understood.

The hypothalamus is recognized as a key center for the regulation of wakefulness and sleep (Lin, 2000). Reciprocal interactions between anterior and posterior hypothalamic areas constitute one of the important hypothalamic mechanisms underlying alternation of sleep and wakefulness. The anterior hypothalamus is regarded to be the sleep center with GABAergic neurons, located in the ventrolateral preoptic area of the anterior hypothalamus, initiating and maintaining sleep, whereas the posterior hypothalamus is considered to be the wake center of the brain. Histaminergic neurons located in the tuberomammillary nucleus (TMN) of the posterior hypothalamus constitute one of the ascending activating systems and their exclusive role for wakefulness and arousal has been demonstrated in animal and clinical studies (Gillson et al., 2002; Lin and Jouvet, 1988; Lin et al., 1989; Lin, 2000; Monti et al., 1986; Parmentier et al., 2002; Welch et al., 2002). Mechanisms of histaminergic arousal involve ascending and descending projections of histaminergic neurons and their interaction with diverse neuronal populations such as wake-promoting regions of the brainstem, including the dorsal raphe and central superior nuclei in the mesencephalon and the locus coeruleus located in the pons (Haas and Panula, 2003; Thakkar, 2011). In general, the hypothalamus contains projections to various brain regions and hypothalamic impairment has been related to cognitive disturbances (Copenhaver et al., 2006). Especially the histaminergic system with its projections to almost all regions of the central nervous system (CNS) has been found to play a major role in the regulation of cognition (Alvarez, 2009).

Despite its relevance for the regulation of wakefulness, arousal and cognition, there are hardly any studies investigating the role of hypothalamic changes in relation to fatigue in MS patients. Huitinga et al. (2004) found hypothalamic lesions in 15 out of 16 MS patients. Moreover, this group identified demyelinating lesions in and adjacent to the hypothalamus in 95% of MS patients (Huitinga et al., 2001). Recently, Zellini et al. (2009) used magnetic resonance imaging (MRI) T1 relaxation time as a sensitive metric for the detection of pathological changes in the hypothalamus of 44 relapsing-remitting MS patients. They found a significant correlation between T1 relaxation time in the hypothalamus and the Fatigue Severity Scale (FSS) score, indicating an association between pathological changes in the hypothalamus and MS-related fatigue. Finally, inflammation-induced suppression of histaminergic neurons was found to be associated with impaired arousal (Gaykema et al., 2008).

These findings suggest that the hypothalamus, especially the histaminergic system located in the TMN of the posterior hypothalamus, is associated with the underlying mechanism responsible for MS-related cognitive fatigue. Therefore, the aim of this study was to investigate the relationship between MS-related cognitive fatigue and the integrity of fibers originating or terminating in the posterior hypothalamus using diffusion tensor imaging (DTI).

Axial diffusivity (AD) and radial diffusivity (RD) strength per voxel may enable us to distinguish between axonal loss and demyelination, the two major aspects of MS pathology (Budde et al., 2007; Fink et al., 2010). Animal studies have demonstrated an increase in RD shortly after inflammation and a decrease in AD that correlated with axonal loss (Budde et al., 2007). Therefore, we used these parameters as measures of fiber integrity. We expected cognitively fatigued MS patients to show an increased RD and a decreased AD for posterior hypothalamic fibers when compared with cognitively non-fatigued MS patients and healthy controls.

To demonstrate the unique role of the posterior hypothalamus in the underlying mechanisms for MS-related cognitive fatigue, we also investigated fibers of the anterior hypothalamus and the anterior and posterior parts of the corpus callosum. If only the posterior hypothalamus is associated with cognitive fatigue, integrity of anterior hypothalamic fibers and the corpus callosum should not differ between cognitively fatigued and non-fatigued MS patients. To corroborate our findings, we replicated these analyses using an earlier collected data set of our group (see Fink et al. (2010)).

2. Methods

2.1. Study population

A total of 49 MS patients with a relapsing-remitting disease course according to the McDonald criteria (Polman et al., 2011) and 14 age- and gender-matched healthy controls participated in this study. Patients were recruited from MS support groups in Bremen and surroundings or have been patients of the Department of Neurology of the Klinikum Bremen-Ost, Germany. Patients received either immunomodulatory therapy (60%) or no disease modifying drugs (40%). Individuals with an MS relapse or using corticosteroids during the last four weeks, under legal care and/or with a diagnosis of any neuropsychiatric illness according to the fourth edition of the diagnostic and statistical manual of mental disorders (American Psychiatric Association, 2000) were excluded from the study. The study was approved by