INTRODUCTION

Narcolepsy is a debilitating disorder, characterised by excessive daytime sleepiness and cataplexy. The disease strikes approximately 1 in 2,000 people, and is the only known neurological disorder that specifically affects the generation and organisation of sleep.

Recent research has implicated the hypothalamic hypocretin (orexin) system in the pathophysiology of narcolepsy. In humans, most patients lack hypocretin-1 in the cerebrospinal fluid (CSF). Furthermore, hypocretin mRNA was undetectable and immunoreactive hypocretin-1 and -2 were greatly diminished in the hypothalamus of a small number of narcoleptic patients studied. Based on these findings, together with the tight association between narcolepsy and the HLA subtype DQB1*0602, it has been hypothesised that an autoimmune mediated degeneration of hypocretin neurons is responsible for the disease. Alternatively, other (non-structural) factors may influence hypocretin synthesis or detection, such as mutations in transcription factors important for hypocretin expression.

Voxel-based morphometry (VBM) is a fully automated, sensitive whole brain morphometric MRI technique that detects regional structural changes on a voxel-by-voxel basis between groups of subjects. VBM has been able to detected subtle hypothalamic changes, for example in patients with cluster headache. In the present study, we investigated whether degeneration of hypocretin neurons in the hypothalamus or their projection areas is associated with macroscopic structural change that can be visualised using VBM.
DISCUSSION
Recent research points to possible degeneration of hypocretin neurons in the hypothalamus of narcoleptic patients. In the present study we used VBM, a sensitive, unbiased MRI morphometric method, to detect structural changes in the brain. The absence of detectable structural changes in the brain of narcoleptic patients is either due to a relative insensitivity of VBM to detect subtle hypothalamic changes, or challenges the hypothesis that a degenerative process is involved.

To consider the first scenario; the hypothalamus has relatively poor contrast resolution, owing to its intrinsic anatomy, with embedded nuclei and adjacent white matter connections. This provides a challenge for segmentation, but VBM would still be sensitive to a systematic difference in the anatomy, and therefore we performed separate grey and white matter analyses. Importantly, VBM has previously detected subtle changes in the hypothalamus in patients with cluster headache matching PET activations, and within the hippocampi of a small group of taxi drivers that corroborated independent, accurate region of interest measurements and functional data. It is possible that the total volume of hypocretin neurons is too small to cause macroscopic structural change detectable by VBM, even if neuronal degeneration is present. If the hypocretin producing cells are destroyed indeed, this would be a remarkably selective process.

Our results may also indicate that the affected hypocretin neurons remain intact. It is worth noting that the two available post mortem studies could not formally prove cell loss, because an independent marker for hypocretin neurons does not exist. Interestingly, remaining hypocretin-positive neurons were normal in size, and showed no abnormal morphology or other signs of neuronal damage. Various mechanisms, other than neuronal degeneration, could be responsible for the hypocretin deficiency in narcolepsy. Genetic factors could play a role: although highly penetrant mutations in the hypocretin gene are extremely rare, several polymorphisms have been described in this locus. Recently, a polymorphism in the promotor region of the hypocretin gene was shown to be linked to narcolepsy. Although functional studies were not performed, such DNA changes may influence the capability of neurons to synthesise hypocretin. Mutations in transcription factors required for hypocretin transcription, or alterations in proteins crucial for proper splicing of the hypocretin mRNA, may have the same effect. In conclusion, there are no macroscopic structural changes detectable in the brains of narcoleptic patients, using a highly sensitive morphometric approach. These results suggest either that narcolepsy is associated with microscopic changes, undetectable by VBM or that functional abnormalities of hypocretin neurons are not associated with structural correlates.

SUBJECTS AND METHODS

Subjects
Fifteen narcoleptic patients (mean age: 44.7±14.3 years, 8 females) and fifteen healthy controls (mean age: 44.5±14.2 years, 8 females) were included after written informed consent. All patients were clinically evaluated by a neurologist experienced with narcolepsy (GJL). They all had findings typical for narcolepsy on overnight polysomnography and a Multiple Sleep Latency Test (MSLT), and were HLA DQB1*0602 positive. Moreover, all patients had no detectable CSF hypocretin-1.

MRI data acquisition
A 1.5 Tesla MRI system (Philips Medical Systems, Best, the Netherlands) was used to perform a 3-dimensional T1-weighted gradient-echo pulse sequence (repetition time: 26 ms, echo time: 12 ms, flip angle: 45 degrees). Image parameters were chosen to optimise grey-white matter contrast. All images were evaluated by an experienced neuroradiologist (MAvB), and were unremarkable.

Data pre-processing for voxel-based-morphometry
VBM is based on a sophisticated whole brain technique which registers images from groups of subjects into a common stereotactic space, in order to detect local differences in grey (or white) matter density. The VBM methodology has been described in detail elsewhere.

Statistical analysis
Data were analysed with statistical parametric mapping (SPM99) employing the framework of the General Linear Model. Regionally specific differences in grey (and white) matter between groups were assessed statistically using a two-tailed contrast, testing for increases or decreases in grey (or white) matter. We controlled for global differences in voxel intensity between scans by including the global mean grey (or white) matter values as a confounding covariate.

RESULTS

Global grey and white matter
There was no significant difference between global grey matter volume, F(1,28)<1, or white matter volume, F(1,28)<1, between patients with narcolepsy and controls.

Regional grey and white matter
VBM detected no significant regional differences in grey or white matter between patients with narcolepsy and controls. Even when we lowered thresholds and applied a small volume correction, no differences between the groups were found.
Ambulatory measurement of critical flicker fusion frequency: reflecting fatigue during mental effort?

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INTRODUCTION
Mental fatigue at work is not only an interesting scientific topic; it is also a pressing social problem. For instance, in The Netherlands about one in every three work disability benefit recipients are assessed as work disabled on mental grounds. The vast majority (approximately 90%) suffer from chronic job stress and burnout, mental states that closely relate to mental fatigue.

Mental fatigue is defined as the change in the psychophysiological control mechanism that regulates the task behaviour, resulting from previous mental and/or physical effort which have become burdensome to such an extent that the individual is no longer able to adequately meet the demands that the job requires on his or her mental functioning; or that the individual is able to meet these demands only at the cost of increasing mental effort and the surmounting of mental resistance. In other words, mental fatigue reflects both lacking capability and lacking motivation. This agrees with Edward Thorndike who concluded over eighty years ago that the basic tenet of mental fatigue is ‘the intolerance of any effort’.

Acute mental fatigue is to be distinguished from chronic mental fatigue. The former is characterised by reversibility, task-specificity, and the functional use of compensation mechanisms. Acute fatigue disappears after a period of rest, when tasks are switched, or when particular strategies are used (e.g. working at a slower pace, using less demanding information processing strategies, or spending additional effort).1 In contrast, chronic mental fatigue is irreversible, not task-specific, and the compensation mechanisms that were useful in reducing acute fatigue are no longer effective.

REFERENCES