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Abstract

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Reference


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Cortical morphometry in narcolepsy with cataplexy

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SUMMARY

The sleep–wake disorder narcolepsy with cataplexy is associated with the loss of hypocretin-(orexin-) producing neurons in the lateral hypothalamus. Several studies have reported abnormal cerebral activation in patients with narcolepsy with cataplexy. It remains unclear, however, whether these functional changes are related to structural alterations, particularly at the cortical level. To quantify structural brain changes associated with narcolepsy with cataplexy, we used high-resolution T1-weighted magnetic resonance imaging (MRI) in 12 patients compared with 12 healthy participants matched for age and gender. Subcortical and regional cortical volumes were measured using a method unbiased by non-linear registration. Further whole-brain analyses were conducted, measuring cortical characteristics, such as cortical thickness and gyriﬁcation, at thousands of points across each hemisphere using validated algorithms. Statistical analyses accounted for an effect of age and gender. We observed decreased cortical volume in the left paracentral lobule and increased cortical volume in the left caudal part of the middle frontal gyrus in narcoleptic patients compared with controls. Cortical thickness in prefrontal areas was inversely correlated with the severity of narcolepsy. Further, we observed several clusters of cortical thinning in patients with childhood or adolescent onset of narcolepsy compared with patients with adult onset of the disease. Our results suggest that specific anatomical changes may differentiate subgroups of narcolepsy patients with different clinical proﬁles (such as varying symptom severity or different age at onset). Future studies with larger groups of sleepy patients are required to assess whether distinct patterns of anatomical changes may distinguish narcolepsy from non-hypocretin-deﬁcient hypersomnia disorders.

INTRODUCTION

Narcolepsy with cataplexy is a sleep–wake disorder affecting one in 2000 individuals, and is characterized by excessive daytime sleepiness and cataplexy, i.e. loss of postural muscle tone when experiencing strong emotion. The pathophysiology of narcolepsy was unravelled mainly by animal studies showing a loss of hypocretin-(orexin-) producing neurons in the lateral hypothalamus (Chemelli et al., 1999), which was conﬁrmed by human postmortem studies in narcolepsy patients (Thannickal et al., 2000).

Hypocretin neurons are connected to multiple brainstem and midbrain arousal systems, and have widespread excitatory connections to the cortex. Thus, the loss of wake-promoting hypocretin neurons is associated with enhanced sleepiness and higher rapid eye movement (REM) sleep pressure.

Functional brain imaging studies in humans using single-photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) have suggested that the loss of hypocretin neurons may be associated with abnormal brain activity across several cortical or subcortical...
regions, in particular those involved in emotion regulation. For instance, decreased basal cerebral perfusion has been reported in the thalamus, caudate and several cortical areas such as the dorsolateral prefrontal cortex, the parahippocampal gyrus and the cingulum during waking state at rest (Joo et al., 2005). Compared to controls, patients showed abnormal activity across limbic–mesolimbic circuits during humour (Schwartz et al., 2008) and reward processing (Ponz et al., 2010). However, only a few studies to date used structural MRI to identify whether morphological brain changes are associated with the disease. Aside from the fact that functional brain changes are often related to structural brain changes, many other arguments suggest altered cortical or subcortical structures in narcolepsy. First, many studies reported structural brain changes in various other sleep–wake disorders, such as insomnia (Altena et al., 2006; Draganski et al., 2002; Joo et al., 2009; Kim et al., 2009), as well as in temporal (Joo et al., 2009; Kaufmann et al., 2002) and limbic (Kim et al., 2009) regions. The variability (and inconsistencies) in previous findings may rely on patient sampling, on methodological issues, or both. VBM is indeed highly affected by the non-linear registration process, possibly showing opposite results as a consequence of the parameter choice (Eckert et al., 2006). The aim of the present study was to quantify structural brain changes associated potentially with narcolepsy using a method unbiased by non-linear registration that provides accurate measurements of the subcortical and cortical volumes. This method, implemented in FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/), produces precise three-dimensional (3D) reconstructions of the cortex which, in turn, also permit the measurement of cortical thickness or folding (gyrification) at thousands of points across the hemisphere.

METHODS

Participants

Patients with narcolepsy–cataplexy

Twelve individuals with narcolepsy with cataplexy who have been reported previously participated in the current study (seven females, five males). The clinical characteristics of the patients are detailed extensively in Poryazova et al. (2009), with the exception that patients 3 and 13 of this previous study could not be included in the present examination because of motion artefacts that impaired accurate 3D cortical reconstructions. All participants had typical cataplexy and had a confirmed human leucocyte antigen (HLA)-DQB1*0602 haplotype. Cerebrospinal fluid (CSF) hypocretin concentrations were available in eight of the 12 participants and were abnormally low in all tested participants. The 12 patients had an average age of 28.8 ± 6.8 years (range 19–39 years).

Patients had an average Epworth sleepiness scale score of 14.8 ± 4.2 (range 7–21, ≥10 in 11 of 12 patients, ≥14 in seven of 12 patients), an average Ullanlinna narcolepsy scale score of 21.7 ± 8.1 (range 9–36, ≥14 in 10 of 12 patients) and an average Swiss narcolepsy scale score of −44.8 ± 29.2 (range −101 to 6). Scores higher than 14 at the Epworth sleepiness scale or at the Ullanlinna narcolepsy scale are typical for narcolepsy. Conversely, scores at the Swiss narcolepsy scale are suggestive of a narcolepsy when below 0. The patients also completed the Sleep Apnea–Sleep Disorders Questionnaire, and had an average sleep apnoea score of 30.5 ± 5.9 (range 21–40). Furthermore, the patient group scored highly at clinical scores measuring anxiety [Beck Anxiety Inventory (BAI)]: 14.2 ± 7.3 (range 4–25, ≥10 in eight of 12) and measuring depression [Beck Depression Inventory (BDI)]: 12.8 ± 10.6 (range 1–31, ≥10 in six of 12). Disease duration varied between 1 and 27 years (mean: 12.7 ± 8.3 years).

All patients on medication discontinued drugs 2 weeks before the study [five were taking modafinil (one in combination with fluoxetine and one in combination with venlafaxine); one was taking clomipramine; one was taking ephedrine].

Healthy control group

The comparison group was comprised of 12 healthy age- and gender-matched controls without sleep–wake or neurological disorders (seven females, five males, aged 31.5 ± 6.2 years, range 24–40). There was no difference in mean age between patients and controls (P = 0.312).

Sleep questionnaires were completed by 10 of the 12 control participants. The control group had an average score of 5.5 ± 2.3 (range 3–10) at the Epworth sleepiness scale, 5.1 ± 2.5 (range 2–8) on the Ullanlinna narcolepsy scale and 25.3 ± 12.2 (range 9–43) on the Swiss narcolepsy scale. Furthermore, the control group had an average sleep apnoea...
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Cortical thickness and cortical gyrification

Cortical thickness was measured in the native space of the images, as the shortest distance between the white (grey–white boundary) and the pial (grey–CSF interface) surfaces. As a result, cortical thickness values with a submillimetre accuracy were available at more than 150 000 points over each hemisphere. Finally, based on the outer cortical surface reconstruction (pial surface), local Gyrification Index (IGI) was measured at thousands of points across each hemisphere using previously validated algorithms (Schaer et al., 2008). IGI is a surface-based measurement of the degree of cortical folding that iteratively quantifies the amount of cortex buried within the sulcal folds in the surrounding circular region. Changes to local gyrification are thought to reflect a disruption in the early process of cortical expansion (in-utero and during the first months of postnatal life).

Statistical analyses

Effect of diagnosis

We used analyses of covariance (ANCOVAs) to compare cerebral, cerebellar and subcortical volumes between groups, adding age and gender as covariates. In order to identify potential regional cortical alterations, we subsequently applied a multivariate analyses of variance (MANCOVA) on the 32 gyral regions in each hemisphere, with diagnosis as the fixed factor and both age and gender as covariates. The comparisons of cortical thickness and gyrification over the whole brain used a study-specific template which was created with the make_average_subject function implemented in Freesurfer. Statistical analyses employed a general linear model (GLM) to estimate the effect of diagnosis, age and gender on thickness or gyrification at each cortical point. Cortical thickness or gyration changes with age were fitted using a linear model. Results are reported both with a statistical threshold of uncorrected \( P < 0.01 \) and after correcting for multiple comparisons using the false discovery rate at the corrected significance threshold of \( P < 0.05 \). Only clusters with an area > 2 cm² are shown.

Effect of disease duration and age at onset

Within the group of patients, whole-brain analyses were conducted to search for any correlation between regional cortical volume or cortical thickness and disease duration. Apart from searching an effect of disease duration, we also aimed at identifying whether cortical volume and thickness differed between patients with early and patients with late onset of narcolepsy. For that purpose, we divided our sample of participants into two groups according to the median age at onset of the narcolepsy symptoms. This resulted in a group of patients with narcolepsy onset during childhood or adolescence (mean age at onset: 10.8 ± 5.0, range 6–16 years) and a group of patients with adult onset of the disease (mean age at onset: 18.6 ± 1.8, range 17–21 years). All the

Regional cortical volumes

Subsequent to cortical reconstruction, the cortex was also subdivided into units based on gyral and sulcal structures (Desikan et al., 2006). This parcellation method based on major sulci has been shown to be both valid and reliable, with high intraclass correlation coefficients between the manual and automated procedures for both cortical volume estimates and region boundaries. The parcellation produces 35 regions subdivided into 11 frontal regions, nine temporal regions, five parietal regions, four occipital regions, four parts of the cingulate cortex, one label for the insula and finally the corpus callosum, which is designed to improve the reliability of the placement of the other cortical labels (for details, please refer to Desikan et al., 2006). In the present study, the frontal pole and the banks of the superior temporal sulcus regions, which exhibited relatively poor reliability in the validation article, were excluded from statistical analyses. Cortical volume was therefore estimated for 32 regions of interest (ROIs) in each hemisphere for each subject.

Written informed consent was received from all patients and controls in accordance with protocols approved by the local ethics committee.

Imaging

Cerebral magnetic resonance images were acquired with a T1-weighted 3D volumetric pulse sequence using a Philips Achieva 3T scanner as a series of 180 contiguous axial slices, with a voxel size of 0.86 × 0.86 × 0.76 mm.

Cortical reconstruction and volumetric segmentation were performed using published algorithms included in the Freesurfer package (Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, MA, USA). Briefly, the processing consisted of removal of non-brain tissue, automatic segmentation of the subcortical grey matter structures and the extraction of cortical surfaces (Fischl et al., 2001). Both intensity and continuity information from the entire 3D MR volume are used in segmentation and deformation procedures, thus producing accurate representation of cortical thickness or volumes. These procedures have been validated against histological studies (Rosas et al., 2002) and shown to be reliable across scanner manufacturers and field strengths (Han et al., 2006). At the end of the reconstruction process, the following volumes were available: total cerebral and cerebellar grey and white matter volume, and the volumes of subcortical structures including thalamus, putamen, pallidum and caudate nucleus, as well as amygdala and hippocampus.

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The comparisons of cortical thickness and gyration over the whole brain used a study-specific template which was created with the make_average_subject function implemented in Freesurfer. Statistical analyses employed a general linear model (GLM) to estimate the effect of diagnosis, age and gender on thickness or gyration at each cortical point. Cortical thickness or gyration changes with age were fitted using a linear model. Results are reported both with a statistical threshold of uncorrected \( P < 0.01 \) and after correcting for multiple comparisons using the false discovery rate at the corrected significance threshold of \( P < 0.05 \). Only clusters with an area > 2 cm² are shown.

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analyses used a GLM and corrected for an effect of age and gender on cortical thickness or regional cortical volumes.

**Correlation with the severity of narcolepsy**

Finally, whole-brain correlation analyses were performed between cortical volume or thickness and measures of severity of narcolepsy. First, to avoid multiple comparisons between cortical structure and similar measurements of symptom severity, we searched for an eventual colinearity between the different measurements available (i.e. MSLT Sleep Latency, Epworth Sleepiness Scale, Ullanlinna Narcolepsy Scale and Swiss Narcolepsy Score). The MSLT did not correlate with any of the other measurements (all \( P > 0.468 \)). However, we observed an important correlation between the scores obtained at the different questionnaires (all \( P < 0.001 \)). For that purpose, we conducted a principal component analysis (PCA) using the scores from the Epworth sleepiness, Ullanlinna narcolepsy and Swiss narcolepsy scales. The PCA resulted in the extraction of one main component, that we denote here ‘composite score’. The correlation analyses were thus conducted between cortical thickness or volume and the composite score of symptom severity. Because the MSLT did not correlate with any of the scores obtained at the questionnaires, correlation analyses were also conducted between cortical thickness or volume and MSLT. All correlation analyses were corrected for age and gender and are reported with a statistical threshold of \( P < 0.01 \), uncorrected. For thickness analyses, only clusters with an area >2 cm\(^2\) are shown.

**RESULTS**

**Effect of diagnosis**

We did not observe any significant difference, either in the total intracranial volume (patients: 1160 ± 131 cm\(^3\), controls: 1168 ± 111 cm\(^3\), \( P = 0.874 \), \( F = 0.026 \)) or in the cerebral volume between patients (954.4 ± 94.4 cm\(^3\)) and controls (953.7 ± 115.1 cm\(^3\), \( P = 0.891 \), \( F = 0.019 \)). Similarly, no group difference was observed in total cerebellar volume (patients: 124.3 ± 14.6 cm\(^3\), controls: 125.3 ± 15.1 cm\(^3\), \( P = 0.996 \), \( F < 0.001 \)). None of the examined subcortical structures showed any significant volume difference between groups.

The whole MANCOVA on the 32 cortical volumes did not pass the significance threshold (left: Wilk’s lambda: \( P = 0.653 \), \( F = 1.078 \); right: \( P = 0.927 \), \( F = 0.279 \)). However, in an exploratory approach, we looked at the individual follow-up ANCOVAs on each regional cortical volume. As illustrated in Fig. 1a, these post-hoc analyses revealed increased cortical volume in the left caudal middle frontal region in patients compared to controls (\( P = 0.038 \)), as well as decreased cortical volume in the left paracentral region (\( P = 0.030 \)).

Cortical maps of between-groups differences in cortical thickness are provided in Fig. 1b. Only one cluster of increased cortical thickness was observed in patients compared with controls. This cluster was located in the right frontal superior gyrus (Talairach coordinates: \( x = 24 \), \( y = 57 \), \( Z = 28 \) mm; cluster area: 361 mm\(^2\); \( P < 0.001 \), \( F = 29.01 \)), but did not hold the correction for multiple comparisons. No cluster of decreased cortical thickness was evidenced. No differences in local gyrification were found between patients and controls.

**Effect of disease duration and age at onset**

We did not find any significant correlation between regional cortical volumes and disease duration. Similarly, no significant cluster of correlation between cortical thickness and disease duration was shown.

No difference in total grey and white matter or in regional cortical volume was observed between the group of patients with early- and late-onset narcolepsy. However, a significant increase in the total volume of intracranial CSF was observed in patients with early- compared with late-onset narcolepsy (\( P = 0.007 \)). After correcting for disease duration, the increased CSF volume in patients with young onset remained moderately significant (\( P = 0.013 \)). Further, using whole-

![Figure 1. Cortical changes in patients with narcolepsy compared to controls. (a) Significant volumetric changes were observed in two regions of interest (ROIs): increased volume in the caudal part of the left middle frontal gyrus (illustrated in blue) and decreased volume in the left paracentral gyrus (illustrated in red). (b) Significantly increased cortical thickness was observed in the superior frontal gyrus of the right hemisphere in patients compared with controls.](image-url)
brain cortical thickness analyses, we observed a significant effect of the age at onset on cortical thickness. Thinner cortex was revealed in four clusters in the group of patients with young age at onset compared with the group of patients with adult onset of the disease. These regions encompass the left precentral gyrus, the right inferior parietal cortex and the right middle and superior temporal gyri (see Fig. 2 for a visual representation and for details about the significance, area and coordinates of these clusters). No region of significantly thicker cortex in the group of patients with early compared with late age at onset was observed. After correction for disease duration, all the clusters in the right hemisphere remained equally significant with $P = 0.001, 0.002$ and $0.004$ for, respectively, clusters 2, 3 and 4, whereas the significance of the cluster in the left hemisphere (cluster 1) increased to $P = 0.030$. To identify whether cortical thickness in the childhood or the adult-onset narcolepsy groups significantly differed from cortical thickness in the controls in these four clusters, we conducted further analyses using Scheffé’s post-hoc tests. As detailed in Fig. 2, cortical thickness in the adult-onset narcolepsy patients did not significantly differ from control participants in any of the four clusters, whereas patients with early onset had significantly thinner cortex in the left precentral and right inferior parietal regions compared with the control group.

**Correlation with the severity of narcolepsy**

When testing for correlations between the cortical thickness and clinical variables within the group of patients, no significant correlation was observed between cortical volume or cortical thickness and the mean sleep latency on MSLT. No correlation was shown between the composite score and any of the regional cortical volumes. However, two clusters of significant correlation between cortical thickness and the composite score were observed (see Fig. 3). These two clusters were located in the right prefrontal region and had the same direction of correlation: higher severity of narcolepsy was associated with decreased cortical thickness. Both clusters were highly significant ($P = 0.001$), and their significance remained unchanged after correction for the disease duration. It is also worthy of note that we did not observe any correlation between disease duration and symptom severity (all $P > 0.327$).

**Figure 2.** Cortical thickness differences between patients with early- and late-onset narcolepsy. The red/yellow colour denotes decreased thickness in patients with early compared to patients with late onset of narcolepsy; no cluster of increased thickness was shown. The first cluster at the left precentral gyrus ($P = 0.003, F = 17.92$) was located at the Talairach coordinates $x = -63, y = -1, Z = 23$ mm and had an area of $228 \text{ mm}^2$. The remaining clusters were situated in the right hemisphere, in the inferior parietal region (cluster 2): Talairach coordinates: $x = 50, y = -77, Z = 24$ mm; cluster area: $696 \text{ mm}^2$; $P < 0.001, F = 85.90$, at the most caudal extremity of the middle temporal gyrus (cluster 3: Talairach coordinates: $x = 55, y = -63, Z = 6$ mm; cluster area: $334 \text{ mm}^2$; $P < 0.001, F = 56.85$) and in the superior temporal gyrus (cluster 4: Talairach coordinates: $x = 70, y = -42, Z = 11$ mm; cluster area: $248 \text{ mm}^2$; $P < 0.001, F = 45.89$). Further comparison of the groups two × two revealed that the patients with early onset had a significantly thinner cortex in clusters 1 and 2 than the control participants ($^*P < 0.01$; $^{**}P < 0.001$).

**Figure 3.** Correlations between cortical thickness and the clinical composite score (lateral and frontal views). In both clusters, the significant correlation reflects that severe sleep disturbances are associated with thinner cortex. Cluster 1 in the right orbitofrontal region had an area of $238 \text{ mm}^2$ (Talairach coordinates: $x = 23, y = 57, Z = -15$ mm; $P = 0.001, F = 30.60$). Cluster 2 was located in the right superior frontal gyrus (Talairach coordinates: $x = 17, y = 71, Z = 5$ mm; cluster area: $213 \text{ mm}^2$; $P = 0.001, F = 30.60$).

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DISCUSSION
To the best of our knowledge, this is the first study measuring cortical and subcortical changes in narcolepsy with cataplexy using a method unbiased by the non-linear registration, as well as further measuring specific cortical features (i.e. thickness and gyration). Moreover, our study may have clinical implications by identifying brain circuits more vulnerable in narcoleptic patients, as revealed by the correlations analyses between structural measurements and severity of the disease. We would like to emphasize that our method identifies the boundaries of anatomical structures to measure their raw volumes. Small structures with unclear boundaries are thus not identified easily and reliably; this is why we do not provide volumetric measurements for the hypothalamus.

The results of the between-group comparisons demonstrated that narcolepsy patients had: (a) increased cortical volume in the caudal part of the left middle frontal gyrus and decreased volume in the left paracentral cortex in the post-hoc analyses; (b) one cluster with increased cortical thickness in patients with narcolepsy compared with controls, located in the right superior frontal gyrus; and (c) no difference in cortical gyration between both groups. Further analyses within the group of patients with narcolepsy revealed: (d) four clusters of significantly decreased cortical thickness in patients with early compared with adult onset of the disease; and (e) significant inverse correlations between cortical thickness in two prefrontal regions of the right hemisphere and a composite score of the severity of narcolepsy.

The volumetric group difference was restricted to the left hemisphere and was not particularly consistent with previously published studies. The first difference in cortical volume was a reduced grey-matter volume at the paracentral region, which corresponds to the medial part of the pre- and postcentral gyrus. Structural alterations in the medial frontoparietal cortex may be a common feature of some sleep–wake disorders, as previous studies have suggested an involvement of nearby cortical regions in primary (Altena et al., 2010) and secondary (Koenigs et al., 2010) insomnia.

Among the three clusters of reduced grey matter identified in patients with chronic primary insomnia (Altena et al., 2010), one was located at the intersection between the paracentral lobule and the precuneus. The same region may also play a role in the development of secondary insomnia, as the most common focal lesion associated with moderate-to-severe insomnia was located in the left dorsomedial frontal region in American war veterans who suffered brain damage from penetrating head injury (Koenigs et al., 2010). In insomnia, alterations to the paracentral region have been suggested to affect the maintenance of sleep through the disruption of the normal pathway of sleep slow waves propagation (Murphy et al., 2009). It is currently unknown if a similar phenomenon plays a role in narcolepsy. Indeed, even though narcolepsy is primarily a disorder of enhanced sleep and particularly REM sleep pressure, there is enough evidence that nocturnal sleep in narcolepsy is fragmented (Khatami et al., 2007), similar to patients with insomnia.

Additionally to a role for the paracentral region in sleep maintenance, altered function of the paracentral cortex may be associated more specifically with narcolepsy with cataplexy. Indeed, in a SPECT study, Joo et al. (2005) observed a widespread reduction in cortical metabolism, including a large cluster which was located around the paracentral region. More recently, another group observed selective hypometabolism of the same region in untreated compared to treated narcoleptic patients (Dauvilliers et al., 2010). Finally, two studies to date have measured the cerebral activation in four patients during classical cataplectic attacks compared to control participants (Dauvilliers et al., 2010), or with themselves during wakefulness or REM sleep (Hong et al., 2006). Both studies observed increased cortical metabolism, which was most prominent around the most dorsal and the medial parts of the sensorimotor cortex.

The second difference in cortical volume that we observed was an enlarged left caudal middle frontal gyrus, a region corresponding to the dorsolateral prefrontal cortex (DLPFC). This finding is compelling with regard to previously published morphometric studies in patients with narcolepsy showing a volume reduction in the right DLPFC and in the bilateral mesial frontal regions (Brenneis et al., 2005). The different direction of volumetric changes remains challenging to explain, and possibly rely upon methodological considerations such as patient sampling (aged 22–72 years in the study by Brenneis et al., compared to age 19–39 years for the present study) or different methods (VBM versus 3D cortical reconstruction). It is widely recognized that the dorsolateral prefrontal cortex plays a critical role in executive functioning, with its left counterpart being involved mainly in verbal working memory. The left DLPFC may be particularly sensitive to sleep quality and quantity, as increased activation was required to achieve the same task difficulty after sleep deprivation (Chee and Choo, 2004). Thus, it remains elusive whether the increased volume of the left DLPFC in our narcoleptic patients reflects a compensatory mechanism to maintain cognitive performances despite excessive daytime sleepiness.

A similar mechanism could explain the increased cortical thickness observed in Fig. 1b. The right superior frontal gyrus has been suggested to be a highly plastic structure underlying attention and short-term memory deficits related to sleep deprivation. Indeed, in a longitudinal study measuring structural brain changes and neurocognitive parameters before and after treatment in patients with obstructive sleep apnoea (Canessa et al., 2011), significantly reduced volume of the right superior frontal gyrus was observed at baseline. After treatment, improvement of the attention and short-term memory was associated with amendment of the right superior frontal gyrus volume. Unfortunately, in the present study we did not have any neurocognitive measurements available. However, we speculate that the unexpected direction of structural changes in the frontal lobe of patients with...
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nalcolepsy support the hypothesis of an increased cognitive pressure to sustain adequate executive functions.

Along with the various findings published to date, the absence of any striking direction of changes in the comparison between patients and controls support the existence of heterogeneous structural brain changes in narcolepsy. In that context, we tested the hypothesis whether within-patient factors, such as disease duration, age at onset or symptom severity, may explain the variability of the cerebral phenotype. Compared with patients who develop the narcolepsy from the age of 17, we observed that patients with earlier onset of the disease showed thinner cortex in the left precentral, right middle and superior temporal gyri and in the right inferior parietal region, along with increased CSF volume. Several explanations may account for the observed differences. First, we can speculate that the neuroanatomical differences reveal that the childhood onset and the adult onset represent distinct subtypes of narcolepsy, resulting from potentially different mechanisms and associated with specific symptoms. However, we did not observe any significant difference in the phenotype, including symptom severity (composite score: \( P = 0.499 \); MSLT: \( P = 0.372 \)), or in the level of anxiety or depression (BAI: \( P = 0.979 \); BDI: \( P = 0.149 \)) between the two patient subgroups. Similarly, Nevsimalova et al. (2009) did not report any relationship between clinical symptoms and age at onset, strengthening the hypothesis that childhood- and adult-onset narcolepsy represent a single disease entity. A second explanation for the cerebral differences related to the age at onset would be that neurodegenerative changes are associated with the ongoing disease process. According to this hypothesis, longer disease duration would be associated with increased cortical thinning. Among the previous morphometric studies, two explored correlations between cortical volume and duration of disease, reporting divergent results. Kim et al. (2009) reported a negative correlation between grey-matter volume in the superior frontal region and duration of disease, whereas Kaufmann et al. (2002) observed that cortical reduction in narcolepsy was independent of disease duration. In the present study, we also did not observe any significant correlation between any of the neuroanatomical variables and disease duration. However, given that our sample of patients was composed of adults, the division into two subgroups also reflects to some extent the disease duration: patients with childhood onset tended to have a longer duration of disease (although not reaching significance, \( P = 0.069 \)). Even if most of the clusters depicted in Fig. 2 remained significant after correcting for the duration of disease, we cannot formally exclude that cortical thinning could result from a combination of early neurodevelopmental influences (leading to younger onset of the narcolepsy) and neurodegenerative processes (associated with longer disease). Independently of the mechanisms responsible for the cortical thinning in the group of patients with early onset of narcolepsy, the location of the most significant finding may have implication for the cognitive function in the disease.

Finally, we conducted correlation analyses to search for a relationship between cortical thickness and the clinical severity of narcolepsy using a score combining the results obtained at the Epworth sleepiness, Ullanlinna and Swiss narcolepsy scales. Among the morphometric studies published to date, only few conducted correlations between cerebral structure and symptom severity. Kim et al. (2009) reported a negative correlation between the hypothalamic volume and the score at the Ullanlinna narcolepsy scale. In this study, we observed two prefrontal regions in the right hemisphere (detailed in Fig. 3), where reduced cortical thickness was associated with more severe symptoms of narcolepsy. The measurement of symptom severity combined both the excessive daytime sleepiness and the severity of cataplexy. It is noteworthy that we did not identify any significant correlation between cortical thickness or volume and the propensity to fall asleep alone (i.e. as measured with the mean sleep latency on MSTL), so that cataplexy may account for part of the findings. Indeed, the location of the most significant cluster in the right orbitofrontal cortex can be explained in the context of altered function of the reward circuitry in patients with narcolepsy with cataplexy. In the same sample of patients, Ponz et al. (2010) observed abnormal activity of the ventral tegmental area (VTA) in a task of monetary gains and losses. The right orbitofrontal cortex, densely connected to the VTA and amygdala, plays a critical role in reward-guided decision-making. The abnormal activity of the VTA, along with the altered orbitofrontal cortex (cluster 1 in Fig. 3), could impair the reinforcing effect of positive reward on behaviour in these patients. In turn, altered reinforcement mediated by abnormal activity in reward-related brain regions could potentiate the executive dysfunction (putatively mediated by the high sensitivity to sleep quality of superior frontal regions), and result in impaired decision-making in patients with narcolepsy.

DECLARATIONS OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES


