Hippocampal but not amygdalar volume loss in narcolepsy with cataplexy

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Abstract
OBJECTIVE: Narcolepsy with cataplexy (NC) and narcolepsy without cataplexy (NwoC) are lifelong neurological disorders characterized primarily by excessive daytime sleepiness. Emotional events such as laughter are a trigger of cataplexy in NC.

METHODS: We compared the volumes of key limbic structures, the amygdala and hippocampus, in 53 NC, 23 NwoC and 37 control subjects. MRI volumetry was performed in FreeSurfer (FS) and by manual delineation.

RESULTS: We found no differences in amygdalar volume in the three groups, however, hippocampal volume was significantly smaller in the NC group than in other groups. Amygdalar and hippocampal volumes assessed by FS were significantly greater, but strong positive correlation between manual and FS results were observed. Thus, both methods are suitable for amygdalar and hippocampal volumetry.

INTRODUCTION
Narcolepsy with cataplexy (NC) and narcolepsy without cataplexy (NwoC) are lifelong neurological disorders characterized primarily by excessive daytime sleepiness (EDS). Despite sharing the common manifestation of EDS, the etiologies of NC and NwoC differ and thus, according to the international classification of sleep disorders, 2nd edition (ICSD-2; American Academy of Sleep Medicine, 2005) are different nosological entities.

Aside from EDS, NC symptoms include cataplexy (short lasting symmetrical loss of muscle tone caused by an emotional trigger), and in roughly half of patients, sleep paralysis and hypnagogic hallucinations. Night sleep in NC is dis-
turbed, including the occurrence of REM sleep within the first 15 minutes of sleep, termed sleep onset REM period (SOREMp), and the occurrence of REM sleep behavior disorder (RBD). EDS must be objectively measured by the multiple sleep latency test (MSLT). Low or undetectable levels of hypocretin-1 (orexin-1) in the cerebrospinal fluid (CSF) is a crucial finding in NC, due to destruction of hypocretin-producing neurons in the lateral hypothalamus (Dauvilliers et al. 2007). Although the exact mechanism of hypocretin deficiency is unknown, evidence from the past 20 years strongly favors an immune-mediated or autoimmune attack, specifically targeting hypocretin neurons in genetically predisposed individuals (Liblau et al. 2015). The hypothesis that a targeted immune-mediated or autoimmune attack causes the specific degeneration of hypocretin neurons arose mainly through the discovery of genetic associations, first with the T-cell receptor α locus (Hallmayer et al. 2009). It has been suggested that a specific autoimmune process is triggered by different environmental stimuli such as streptococcal infection, anti-H1N1 vaccination or H1N1 infection itself in genetically predisposed subjects (Partinen et al. 2014). The age of onset varies from early childhood to the fifth decade, with a bimodal distribution including a large peak around 15 years of age and a smaller peak around 36 years of age (Dauvilliers et al. 2001). NC manifestations generally remain stable throughout life.

NwoC is characterized by EDS and the absence of cataplexy. MSLT diagnostic criteria are the same as for NC including the number of SOREMPs. CSF hypocretin-1 is within the normal range. The etiology of NwoC is unknown and the prevalence is lower compared to NC. Furthermore, it has been suggested that NwoC is not a homogenous nosological entity (Śonka et al. 2015).

The amygdaloid body (or amygdala) is part of the limbic system. It plays a key role in the detection and processing of emotional stimuli. Connections to sensory, motor and autonomic output systems provide the anatomical basis for adaptive responses to stimuli that signal fear (Amaral & Price 1984; Le Doux, 1992). Although the amygdala appears to play a more extensive role in negative emotion, it is involved in positive emotion as well. Activation of the right amygdala has been detected by positron emission tomography with the presentation of stimuli that elicit positive emotions (Hamann et al. 2002).

Emotions are important as the trigger of cataplexy in NC (Dauvilliers et al. 2007) and abnormal activity in the amygdala during the processing of humorous stimuli has been detected by functional magnetic resonance imaging (fMRI; Swartz et al. 2008; Nakamura et al. 2012). It has been reported that NC patients do not show any increase in amygdalar response on fMRI in emotional learning (Ponz et al. 2010), although changes have been detected by proton resonance spectroscopy in the amygdala and the hypothalamus suggesting metabolic dysfunction in NC (Poryazova et al. 2009). Direct inhibitory output from amygdala to the pontomesencephalic tegmental areas activates (desinhibits) the glycnergic inhibitory neurons of oblongate and thus it causes the muscle atonia during the REM sleep (Burgess et al. 2013). In narcoleptic dogs, two populations of amygdalar cells showed a significant change in activity within cataplexy. A population of sleep active cells localized to the central and basal nucleus of the amygdala increased discharges prior to and during cataplexy. A population of wake active cells localized to the cortical nucleus of amygdala decreased activity prior to and during cataplexy. These cell populations play a role in mediation or modulation of cataplexy through interactions with mesopontine regions controlling muscle atonia (Gulyani et al. 2002). In hypocretin knock-out mice, cataplexy (frequency and duration of cataplexy bouts) was increased by stimuli associated with positive emotions and an amygdalar lesion in the central nucleus decreased cataplexy (Burgess et al. 2013). These studies suggest a key role of the amygdala in the generation of cataplexy. The amygdala has rich reciprocal interconnections with the hypothalamic nuclei.

The hippocampal formation (hippocampus) is also part of the limbic system. The hippocampus participates in learning and memory, in the regulation of emotional behavior, in certain aspects of motor control, and in the regulation of some hypothalamic functions (Duvernoy et al. 2005). The hippocampus is highly interconnected with the hypothalamus (Swanson & Cowan, 1975; Stranahan et al. 2007) and the amygdala (Aggelton, 1986; Fudge et al. 2012). The hippocampus consists of the subiculum on the upper surface of the parahippocampal gyrus, the dentate gyrus in the depth of the sulcus hippocampi and cornu Ammonis bulging into the temporal horn of the lateral ventricle.

Our preliminary results (Brabec et al. 2011) showed reduced amygdalar volume in NC, thus we elected to measure and compare the volumes of the amygdala and hippocampus in NC, NwoC, and healthy subjects.

**METHODS**

**Participants**

Fifty-three subjects diagnosed with NC, 23 subjects diagnosed with NwoC, and 37 control subjects were included. Control subjects were interviewed to exclude a history of neurological, psychiatric, cardiovascular and metabolic disease. The evaluation of all patients was conducted at our center specializing in sleep disorders and included a detailed clinical history, complete physical examination including anthropometric measurements such as weight, height and BMI, and the Epworth Sleepiness Scale (ESS). Only patients with an unambiguous diagnosis of NC or NwoC without any other brain disease were included in the study. The
study was approved by the local ethics committee, and all participants provided signed, informed consent. Demographic data are presented in Table 1.

The diagnoses of NC and NwoC were made according to the ICSD-2 (American Academy of Sleep Medicine, 2005). The clinical diagnostic criteria of NC included the presence of EDS lasting ≥3 months and typical cataplexy not explained by other medical or psychiatric disorders. The clinical criteria of NwoC were EDS duration of ≥3 months and the absence of typical cataplexy. The diagnosis was confirmed by night video-polysomnographic recording (EEG, EOG, mental and tibialis anterior EMG, ECG, nasal-oral air flow, thoracic and abdominal effort, respiration noises and saturation of peripheral blood by oxygen) followed by MSLT the next day. The MSLT criteria were identical for the diagnosis of NC and NwoC (mean sleep latency ≤8 minutes and ≥2 SOREMPs). Night polysomnography and MSLT were performed in drug-naive patients or patients abstaining from medications that affect sleep and mood for two or more weeks. HLA typing for DQB1*06:02 was additionally performed (unavailable in one NC subject), and positivity was found in 96% of NC patients and 48% of NwoC patients.

**Magnetic resonance imaging (MRI)**

All participants were examined in the same MRI scanner 1.5 T (Gyrosan, Philips Medical Systems, Best, The Netherlands). The intergroup comparisons were made by T-test (2-sided, with different sample variances), nonparametric data by the Mann-Whitney U-test (indicated), and percentage by chi-square test (indicated). N, number; ESS, Epworth sleepiness scale; BMI, body mass index; nPSG, night polysomnography; SE, sleep efficiency; SOREM, sleep onset REM period; PLMI, periodic limb movements index; AHI, apnoe/hypopnoe index; MSLT, multiple sleep latency test; MWU, Mann-Whitney U-test; NA, not applicable.

### Tab. 1. Demographic information.

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>NwoC</th>
<th>controls</th>
<th>NC vs. NwoC</th>
<th>p-value</th>
<th>NwoC vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>53</td>
<td>23</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men/women (N), chi-square</td>
<td>28/25</td>
<td>14/9</td>
<td>16/21</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>39.6 (16.9)</td>
<td>40.4 (14.8)</td>
<td>36.3 (8.8)</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Disease duration, years (mean, SD)</td>
<td>18.5 (15.3)</td>
<td>14.7 (11.8)</td>
<td>NA</td>
<td>n.s.</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Previous treatment by antidepressants (N, %)</td>
<td>20 (38%)</td>
<td>3 (13%)</td>
<td>NA</td>
<td>0.030 (chi-square)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Previous treatment by stimulants (N, %)</td>
<td>24 (45%)</td>
<td>8 (35%)</td>
<td>NA</td>
<td>n.s. (chi-square)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Previous treatment by sodium oxybate(N, %)</td>
<td>5 (9%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ESS (mean, SD)</td>
<td>17.4 (3.6)</td>
<td>15.2 (5.0)</td>
<td>NA</td>
<td>0.048</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BMI (mean, SD)</td>
<td>29.6 (5.6)</td>
<td>27.3 (4.5)</td>
<td>NA</td>
<td>n.s.</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>nPSG SE, % (mean, SD)</td>
<td>83.6 (10.2)</td>
<td>87.7 (5.8)</td>
<td>NA</td>
<td>n.s. (MWU)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>nPSG awakenings, N (median, quartil range)</td>
<td>34 (27–51)</td>
<td>25 (20–27)</td>
<td>NA</td>
<td>0.002 (MWU)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Subjects with nPSG SOREM (%)</td>
<td>56.0</td>
<td>25.0</td>
<td>NA</td>
<td>0.019 (chi square)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PLMI (mean, SD)</td>
<td>20.9 (28.6)</td>
<td>5.8 (13.7)</td>
<td>NA</td>
<td>0.002 (MWU)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>AHI (mean, SD)</td>
<td>9.0 (18.3)</td>
<td>3.7 (3.9)</td>
<td>NA</td>
<td>n.s. (MWU)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MSLT SL min (mean, SD)</td>
<td>2.3 (1.7)</td>
<td>5.1 (2.3)</td>
<td>NA</td>
<td>&lt;0.001 (MWU)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MSLT SOREM (median N, quartil range)</td>
<td>4 (3–4)</td>
<td>3 (2–4)</td>
<td>NA</td>
<td>0.013 (MWU)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Hippocampal but not amygdalar volume loss in narcolepsy with cataplexy

Netherlands). Images were acquired using a T1-weighted 3-dimensional fast field echo sequence (TR=25 ms, TE=5 ms, flip angle=30°, matrix size=256×256, slice thickness/gap=1/0 mm, field of view (FOV)=256 mm), axial and coronal images T1-weighted IR (inversion recovery); TR=2820 ms, TE=15 ms, TI=400 ms, matrix size=410×512, flip angle=90°, slice thickness/gap=2/0 mm, FOV=200/156 mm) in transversal plain.

Images were analyzed by two methods. An automated analysis was performed in Freesurfer (FS) version 4.5.0 (http://surfer.nmr.mgh.harvard.edu) and ScanView.cz. Manual delineation was performed by an experienced neuroanatomist (V.N.) blinded to the diagnosis and the process is described in detail below.

Manual delineation
Manual measurements were performed using ScanView software (scanview.cz). First, non-normalized brain volume was measured using T1-weighted images thresholded above 4,000 artificial units. The delineation of structures of interest was performed in coronal (amygdala) and sagittal (hippocampus) orientations on 1 mm isotropic T1-weighted images (Figures 1 and 2). Coronal, sagittal and horizontal views were available to aid in the delineation. Each 1 mm² pixel was divided into 16 subpixels 0.25×0.25 mm. All subpixels inside the delineated area were counted and divided by 16. The volume of delineated structures was assessed by counting delineated areas, as the slice thickness was 1 mm. The volume of structures of interest was related to the total brain volume from automated image analysis obtained by ScanView.cz.

Manual amygdalar delineation
We measured the volume of the “classic amygdala” (Brabec et al. 2010), which includes the subnucleus centralis, medialis, corticais, basalis accessorius, basalis lateralis, intercalaires, area amygdalaris anterior, area cortico-amygdalearis transita, amygdalo-striatica transitiva and the sublenticular part of the extended amygdala as it continues to the substantia innominata under the globus pallidus. The area preamygdalaris (anterior to the amygdala) was not included in the measurement.

The anterior pole of the amygdala was particularly difficult to differentiate from the surrounding gray matter (piriform cortex, periamygdalar area and preamygdalar claustrum). Therefore, sagittal and horizontal views were used in its definition (Figure 1). Other parts of the amygdala were more clearly visible. The lateral amygdalar border (lateral and basolateral subnuclei) is orientated toward the external capsule, which divides the amygdala from the claustrum. Dorsomedially, the cortical nuclei of the amygdala form the semilunar gyrus; this part of the amygdala is on the surface of the hemisphere. Ventromedially, the amygdala bor-

Fig. 1. Manual delineation of the amygdala and hippocampus on T1-weighted images. a) in the sagittal plane, b) rostral amygdalar border on coronal section, c) middle part of the amygdala on coronal section, d) caudal end of the amygdala on coronal section. A, amygdala; H, hippocampus.

Fig. 2. Delineation of the hippocampus on T1-weighted images in the sagittal plane laterally, b) in the middle and c) medially.
ders the white matter of the ambient gyrus. The sub-
lenticular part of the extended amygdala continues to
the substantia innominata under the globus pallidus.
More caudally, the optic tract forms the medial amyg-
dalar border. The ventral amygdalar border is formed
by the temporal horn of the lateral ventricle on caudal
sections, by the hippocampus more rostrally, and by the
white matter of the temporal lobe rostrally.

Manual hippocampal delineation
The cornu Ammonis, dentate gyrus and subiculum
were delineated as the hippocampus. The alveus and
fimbria fornicis were excluded from measurements
(Figure 2). The hippocampus may be divided to three
parts along the longitudinal axis: the head, body and
tail (Duvernoi et al. 2005). The head (digitationes hip-
pocampi) is anteriorly bordered by the amygdala and
the uncal recess of the temporal horn of the lateral ven-
tricle. The body of the hippocampus is dorsolaterally
covered by the alveus. The ambient cistern is medial
to the body of the hippocampus. The tail is covered med-
ially by the fimbria fornici and the ambient cistern and
ends with the subplenial gyrus. The splenium corporis
callosi is localized above the tail of the hippocampus
and the white matter of the temporal lobe is found later-
ally. The inferior border of the hippocampus is formed
by the white matter of the parahippocampal gyrus.

Statistical analyses
All statistical tests were performed using STATISTICA
software version 12 (statsoft.com). Volumetric data
were found to be normally distributed by the Shapiro-
Wilk’s W test and are presented by both uncorrected in
cm$^3$ and as per mille portion of the total brain volume.
Intergroup comparisons for raw volumetric data were
performed by ANCOVA using total brain volume as
a covariate, with post-hoc comparison by the HSD
test. Other parameters were compared either by T-test
(2-sided, with different sample variances), the Mann-
Whitney U test, or chi square test where appropriate.
Correlation in continuous variables was evaluated by
Pearson correlation. The Bonferroni correction for
multiple comparisons was applied, and $p$-values <0.05
were considered significant.

RESULTS
Amygdalar and hippocampal volumes obtained by
manual delineation and FS analysis are displayed in
Table 2. The post hoc HSD test showed only significant
differences between NC and control groups, for hip-
pocampus manually measured in was $p<0.001$ for both
sides, for automatical methods $p<0.01$.

No clinically relevant differences in right and left
amygdalar or hippocampal volumes were found. Absol-
ute amygdalar and hippocampal volumes were larger
in males than in females, but after correction for whole-
brain volume no sex differences were found.

There were no correlations between amygdalar and
hippocampal volume and percentage of sleep stages
during night polysomnography after correction for
multiple comparisons. Only relative volume of the right

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>NwoC</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Mean (cm$^3$)</td>
<td>Relative volume (%)</td>
<td>Mean (cm$^3$)</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td></td>
<td>SD</td>
</tr>
<tr>
<td>Brain volume</td>
<td>1216.8 (154.0)</td>
<td>1239.0 (164.6)</td>
<td>1270.4 (151.3)</td>
</tr>
<tr>
<td>Amy R man</td>
<td>1.13 (0.16)</td>
<td>1.09 (0.12)</td>
<td>1.14 (0.19)</td>
</tr>
<tr>
<td>Amy L man</td>
<td>1.15 (0.17)</td>
<td>1.15 (0.14)</td>
<td>1.17 (0.18)</td>
</tr>
<tr>
<td>Hip L man</td>
<td>2.40 (0.31)</td>
<td>2.54 (0.30)</td>
<td>2.67 (0.36)</td>
</tr>
<tr>
<td>Hip R man</td>
<td>2.40 (0.32)</td>
<td>2.54 (0.33)</td>
<td>2.64 (0.35)</td>
</tr>
<tr>
<td>Amy_L FS</td>
<td>1.47 (0.19)</td>
<td>1.53 (0.19)</td>
<td>1.58 (0.25)</td>
</tr>
<tr>
<td>Amy_R FS</td>
<td>1.56 (0.18)</td>
<td>1.63 (0.22)</td>
<td>1.62 (0.22)</td>
</tr>
<tr>
<td>Hip. L FS</td>
<td>4.31 (0.44)</td>
<td>4.54 (0.45)</td>
<td>4.68 (0.9)</td>
</tr>
<tr>
<td>Hip R FS</td>
<td>4.25 (0.40)</td>
<td>4.45 (0.51)</td>
<td>4.57 (0.62)</td>
</tr>
</tbody>
</table>

Results are presented as mean (±standard deviation) in cm$^3$, and as per mille (±standard deviation) of whole-brain volume in the amygdala and hippocampus. L, left; R, right; man, manual delineation; FS, FreeSurfer assessment; Amy, amygdala; Hip, hippocampus.
amygdala positively correlated with age after correction for multiple comparisons in NC patients. In NwoC patients, all hippocampal parameters positively correlated with age at MRI examination and age at disease onset.

Automated amygdalar and hippocampal volume measurements were larger than manually delineated volumes ($p<0.001$). However, the results of both methods were highly correlated (Table 3) and hippocampal values had significantly higher correlation coefficient than amygdalar volumes ($p<0.05$), as r-to-Fisher-z transformation. Correlation of automated and manually assessed amygdalar and hippocampal volume is presented in Figure 3 for the right side. The correlation parameters of the both left sided structures were same as on the right side.

**DISCUSSION**

The most significant finding of the present study is the demonstration of very high correlation between manual and FS measurements in the hippocampus and amygdala, although absolute sizes differed. Both methods are useful in these two structures with the knowledge that FS provides greater volumes. We found that FS includes the preamygdalar area as part of the amygdala, thus the final volume is larger. In the hippocampus, FS includes the alveus, which leads to greater hippocampal volume. In manual volumetry, the alveus is not part of the measured hippocampal formation. To our knowledge, this is the first such comparison in these structures.

Following correction for whole-brain volume, we detected smaller hippocampal volume in NC subjects than in controls, while no differences in amygdalar volume between NC patients and controls were found. We did not discover any differences in amygdalar or hippocampal volumes in NwoC subjects in comparison to NC subjects and controls. In NC subjects the volume of the right amygdala delineated manually correlated with age and disease duration and the volume of the left hippocampus also correlated with disease duration. The importance of our amygdalar and hippocampal volume measurements is overshadowed by a recently published study by Kim et al. (2015). They compared drug-naïve NC patients (similar group size in comparison to the present study) and controls. Higher resolution images were acquired at 3 tesla and processed manually, which allowed the authors to evaluate amygdalar and hippocampal subfield volumes and correlate them with clinical data. They found bilateral hippocampal atrophy localized mainly in the CA1 region and amygdalar reduction in the area of the centromedial nucleus and laterodorsal groups. Hippocampal CA1 atrophy and amygdalar centromedial atrophy were associated with a longer duration of EDS and shorter mean REM sleep latency. Amygdalar centromedial atrophy was associated with a longer duration of cataplexy (Kim et al. 2015). Our work confirms correlation between NC duration and amygdalar volume, but only on the right and only by automated measurement. There are some differences between patient’s population studied by Kim et al. and by us. The age at onset of NC was 15 years in the study by Kim et al., as opposed to 21 years in our study. Some of our patients were already treated before they had undergone MRI and disease duration was longer in our patients (18 vs. 12 years). We also detected atrophy of the hippocampus, albeit without detailed division. In contrast to the results of Joo et al.
(2012), we have not found lower hippocampal volume in NC subjects related to sleep and REM sleep latencies (Joo et al. 2012). In the present study, the volume of the right amygdala positively correlated with age at NC onset. In NwoC, a positive correlation between age and disease onset (and age at MRI) with bilateral hippocampal volume (manual and automated) was detected.

We did not detect any laterality differences in hippocampal volume by manual or automated methods in any subjects (controls, NC, NwoC), in contrast to reports in healthy subjects (Lucarelli et al. 2012; Woolard & Heckers, 2012).

The results of the present study differ from our previous study (Brabec et al. 2011), in which decreased amygdalar volume was detected in narcolepsy. This discrepancy may be related to the use of higher-resolution data in the present study (1 mm isotropic) and by the greater number of NC participants (53 in the present study, 11 in the previous study). Interestingly, the amygdalar volumes in the previous study were more homogeneous (smaller standard deviation) while the differences between NC subjects and controls more pronounced. In the present study we detected a similar trend, however the differences did not reach significance.

CONCLUSION

Amygdalar and hippocampal volumes obtained by manual and automated methods differ (automated resulted in greater volumes), however, we observed strong positive correlation between both methods. Thus, both methods are suitable for amygdalar and hippocampal volumetry. We found smaller hippocampal volumes in NC subjects in comparison to controls. We did not detect any differences in amygdalar volume between NC subjects and controls, nor between NC and NwoC subjects. No clinically important correlations between hippocampal or amygdalar volumes and symptoms of narcolepsy were detected.

ACKNOWLEDGEMENT

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