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Data-Driven Phenotyping of Central Disorders of Hypersomnolence With Unsupervised Clustering

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Abstract

Background and Objectives: Recent studies fueled doubts as to whether all currently defined central disorders of hypersomnolence are stable entities, especially narcolepsy type 2 and idiopathic hypersomnia. New reliable biomarkers are needed and the question arises whether current diagnostic criteria of hypersomnolence disorders should be reassessed. The main aim of this data-driven observational study was to see if data-driven algorithms would segregate narcolepsy type 1 and identify more reliable subgrouping of individuals without cataplexy with new clinical biomarkers.

Methods: We used agglomerative hierarchical clustering, an unsupervised machine learning algorithm, to identify distinct hypersomnolence clusters in the large-scale European Narcolepsy Network database. We included 97 variables, covering all aspects of central hypersomnolence disorders such as symptoms, demographics, objective and subjective sleep measures, and laboratory biomarkers. We specifically focused on subgrouping of patients without cataplexy. The number of clusters was chosen to be the minimal number for which patients without cataplexy were put in distinct groups.

Results: We included 1078 unmedicated adolescents and adults. Seven clusters were identified, of which four clusters included predominantly individuals with cataplexy. The two most distinct clusters consisted of 158 and 157 patients respectively, were dominated by those without cataplexy and, amongst other variables, significantly differed in presence of sleep drunkenness, subjective difficulty awakening and weekend-week sleep length difference. Patients formally diagnosed as narcolepsy type 2 and idiopathic hypersomnia were evenly mixed in these two clusters.

Discussion: Using a data-driven approach in the largest study on central disorders of hypersomnolence to date, our study identified distinct patient subgroups within the central disorders of hypersomnolence population. Our results contest inclusion of sleep-onset rapid eye moment periods (SOREMPs) in diagnostic criteria for people without cataplexy and provide promising new variables for reliable diagnostic categories that better resemble different patient

phenotypes. Cluster-guided classification will result in a more solid hypersomnolence classification system that is less vulnerable to instability of single features.

Introduction

The classification of central disorders of hypersomnolence has been a topic of debate for decades and has been revised multiple times. This is mainly due to insufficient knowledge about the pathophysiology, reflected in a lack of validated and reliable biomarkers within this group of disorders, apart from narcolepsy with cataplexy. Different opinion papers have recently been published, all stressing the need for revision of the current classification because its application causes problems for physicians as well as patients when applied in daily practice.¹⁻⁶ The current version of the International Classification of Sleep Disorders (ICSD-3) is based largely on a consensus of expert opinion and describes three different categories of chronic central disorders of hypersomnolence: narcolepsy type 1 (almost completely overlapping the former category ‘narcolepsy with cataplexy’), narcolepsy type 2 (almost completely overlapping the former category ‘narcolepsy without cataplexy’) and idiopathic hypersomnia. The disorders share the symptom of excessive daytime sleepiness (EDS) and, in the absence of cataplexy and hypocretin-1 deficiency, the multiple sleep latency testing (MSLT) results and/or possible increased sleep duration differentiates between them. Only narcolepsy type 1 is a clinically distinct phenotype because of the specific presence of cataplexy and its strong correlation with hypocretin-1 deficiency (<110 pg/mL in the CSF).⁷

Despite these apparently clear and distinct criteria, it often proves difficult to differentiate reliably between narcolepsy type 2 and idiopathic hypersomnia. Recent studies have shown that test-retest reliability of the MSLT is poor in the absence of cataplexy, and diagnostic crossover of up to 53% was seen for narcolepsy type 2 and 75% for idiopathic hypersomnia.⁸⁻¹⁰ Narcolepsy type 2 may also evolve over time in some individuals; for example, individuals in whom daytime sleepiness is the sole initial manifestation may, develop cataplexy many years later and thereby transition into narcolepsy type 1.^{11, 12} More reliable biomarkers are needed to better differentiate between individuals with central hypersomnolence disorders, specifically in those without cataplexy. As a data-driven approach, agglomerative hierarchical clustering has previously proved useful in other diseases, objectively identifying subgroups and corresponding divisive variables by grouping people with similar characteristics in clusters.¹³⁻¹⁷

In this study, we used an unsupervised machine learning approach, agglomerative hierarchical clustering, to identify clusters of clinically distinct central hypersomnolence disorders. We used the advantageously large-scaled European Narcolepsy Network (EU-NN) database.¹⁸⁻²⁰ The EU-NN is an association of 21 leading European sleep centers that launched the first prospective European web-based database for narcolepsy and idiopathic hypersomnia. One main goal of the EU-NN database is to identify new biomarkers specific to central hypersomnolence disorders and to improve definitions and understanding of its subtypes. The comprehensiveness of variables and large number of individuals across different European countries provide the opportunity to implement unsupervised machine learning algorithms in an unprecedented fashion and allows for comprehensive data-driven insights into the different phenotypes of central hypersomnolence disorders.

We hypothesized that clustering would result in clear separation of individuals with the current diagnosis of narcolepsy type 1 from those without cataplexy, while mixing people currently diagnosed as narcolepsy type 2 and idiopathic hypersomnia over multiple clusters based on differences in sleep duration and presence of sleep drunkenness. Given the known poor test-retest reliability of narcolepsy type 2 and idiopathic hypersomnia diagnoses,⁸⁻¹⁰ our main focus was on grouping those without cataplexy.

Methods

The analysis steps are divided into core and advanced analyses (Table 1). The core analyses are essential for understanding the clinical implications of the clustering results, whereas the advanced analyses in eAppendix 1 validate why we deem the clustering results trustworthy.

EU-NN database

Records of 1078 adults and adolescents (≥ 13 years old) with central hypersomnolence disorders from 21 European sleep centers were included. In line with diagnostic ICSD-3 recommendations, only data of individuals unmedicated at the time of evaluation (including polysomnography and MSLT) was used. In total, 97 variables were input into the hierarchical clustering (eAppendix 2). Variables were assessed by sleep experts (e.g., symptom presence), objectively assessed (e.g., sleep tests, hypocretin and HLA-DQB1*0602 positivity) or self-reported through questionnaires (Epworth sleepiness scale and fatigue severity score). Except for the questionnaire results that were fully patient-rated, other subjective variables were entered by the clinician after the clinical interviews. For the database preprocessing steps we refer to eAppendix 3.

Clustering algorithm

In clustering, similarity is measured by calculating the distance between individuals, where similar values on the input variables results in a smaller distance. Each individual is initially a cluster of its own and the closest individuals (or clusters) are then sequentially combined into larger clusters, until there is only one cluster left. Details on the distance calculations are reported in eAppendix 3.

Number of clusters

The number of clusters was determined combining two techniques. We first calculated multiple standard clustering evaluation metrics (i.e., clustering quality scores) that describe how well the clustering algorithm performs with different numbers of clusters (eAppendix 3). These metrics are normally high when individuals are similar to others in its cluster and distinct from the individuals in other clusters. The main aim of this study was to see if data-driven algorithms

would segregate narcolepsy type 1 and identify more reliable subgrouping of individuals without cataplexy as current diagnostic criteria struggle most with this subpopulation. We therefore also focused on subgrouping of individuals without cataplexy by visual inspection of the clustering steps of the full dataset from 15 to two clusters to better understand how people without cataplexy were subdivided and when these clusters were merged. The final model is usually a compromise of the evaluation metrics and the clinical aim of the study.

Clustering outcome

Clustering results were visualized as barcodes representing the mean normalized values per cluster on all variables (also called “means barcodes”). Variables were ordered based on the aforementioned categories and clustering mean values were left blank when fewer than 10 values were present within a cluster.

Differentiating variables

Two methods were used to quantify differentiating variables between clusters. First, we used a resampling technique to test how different the clustering means were from the entire EU-NN database. We then also formally compared clusters dominated by individuals without cataplexy on all variables.

A resampling technique was implemented to test whether the clustering results deviated from the entire EU-NN database. The resampling technique enabled us to deduce the extent to which the means barcodes were different from what would be expected if the same number of clusters with the same sizes were randomly drawn from the entire EU-NN database. We generated 10,000 such draws and calculated the mean and standard deviation of each draw per cluster per variable. For each variable, we divided the difference between the resampled mean and corresponding original clustering mean by the standard deviation of the resampled means. This was done per variable per cluster and visualized as the “significances barcodes”. Only values with more than 25 observations were displayed. The significances barcodes better represent how substantially different the means barcodes are from the entire EU-NN database.

We post-hoc statistically compared the resulting clusters with a substantial proportion of individuals without cataplexy on all included variables using Mann–Whitney tests. If the

variables contained count data, chi-square tests were used instead. Corrected p-values below 0.05 were reported, after multiple comparisons correction using the Benjamini–Hochberg procedure to decrease the false discovery rate to 0.05.

Current diagnosis & centers of inclusion

Researchers were blinded for the center of inclusion and current diagnosis of the individuals until the hierarchical clustering was completed. After finishing the clustering, pie charts were generated per cluster representing the current diagnosis (with physician's diagnostic certainty) and centers of inclusion. Contingency table statistics (sensitivity, specificity, positive predictive value and negative predictive value) were separately computed for clusters dominated by NT1, and NT2 and IH. Centers of inclusion were shown to check whether these could have influenced the clustering. To better understand the general characteristics of the study population, the characteristics of the current ICSD-3 diagnoses are included in eAppendix 2.

Data availability

For this study we used the newly developed clustering package *Bowerbird*, that integrates widely used agglomerative hierarchical clustering algorithms with clustering validation methods and intuitive data visualization options. This flexible, open-source clustering package is Python-based and available online (<https://github.com/MartijnOei/Bowerbird>). The data that support the findings of this study are available from the authors on reasonable request.

Results

EU-NN database

The database included 1078 individuals, of whom 108 were adolescents (between 13 and 18 years old) and 970 were adults. There were 489 females and 589 males. Cataplexy was present in 724 and absent in 353. In line with ICSD-3 criteria, 752 people were diagnosed as narcolepsy type 1 (646 definite, 51 probable, 33 possible and 33 unknown diagnostic certainty), 200 as narcolepsy type 2 (132 definite, 49 probable, 10 possible and 9 unknown certainty) and 126 as idiopathic hypersomnia (83 definite, 32 probable, 6 possible and 5 unknown certainty). For an overview of the number of inclusions per center and ethical approval see eAppendix 4. The clustering algorithm and the researchers were blinded for the current diagnosis and inclusion center until the analyses were finished.

Clustering algorithm & number of clusters

The clustering evaluation metrics did not clearly favor any single number of clusters below 15 (eAppendix 5). This suggests that individuals in the EU-NN database are not organized according to a single number of archetypes. This means subdivision can still result in distinct clusters, but in presence of individuals closely bordering different clusters. The number of clusters was therefore based on subgrouping of people without cataplexy, as data-driven subdivision of these individuals was our main aim. A simple model with a small total number of clusters was preferred. Visual inspection of the clustering steps from 13 to 7 clusters revealed that changes only occurred in clusters with people with cataplexy and that people without cataplexy were consistently divided in the same two clusters. Thus, seven was chosen as the final number of clusters.

The dendrogram showing the clustering steps from seven to two clusters is included in eAppendix 5. People without cataplexy were generally grouped as one large cluster when selecting six and five clusters. This large cluster of people without cataplexy was subsequently combined with people with cataplexy at four clusters. This resulted in a steep worsening of clustering evaluation metrics, indicating poorer performance below five clusters.

Clustering outcome

The means barcodes (Figure 1) show that people with cataplexy were grouped in four clusters (1-4), with 231, 298, 92 and 99 individuals, respectively. Those without cataplexy were grouped in clusters 5 (157 people) and 6 (158 people) and there was one smaller cluster mixing 43 people with and without cataplexy (7). The variable categories nighttime sleep, difficulties in waking up, cataplexy, hypnagogic hallucinations, sleep paralysis, sleepiness and biomarkers were most often different between clusters. For a full overview of raw variable values per cluster, we refer to eAppendix 6.

Differentiating variables

From the significances barcodes (Figure 2) it is noticeable that the first four clusters were mainly different in non-cataplectic symptoms and represented different narcolepsy with cataplexy subtypes. Cluster 1 included the most severe phenotype with frequent presence of disturbed nocturnal sleep (72%), sleep attacks (94%), cataplexy attacks (97%) that were most often complete with many potential triggers, hypnagogic hallucinations (90%) and sleep paralysis (82%). Cluster 2 was the largest, but least affected cluster where hypnagogic hallucinations (22%) and sleep paralysis (5%) were notably absent. In contrast to the other clusters of people with cataplexy, those in cluster 3 reported more difficulty in waking up (77%) with frequent presence of sleep drunkenness (83%), fatigue complaints (88%) and people not feeling refreshed after sleep (36% not refreshed, 36% not always refreshed). This cluster was predominantly composed of males (74%). Cluster 4 mainly consisted of females (99%) with present (but infrequent) hypnagogic hallucinations (61%) and sleep paralysis (73%). Clusters 1-4 all had frequent MSLT sleep-onset rapid eye moment periods (SOREMPs), HLA-DQB1*0602 positivity and low mean hypocretin-1 levels.

People without cataplexy were generally grouped in clusters 5 and 6 (157 and 158 people, respectively). As displayed in Table 2, individuals in cluster 5 presented with significantly more sleep drunkenness, subjective difficulty awakening, memory complaints, fatigue, and larger weekend to week sleep length difference compared to those in cluster 6. Additionally, cluster 6 had a relatively higher percentage of HLA-DQB1*0602 positivity and lower hypocretin-1

concentrations. No significant differences were found between clusters 5 and 6 on MSLT-related variables and the Epworth sleepiness scale.

Cluster 7 is a smaller cluster evenly mixing individuals with and without cataplexy. Apart from presence of hypnagogic hallucinations and sleep paralysis, there are no clear distinguishing variables from other clusters.

Current diagnosis & centers of inclusion

Physicians were, in general, most confident in diagnosing narcolepsy type 1 and more doubtful with narcolepsy type 2 and idiopathic hypersomnia (Figure 3A). Clusters 1-4 included mainly people diagnosed with narcolepsy type 1 with a definite diagnostic certainty (respectively 91%, 75%, 65% and 83%). Contingency table statistics for NT1 within clusters 1-4 showed a sensitivity of the clusters of 0.76, specificity of 0.83, positive predictive value of 0.93 and negative predictive value of 0.76. Within cluster 3 there were 18 individuals (20%) without cataplexy, but with sleep drunkenness, hypnagogic hallucinations and often sleep paralysis. Cluster 5 and 6 were dominated by people without cataplexy, and narcolepsy type 2 and idiopathic hypersomnia diagnoses were similarly mixed over the two clusters (cluster 5: 45% narcolepsy type 2 and 40% idiopathic hypersomnia; cluster 6: 45% narcolepsy type 2 and 27% idiopathic hypersomnia). Contingence table statistics for NT2 and IH within clusters 5 and 6 showed a sensitivity of the clusters of 0.76, specificity of 0.91, positive predictive value of 0.78 and negative predictive value of 0.90. There was also a considerable proportion of individuals with narcolepsy type 1 in clusters 5 and 6 (cluster 5: 15%; cluster 6: 28%). Most of these had atypical or mild cataplexy (cluster 5: 35%; cluster 6: 38%), or absent cataplexy but low hypocretin-1 levels (cluster 5: 26%; cluster 6: 33%). Cluster 7 was a mixed cluster of mainly narcolepsy type 1 and type 2. Centers of inclusion were evenly spread over the clusters (Figure 3B). In eAppendix 2, we present summary measures of the population using current ICSD-3 diagnoses.

Discussion

This work presents the largest study to date on central hypersomnolence disorders including more than 1000 adolescents and adults and the full scope of central hypersomnolence disorder characteristics. Our results provide important data-driven insights to new clinical biomarkers to improve future diagnostic criteria, especially for individuals without cataplexy. The clustering algorithm is able to identify distinct subgroups, principally separating people with cataplexy from those without. Further subdivision of those without cataplexy resulted in two clusters evenly mixing individuals with narcolepsy type 2 and idiopathic hypersomnia, which were separated based on variables related to awakening (e.g., sleep drunkenness and subjective difficulty awakening), sleep need (e.g., weekend-week sleep length difference) and objective biomarkers (HLA DQB1*0602 positivity and hypocretin-1 level). Interestingly, MSLT parameters were not significantly different between the two clusters with individuals without cataplexy. The advanced cluster distinctness and resampling analyses revealed (eAppendix 1) that the two clusters of people without cataplexy were most distinctly grouped of all clusters (also from each other) and had good cluster reproducibility. People with cataplexy (generally diagnosed as narcolepsy type 1) were further split into multiple subtypes that likely reflect different disease severities. These subtypes were mainly different in gender distribution and presence and severity of cataplexy, hypnagogic hallucinations, sleep paralysis and sleep drunkenness.

Thanks to the large number of patients and hypersomnolence-related variables, our analyses have produced more reliable and detailed results than two other studies that have previously tried to identify subtypes in central hypersomnolence disorders using agglomerative hierarchical clustering.^{21, 22} Šonka *et al.*²¹ studied only 96 subjects and Cook *et al.*²² included only people with idiopathic hypersomnia. Clustering in both studies was performed on just seven and three variables, respectively. The small number of clustered variables in these studies limited their ability to identify differentiating variables among all hypersomnolence aspects.

Multiple narcolepsy experts have advocated revising the current classification, but lack guidance in defining new subgroups and corresponding diagnostic criteria.¹⁻⁶ Our data-driven approach provides the opportunity to critically evaluate current ICSD-3 classification and shows that refinement of the hypersomnolence without cataplexy criteria is needed that would yield more

consistent categorization. The advanced analyses in eAppendix 1 revealed that the two clusters with people without cataplexy had good reproducibility and were most distinctly grouped compared to other clusters. The most prominent differential variables for subgrouping people without cataplexy include the presence of sleep drunkenness, subjective difficulty awakening, mean weekend-week sleep length difference and HLA-DQB1*0602 positivity. These differentiating symptoms suggest that certain subtypes/phenotypes of central disorders of hypersomnolence involve neuronal networks different from the cataplectic phenotype, probably mediated by other (still largely unknown) pathophysiology and/or comorbidities. Redefining key symptoms may help to establish new diagnostic methods, such as forced awakening, unrestricted/extended sleep opportunity and other biomarkers.

Sleep inertia is the complaint of difficulty in achieving complete wakefulness at the end of a sleep period, potentially accompanied by confusion, disorientation, and poor motor coordination or even ataxia. Sleep drunkenness is considered a severe manifestation of this phenomenon.²³ Historically speaking, sleep drunkenness had already been introduced by Bedřich Roth as an important differential marker when idiopathic hypersomnia was first conceptualized in the 1950s.²⁴⁻²⁶ To date quality of awakening has consistently been undervalued by the ICSD criteria for central hypersomnolence disorders, despite multiple studies suggesting its importance in people without cataplexy.²³⁻³¹ Besides the presence of subjective sleep drunkenness by patient history, the sensitivity and specificity of standard vigilance testing directly before and after MSLT naps could be explored to quantify the level of sleep drunkenness. The sustained attention to response task (SART)³²⁻³⁴ or psychomotor vigilance test (PVT)³⁵ have previously been used to quantify vigilance deficits in people with central hypersomnolence disorders, but not yet in relation to sleep drunkenness. A smaller study including different central hypersomnolence disorders has also previously reported event-related potentials during forced awakening to potentially quantify sleep inertia.³⁶

Difficulties in waking up and increased sleep demand frequently, but not always, coexist in people without cataplexy.^{26, 27, 29, 30, 37} Classically, these individuals were grouped in the ICSD-2 diagnosis idiopathic hypersomnia with long sleep time.³⁸ In our results, cluster 5 reported a substantially greater subjective weekend-week sleep length difference, a variable quantifying unfulfilled sleep need. People with increased sleep need are often unable to satisfy sleep

requirements during the week because of professional/social obligations, whereas the weekend generally allows opportunity for more unrestricted sleep.³⁹ The mean duration of nocturnal sleep during actigraphy may therefore not always reliably reflect the presence of an increased need for sleep. Moreover, in most sleep clinics the MSLT routine prevents the objective confirmation of a long duration of nocturnal sleep because individuals are forced to wake early in the morning. We previously applied supervised machine learning to classify people with narcolepsy type 1 and narcolepsy type 2 in the EU-NN database and longer weekend-week sleep length difference was a more important deterministic parameter for narcolepsy type 2 than for type 1, further highlighting its potential to become a new clinical biomarker.²⁰ It is important to keep in mind that also chronic sleep deprivation and sometimes circadian disturbances may show a similar difference. These disorders are however, currently, not included in our database. Extended 32-hour polysomnography recordings^{6, 40} and/or actigraphy assessment of weekend-week sleep length differences during consecutive weekends may solve to find all potential causes for hypersomnolence without cataplexy.^{39, 41} Our analyses highlight the potential of adding quality of awakening variables and weekend-week sleep length difference as sensitive new clinical biomarkers for future diagnostic criteria as they are potentially more reliable than exclusively using overall mean sleep duration. Clinical interviews and questionnaires are normally used to assess these variables,⁴² but optimal quantification practices need to be validated through future studies.

As the number of clusters was determined on the subgrouping of people without cataplexy, the differences between clusters 1-4 and 7 should not be overinterpreted. Clusters 1-4 should instead be treated as validation of the algorithm to separate people with and without cataplexy, and identify subtypes – rather than strict subgroups – within the narcolepsy type 1 population that likely reflect different severities. Among clusters 1-4, the dendrogram (eAppendix 5A) indicates that cluster 2 – mild severity with virtually absent hypnagogic hallucinations and sleep paralysis – is the closest to clusters 5 and 6 (clusters without cataplexy). The striking female preponderance within cluster 4 in combination with mild cataplexy, hypnagogic hallucinations and sleep paralysis, speculates the existence of a female narcolepsy type 1 subtype. Possible sex-specific narcolepsy and the influence of hormone levels should be investigated in future studies, since such mild cataplexy with fewer triggers may be easily overlooked by clinicians. The influence of sex on narcolepsy symptomatology remains essentially understudied, even though

longer diagnostic delay in females has previously been reported.⁴³ Interpretation of cluster 7 remains difficult without evident differential variables, apart from the presence of hypnagogic hallucinations and sleep paralysis. Cluster 7 is the smallest cluster among all with poor distinctness and clustering reproducibility (eAppendix 1), and could therefore reflect an inhomogeneous group of borderline phenotypes with limited clinical relevance.

The strong differences between clusters in the significances barcodes (Figure 2) and the substantially better goodness of fit in the original clustering compared with the randomly generated datasets (eAppendix 1) emphasize the possibility of identifying distinct subgroups within the larger central hypersomnolence population. Lack of a clear clustering evaluation metrics peak suggests that independent of the number of subgroups, there will always be people with central hypersomnolence that are difficult to categorize, especially when strict cutoffs are used (e.g., during the MSLT). This impression matches our clinical experience and our results suggest that the introduction of diagnostic certainties in new diagnostic criteria could better depict confidence levels in diagnosing hypersomnolence subtypes. This idea has recently been proposed by different European experts,³ and should be further investigated in future studies.

As well as direct implications on current classification, the organization of the hypersomnolence disorders in multiple clusters also offers opportunities for new hypothesis testing on disease etiology, progression and treatment effects. Longitudinal studies will provide the opportunity to see whether some individuals are prone to change from one cluster to another, either due to the natural course of the disease or due to the effects of medication. This could provide important insights in pre-stages of narcolepsy and data-driven treatment regimens for newly diagnosed individuals. More frequent HLA-DQB1*0602 positivity and lower hypocretin-1 levels were, for example, seen in cluster 6 than in cluster 5, suggesting a pathophysiological nature of hypersomnolence complaints closer to narcolepsy type 1. Individuals within cluster 6 may be more likely to show disease progression and should therefore be closely monitored for development of cataplexy.

A major strength of the EU-NN database is the harmonized prospective data acquisition protocol, resulting in a true Pan-European collaboration with minimal inclusion-site-specific biases. This is supported by the uniform distribution of inclusion sites over the clusters (Figure 3B). We included both adolescents and adults to best incorporate different stages of disease in our

clustering analyses. Post-hoc testing indicated a similar distribution of age at evaluation over different clusters. Children younger than 13 years old were however, currently, not included and should be studied in light of our proposed clusters in future studies. Even though the EU-NN database covers most important hypersomnolence-related aspects, incomplete availability of non-mandatory variables related to vigilance, cognitive functioning and mood has hindered their full integration into our clustering analyses. Future studies should focus on these variables in relation to our proposed subgroups.

Our analyses cannot be considered fully unbiased as agglomerative hierarchical clustering algorithms require manual input of variable weightings. We tried to overcome this issue by carefully designing the analysis strategy with pre-determined weighting and grouping of variables, potentially to give every asset of central hypersomnolence disorders a fair chance of influencing the clustering. Post-hoc testing to determine the influence of clustering settings by resampling with random subsets of the entire database (eAppendix 1) showed that the EU-NN database is adequately sized with solid cluster (and biomarker) reproducibility for people without cataplexy. Separate post-hoc analyses were performed to test whether our methodological choices could have influenced the results. Clustering was repeated three times by respectively excluding those with cataplexy and/or hypocretin deficiency (<110 pg/mL), with uniform weightings for all variables, and by recoding the polysomnography REM latency variable to polysomnography SOREMP presence. All three analyses demonstrated similar grouping and differentiating variables for subgrouping of those without cataplexy as in the full dataset (sleep drunkenness, subjective difficulty awakening and weekend-week sleep length difference). These robustness checks further validate that the differentiating variables for those without cataplexy are reproducible.

Within the EU-NN database, no data entries are available for people with other conditions that could lead to daytime sleepiness complaints, such as chronic sleep deprivation, myalgic encephalomyelitis/chronic fatigue syndrome and circadian rhythm disorders. These disorders could function as control groups in future clustering analyses on central hypersomnolence disorders to test the specificity of our results. Narcolepsy type 1 could also be considered a control group with a distinct cataplectic phenotype. The fact that the clustering algorithm recognized narcolepsy type 1 as separate clusters while we were blinded for the current

diagnosis, provides an important argument that the algorithm is able to identify distinct, clinically relevant, subgroups. Future studies should focus on external validation of our clustering results in a substantially sized independent dataset and prove internal validation by standardized follow-up data. Both approaches will validate the clinical impact of our clustering results by assessing how cluster assignments relate to clinical decisions like treatment planning, prognosis and mechanisms of disease.

We report an exceptionally sized quantitative subgroup assessment in people with central hypersomnolence disorders using the full range of clinical and diagnostic variables. Our study further illustrates the urgent need for new biomarkers in central hypersomnolence disorders that allow for robust subclassification and improve our understanding of disease etiology. The main finding is not the number of clusters, but the fact we found subgrouping consistent with current diagnosis of narcolepsy type 1, and not type 2 or idiopathic hypersomnia. Instead, people with narcolepsy type 2 and idiopathic hypersomnia were divided over two distinctly separated clusters, mainly differing on clinical variables related to quality of awakening, including presence of sleep drunkenness and feeling refreshed after daytime sleep, weekend-week sleep length difference and HLA-DQB1*0602 positivity. Subdivision of these individuals based only on absolute sleep duration or presence of SOREMPs is not supported by our findings. Introduction of new clinical biomarkers such as sleep drunkenness and weekend-week sleep length difference provides necessary opportunity to develop improved diagnostic criteria for people without cataplexy. At its very best, new data-driven classification of hypersomnolence disorders with levels of certainty would result in a reproducible, holistic classification system that better identifies borderland individuals and is less susceptible to volatility in single features.

References

1. Fronczek R, Arnulf I, Baumann CR, Maski K, Pizza F, Trotti LM. To split or to lump? Classifying the central disorders of hypersomnolence. *Sleep*. 2020;43(8):zsaa044; doi:10.1093/sleep/zsaa044
2. Gauld C, Ouazzani K, Micoulaud-Franchi JA. To split or to lump? Classifying the central disorders of hypersomnolence: sleep split requires epistemological tools and systematic data-driven conceptual analysis. *Sleep*. 2020;43(9):zsaa091; doi:10.1093/sleep/zsaa091
3. Lammers GJ, Bassetti CLA, Dolenc-Groselj L, et al. Diagnosis of central disorders of hypersomnolence: A reappraisal by European experts. *Sleep Med Rev*. 2020;52:101306; doi:10.1016/j.smr.2020.101306
4. Maski K, Mignot E, Scammell TE. COMMENTARY on Lammers et al, Diagnosis of central disorders of hypersomnolence: Challenges in defining central disorders of hypersomnolence. *Sleep Med Rev*. 2020;52:101327; doi:10.1016/j.smr.2020.101327
5. Baumann CR, Mignot E, Lammers GJ, et al. Challenges in diagnosing narcolepsy without cataplexy: a consensus statement. *Sleep*. 2014;37(6):1035-1042; doi:10.5665/sleep.3756
6. Evangelista E, Lopez R, Barateau L, et al. Alternative diagnostic criteria for idiopathic hypersomnia: A 32-hour protocol. *Ann Neurol*. 2018;83(2):235-247; doi:10.1002/ana.25141
7. Medicine AAoS. *International classification of sleep disorders - third edition (ICSD-3)*. American Academy of Sleep Medicine; 2014:
8. Lopez R, Doukkali A, Barateau L, et al. Test-Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence. *Sleep*. 2017;40(12):zsx164; doi:10.1093/sleep/zsx164
9. Trotti LM, Staab BA, Rye DB. Test-retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. *J Clin Sleep Med*. 2013;9(8):789-795; doi:10.5664/jcsm.2922
10. Cairns A, Trotti LM, Bogan R. Demographic and nap-related variance of the MSLT: results from 2,498 suspected hypersomnia patients: Clinical MSLT variance. *Sleep medicine*. Mar 2019;55:115-123; doi:10.1016/j.sleep.2018.12.013
11. Morrish E, King MA, Smith IE, Shneerson JM. Factors associated with a delay in the diagnosis of narcolepsy. *Sleep Med*. 2004;5(1):37-41; doi:10.1016/j.sleep.2003.06.002
12. Luca G, Haba-Rubio J, Dauvilliers Y, et al. Clinical, polysomnographic and genome-wide association analyses of narcolepsy with cataplexy: a European Narcolepsy Network study. *J Sleep Res*. 2013;22(5):482-495; doi:10.1111/jsr.12044
13. Stevens MC, Fein DA, Dunn M, et al. Subgroups of children with autism by cluster analysis: a longitudinal examination. *J Am Acad Child Adolesc Psychiatry*. 2000;39(3):346-352; doi:10.1097/00004583-200003000-00017

14. Calamari JE, Wiegartz PS, Janeck AS. Obsessive-compulsive disorder subgroups: a symptom-based clustering approach. *Behav Res Ther.* 1999;37(2):113-125; doi:10.1016/s0005-7967(98)00135-1
15. Tokuda T, Yoshimoto J, Shimizu Y, et al. Identification of depression subtypes and relevant brain regions using a data-driven approach. *Sci Rep.* 2018;8(1):14082; doi:10.1038/s41598-018-32521-z
16. Bailly S, Destors M, Grillet Y, et al. Obstructive Sleep Apnea: A Cluster Analysis at Time of Diagnosis. *PloS one.* 2016;11(6):e0157318; doi:10.1371/journal.pone.0157318
17. Mu J, Chaudhuri KR, Bielza C, de Pedro-Cuesta J, Larranaga P, Martinez-Martin P. Parkinson's Disease Subtypes Identified from Cluster Analysis of Motor and Non-motor Symptoms. *Front Aging Neurosci.* 2017;9:301. doi:10.3389/fnagi.2017.00301
18. Khatami R, Luca G, Baumann CR, et al. The European Narcolepsy Network (EU-NN) database. *J Sleep Res.* 2016;25(3):356-364; doi:10.1111/jsr.12374
19. Zhang Z, Gool J, Fronczek R, et al. New 2013 incidence peak in childhood narcolepsy: more than vaccination? *Sleep.* 2020;44(2):zsa172; doi:10.1093/sleep/zsa172
20. Zhang Z, Mayer G, Dauvilliers Y, et al. Exploring the clinical features of narcolepsy type 1 versus narcolepsy type 2 from European Narcolepsy Network database with machine learning. *Sci Rep.* 2018;8(1):10628; doi:10.1038/s41598-018-28840-w
21. Sonka K, Susta M, Billiard M. Narcolepsy with and without cataplexy, idiopathic hypersomnia with and without long sleep time: a cluster analysis. *Sleep Med.* 2015;16(2):225-231; doi:10.1016/j.sleep.2014.09.016
22. Cook JD, Rumble ME, Plante DT. Identifying subtypes of Hypersomnolence Disorder: a clustering analysis. *Sleep Med.* 2019;64:71-76; doi:10.1016/j.sleep.2019.06.015
23. Trotti LM. Waking up is the hardest thing I do all day: Sleep inertia and sleep drunkenness. *Sleep Med Rev.* 2017;35:76-84; doi:10.1016/j.smr.2016.08.005
24. Roth B. Sleep drunkenness and sleep paralysis. *Neurol Psychiatr Cechoslov.* 1956;19:48-58;
25. Roth B, Nevsimalova S, Rechtschaffen A. Hypersomnia with "sleep drunkenness". *Arch Gen Psychiatry.* 1972;26(5):456-462. doi:10.1001/archpsyc.1972.01750230066013
26. Roth B, Nevsimalova S, Sagova V, Paroubkova D, Horakova A. Neurological, psychological and polygraphic findings in sleep drunkenness. *Schweiz Arch Neurol Neurochir Psychiatr.* 1981;129(2):209-222;
27. Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. *Sleep.* 2009;32(6):753-759; doi:10.1093/sleep/32.6.753
28. Bassetti C, Gugger M, Bischof M, et al. The narcoleptic borderland: a multimodal diagnostic approach including cerebrospinal fluid levels of hypocretin-1 (orexin A). *Sleep Med.* 2003;4(1):7-12; doi:10.1016/s1389-9457(02)00191-0
29. Billiard M, Sonka K. Idiopathic hypersomnia. *Sleep Med Rev.* 2016;29:23-33; doi:10.1016/j.smr.2015.08.007
30. Billiard M, Dauvilliers Y. Idiopathic Hypersomnia. *Sleep Med Rev.* 2001;5(5):349-358; doi:10.1053/smr.2001.0168
31. Nevsimalova S, Susta M, Prihodova I, Horvat EM, Milata M, Sonka K. Idiopathic hypersomnia: a homogeneous or heterogeneous disease? *Sleep Med.* 2021;80:86-91; doi:10.1016/j.sleep.2021.01.031
32. Gool JK, van der Werf YD, Lammers GJ, Fronczek R. The Sustained Attention to Response Task Shows Lower Cingulo-Opercular and Frontoparietal Activity in People with

- Narcolepsy Type 1: An fMRI Study on the Neural Regulation of Attention. *Brain Sci.* 2020;10(7):419; doi:10.3390/brainsci10070419
33. Fronczek R, Middelkoop HA, van Dijk JG, Lammers GJ. Focusing on vigilance instead of sleepiness in the assessment of narcolepsy: high sensitivity of the Sustained Attention to Response Task (SART). *Sleep.* 2006;29(2):187-191;
34. Van Schie MK, Thijs RD, Fronczek R, Middelkoop HA, Lammers GJ, Van Dijk JG. Sustained attention to response task (SART) shows impaired vigilance in a spectrum of disorders of excessive daytime sleepiness. *J Sleep Res.* 2012;21(4):390-395; doi:10.1111/j.1365-2869.2011.00979.x
35. Thomann J, Baumann CR, Landolt HP, Werth E. Psychomotor vigilance task demonstrates impaired vigilance in disorders with excessive daytime sleepiness. *J Clin Sleep Med.* 2014;10(9):1019-1024; doi:10.5664/jcsm.4042
36. Bastuji H, Perrin F, Garcia-Larrea L. Event-related potentials during forced awakening: a tool for the study of acute sleep inertia. *J Sleep Res.* 2003;12(3):189-206; doi:10.1046/j.1365-2869.2003.00358.x
37. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. *Sleep.* 2007;30(10):1274-1281; doi:10.1093/sleep/30.10.1274
38. Medicine AAoS. *International Classification of Sleep Disorders: Diagnostic and Coding Manual.* 2 ed. American Academy of Sleep Medicine; 2005.
39. Vernet C, Leu-Semenescu S, Buzare MA, Arnulf I. Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. *J Sleep Res.* 2010;19(4):525-534; doi:10.1111/j.1365-2869.2010.00824.x
40. Evangelista E, Rassa AL, Barateau L, et al. Characteristics associated with hypersomnia and excessive daytime sleepiness identified by extended polysomnography recording. *Sleep.* 2020;44(5):zsa264; doi:10.1093/sleep/zsa264
41. Dietmann A, Gallino C, Wenz E, Mathis J, Bassetti CLA. Multiple sleep latency test and polysomnography in patients with central disorders of hypersomnolence. *Sleep Med.* 2021;79:6-10; doi:10.1016/j.sleep.2020.12.037
42. Dauvilliers Y, Evangelista E, Barateau L, et al. Measurement of symptoms in idiopathic hypersomnia: The Idiopathic Hypersomnia Severity Scale. *Neurology.* 2019;92(15):e1754-e1762; doi:10.1212/WNL.00000000000007264
43. Won C, Mahmoudi M, Qin L, Purvis T, Mathur A, Mohsenin V. The impact of gender on timeliness of narcolepsy diagnosis. *J Clin Sleep Med.* 2014;10(1):89-95; doi:10.5664/jcsm.3370

Table 1 – Overview of clustering analysis steps

Core analysis steps:

1. EU-NN database: In the data preparation phase we explain how the EU-NN database was prepared for the clustering algorithm and how variable weightings were determined.

2. Clustering algorithm: In this step we explain how the clustering algorithm works and how similarity between individuals is assessed through calculating distances between them.

3. Number of clusters: To determine at which number of clusters to stop the clustering algorithm, we combined standard clustering evaluation metrics (i.e., clustering quality scores) and visual inspection of grouping of individuals without cataplexy.

4. Clustering outcome: Once the number of clusters was determined, the cluster characteristics were visualized as barcodes per cluster per variable.

5. Differentiating variables: To identify the distinguishing variables, we visualized how distinct the clusters were per variable from the entire EU-NN database. We post-hoc statistically compared the clusters mainly containing individuals without cataplexy on all variables.

6. Current diagnosis & centers of inclusion: After finishing the clustering algorithm we identified the distributions of current diagnoses per cluster. We also checked the possible influence of center of inclusion on cluster formation.

Advanced analysis steps (eAppendix 1):

1. Clusterability of the EU-NN database: The intrinsic clusterability of the EU-NN database was assessed to test whether the EU-NN database entries show sufficient tendency (similarities) to be clustered, by comparing the coefficient of determination of the clustering results in the EU-NN database with similarly shaped, but randomly generated datasets.

2. Cluster distinctness: To test which clusters were most distinctly grouped, we calculated the silhouette coefficients per cluster. This metric of distinctness represents the ratio between the mean distance to individuals in the same cluster and the mean distance to individuals in the nearest other cluster.

3. Cluster reproducibility: To test whether the EU-NN database had sufficient entries to ensure that sample size variations are unlikely to change the clustering results, we repeated the clustering algorithm on random subsets of 80% of the EU-NN database and quantified similarity to the original clustering through mixing of individuals between clusters.

Table 2: Significant differences Between Clusters 5 & 6

Variable (>50% data available)	Cluster 5		Cluster 6		Effect size	Corrected p-value
	n ₅	Median (IQR) / Percentage	n ₆	Median (IQR) / Percentage		
Presence - Sleep drunkenness ^a	157	96.2%	158	1.3%	0.950	<0.0001
Difficulty waking daytime sleep	93	On average easy to wake up: 36.6% On average difficult to wake up: 51.6% On average nearly impossible to wake up: 11.8%	65	On average easy to wake up: 78.5% On average difficult to wake up: 21.5% On average nearly impossible to wake up: 0.0%	-0.427	<0.0001
Presence – Hypnagogic hallucinations	157	No: 72.0% Possible: 0.0% Probable: 5.1% Definite: 22.3%	158	No: 90.5% Possible: 0.6% Probable: 1.9% Definite: 7.0%	-0.239	0.0007
PSG – AHI	123	1.1 (0.2-3.1)	109	2.8 (0.6-7.0)	-0.239	0.0054
Weekend-week sleep length difference (hours)	155	1.0 (0.0-2.5)	158	0.1 (0.0-1.5)	-0.191	0.0086
Presence – Sleep paralysis	157	No: 77.1% Possible: 0.6% Probable: 2.5% Definite: 19.7%	158	No: 89.9% Possible: 0.6% Probable: 5.1% Definite: 4.4%	-0.185	0.0101
Subjective daily sleep length (hours)	157	8.0 (7.3-9.0)	158	7.8 (7.0-8.3)	-0.182	0.0128
Subjective daytime sleep length (hours)	138	1.0 (0.3-2.0)	135	1.0 (0.0-1.0)	-0.192	0.0134
Hypnagogic hallucinations frequency	156	Never: 91.0% <1/year: 0.6% 1/year-1/month: 2.6% 1/month-1/week: 4.5% 1/week-1/day: 1.3% >1/day: 0.0%	158	Never: 98.7% <1/year: 0.6% 1/year-1/month: 0.6% 1/month-1/week: 0.0% 1/week-1/day: 0.0% >1/day: 0.0%	-0.175	0.0168
Number of scheduled naps per day	154	Never: 47.4% 1/day: 40.9% >1/day: 11.7%	152	Never: 63.2% 1/day: 32.9% >1/day: 3.9%	-0.176	0.0168
Hypnagogic hallucinations – appears waking up ^a	125	8.0%	145	0.7%	0.184	0.0183
Sleep paralysis frequency	156	Never: 89.7% <1/year: 0.6% 1/year-1/month: 4.5% 1/month-1/week: 2.6% 1/week-1/day: 1.9% >1/day: 0.6%	158	Never: 97.5% <1/year: 1.3% 1/year-1/month: 1.3% 1/month-1/week: 0.0% 1/week-1/day: 0.0% >1/day: 0.0%	-0.161	0.0273
PSG – PLMI	114	1.0 (0.0-4.5)	91	3.7 (0.0-12.1)	-0.196	0.0281
Feeling refreshed after sleep	103	No: 43.7% Not always: 26.2%	89	No: 24.7% Not always: 30.3%	-0.198	0.0327

EIDS length per day	105	Yes: 30.1% 60 minutes: 18.1% 15-60 minutes: 32.4% 1-15 minutes: 39.0% <1 minute: 10.5%	91	Yes: 44.9% 60 minutes: 3.3% 15-60 minutes: 28.6% 1-15 minutes: 58.2% <1 minute: 9.9%	-0.190	0.0373
Variable (<50% data available)	Cluster 5		Cluster 6		Effect size	Corrected p-value
	n ₅	Median (IQR) / Percentage	n ₆	Median (IQR) / Percentage		
HLA-DQB1*0602 positivity ^a	66	33.0%	80	65.0%	0.315	0.0034
Presence - Memory complaints ^a	41	68.3%	30	26.7%	0.411	0.0086
Length of scheduled naps	81	52.2 (20.9-114.8)	55	20.9 (10.4-52.2)	-0.247	0.0273
CSF Hypocretin-1 level	43	259.0 (173.0-366.0)	41	179.0 (73.0-299.5)	-0.308	0.0281
Presence - Fatigue [†]	35	71.4%	27	37.0%	0.344	0.0346

Variables are sorted based on corrected p-values and separated based on the data availability (>50% or <50% of data available on that variable). Mann-Whitney U tests were performed (with effect size r), except for variables indicated with a, where chi-square tests (and phi effect sizes) were used. AHI = Apnea-hypopnea index; EIDS = Episodes of irresistible daytime sleep; HLA = Human leukocyte antigen; IQR = Interquartile range; PLMI = Periodic leg movement index; PSG = Polysomnography.

Figure legends

Figure 1. Cluster means barcodes. Blue represents a low mean value or infrequent presence on a variable, whereas red means a high mean value or frequent presence. Cluster sizes are displayed under the cluster number. For details on individual variables, see eAppendix 2.

ACCEPTED

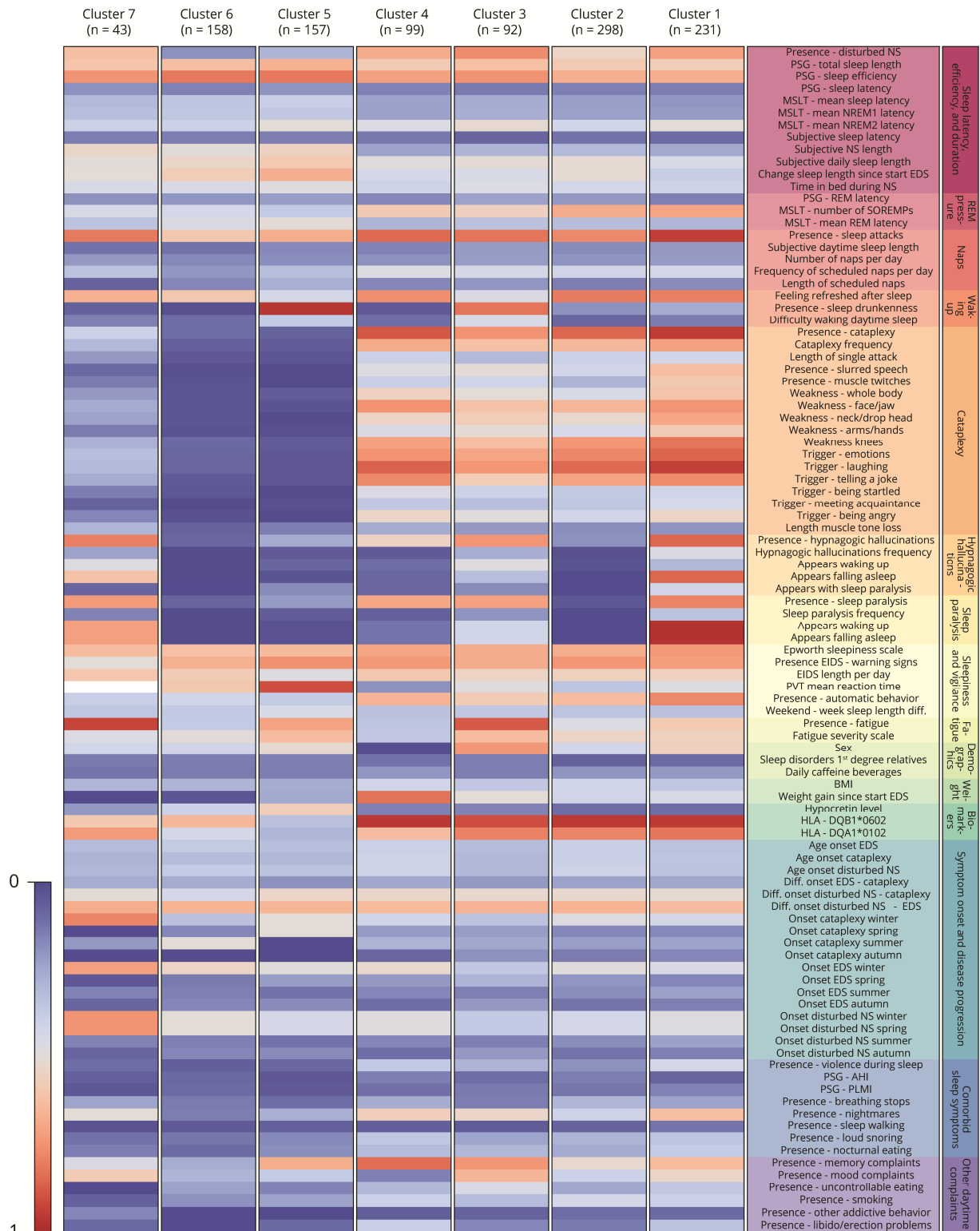


Figure 2. Cluster significances barcodes. Blue represents a significantly lower value on a variable for a cluster as compared to the entire EU-NN database, whereas red means a significantly higher value. The difference with the entire EU-NN database is displayed in standard deviations. Cluster sizes are displayed under the cluster number. For details on individual variables, see eAppendix 2. Blank fields included <25 observations.

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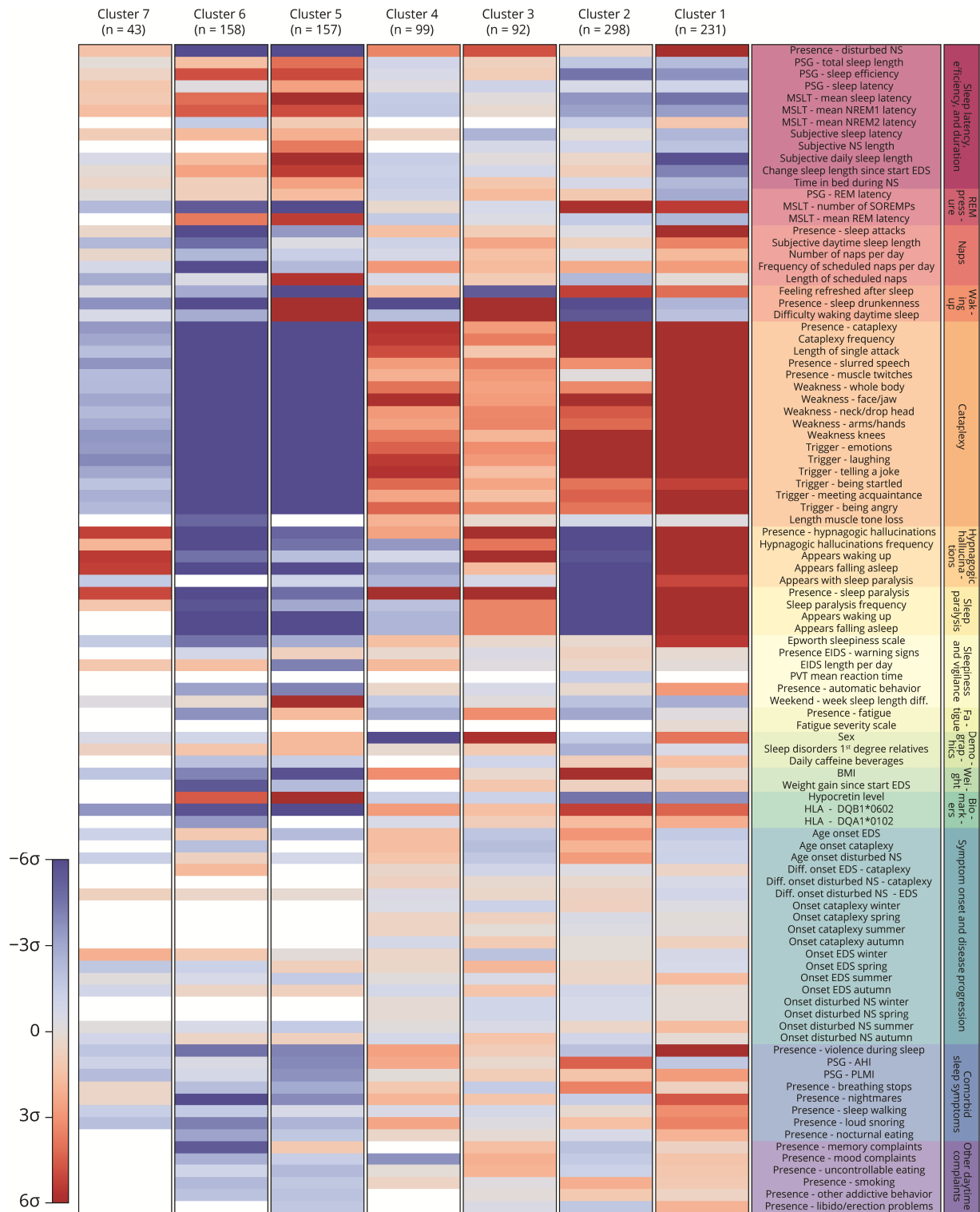
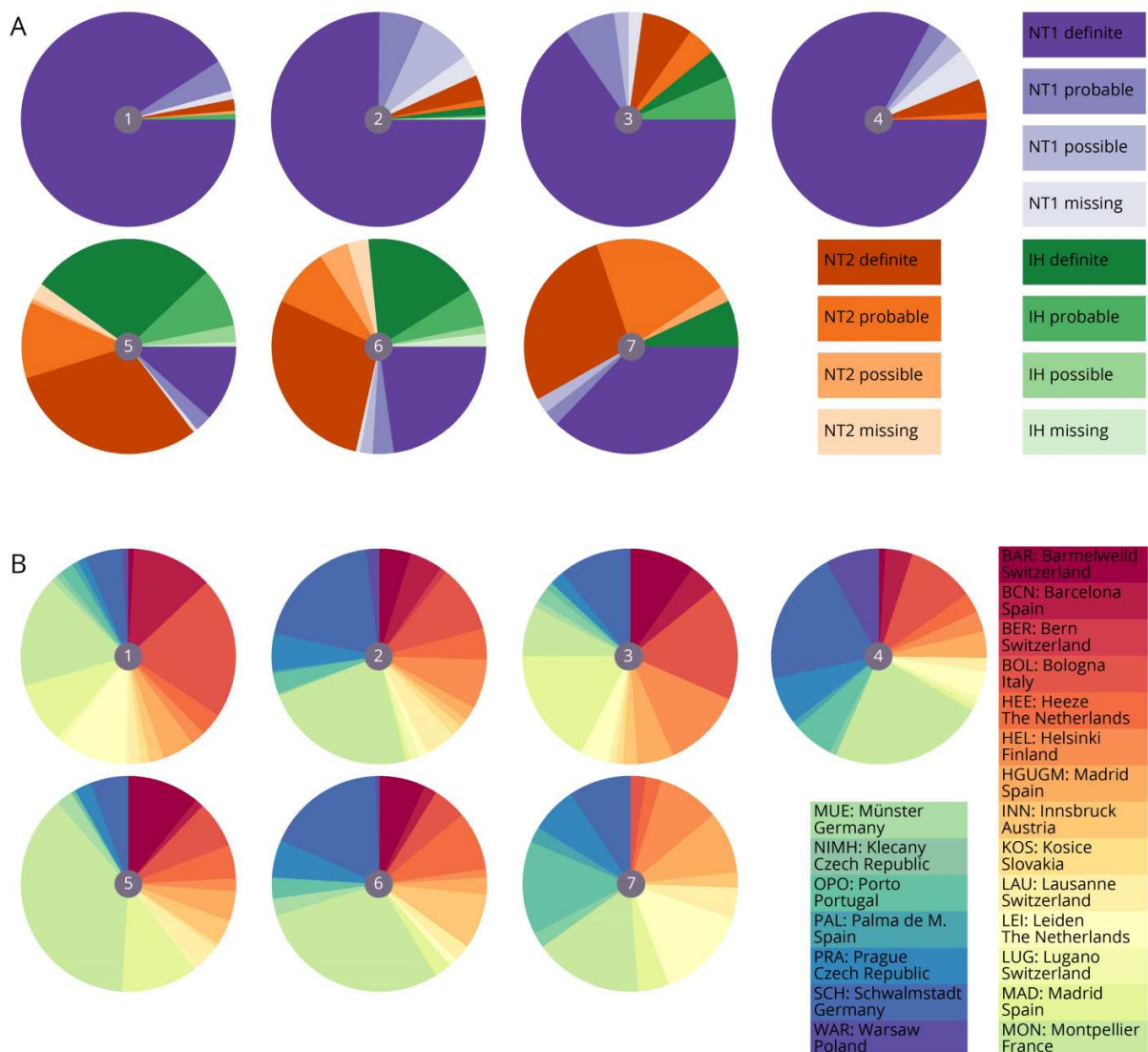


Figure 3. Current diagnoses and centers of inclusion. (A) Current diagnosis with physician's diagnostic certainty, visualized as pie charts per cluster. The central number in the pie charts corresponds to the cluster id. Clusters 1-4 are dominated by narcolepsy type 1, whereas narcolepsy type 2 and idiopathic hypersomnia are more common in clusters 5-7. (B) To check whether center of inclusion (or country) could have introduced bias in the clustering, the distribution of the centers of inclusion is visualized as pie charts per cluster. This shows that there is no clear dominance of single centers in individual clusters and that individuals from one center are spread over multiple clusters.



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