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Authors

Levendowski, Daniel
Walsh, Christine
Boeve, Bradley
et al.

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Non-REM sleep with hypertonia in Parkinsonian Spectrum Disorders: A pilot investigation

Daniel J. Levendowski[a,*], **Christine M. Walsh**[b,c], **Bradley F. Boeve**[d], **Debby Tsuang**[e], **Joanne M. Hamilton**[f], **David Salat**[g], **Chris Berka**[a], **Joyce K. Lee-Iannotti**[h], **David Shprecher**[i], **Philip R. Westbrook**[a], **Gandis Mazeika**[a], **Leslie Yack**[b], **Sarah Payne**[e], **Paul C. Timm**[d], **Thomas C. Neylan**[c], **Erik K. St. Louis**[d]

[a]Sleep and Respiratory Research, Advanced Brain Monitoring, Inc., Carlsbad, CA, USA

[b]Memory and Aging Center, University of California, San Francisco, San Francisco, CA, USA

[c]Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, USA

[d]Department of Neurology and Center for Sleep Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN, USA

[e]Geriatric Research Education and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, USA

[f]Neurocognitive Assessment Group, Advanced Neurobehavioral Health, San Diego, CA, USA

[g]Athinoula A. Martinos Center for Biomedical Imaging and Department of Radiology, Massachusetts General Hospital, Charlestown, MA, USA

[h]Department of Neurology and Sleep Medicine, Banner University Medical Center, Phoenix, AZ, USA

[i]Banner Sun Health Research Institute, Sun City, AZ, USA

Abstract

[*]Corresponding author. 2237 Faraday Avenue Suite 100 Carlsbad, CA, 92008, USA. Dan@b-alert.com (D.J. Levendowski).

Authorship

Daniel J. Levendowski : Formal analysis, data curation, investigation, software, validation, writing - original draft. **Christine M. Walsh :** Funding acquisition, methodology, project administration, writing - review & editing. **Bradley F. Boeve :** Investigation, methodology, writing - review & editing. **Debby Tsuang :** Funding acquisition, methodology, project administration, writing - review & editing. **Joanne M. Hamilton :** Funding acquisition, project administration, writing - review & editing. **David Salat:** Resources, project administration, supervision. **Joyce K. Lee-Iannotti :** Project administration, resources supervision. **David Shprecher :** Funding acquisition, resources, writing - review & editing. **Chris Berka :** Funding acquisition, project administration, writing - review & editing. **Philip R. Westbrook :** Writing - review & editing. **Gandis Mazeika :** Writing - review & editing. **Leslie Yack :** Project administration, supervision. **Sarah Payne :** Project administration. **Paul C. Timm :** Formal analysis, Project administration. **Thomas C. Neylan :** Conceptualization, methodology, visualization, writing - review & editing. **Erik K. St. Louis :** Conceptualization, investigation, methodology, writing - original draft.

Institutions where work was performed

Advanced Brain Monitoring, Inc. Carlsbad CA; Advanced Neurobehavioral Health, San Diego, CA; Massachusetts General Hospital, Boston, MA; Mayo Clinic Rochester, MN; University of California, San Francisco, CA; VA Puget Sound Health Care System, Seattle, WA.

Introduction: From an ongoing multicenter effort toward differentiation of Parkinsonian spectrum disorders (PSD) from other types of neurodegenerative disorders, the sleep biomarker non-rapid-eye-movement sleep with hypertonia (NRH) emerged.

Methods: This study included in the PSD group patients with dementia with Lewy bodies/Parkinson disease dementia (DLB/PDD = 16), Parkinson disease (PD = 16), and progressive supranuclear palsy (PSP = 13). The non-PSD group included patients with Alzheimer disease dementia (AD = 24), mild cognitive impairment (MCI = 35), and a control group with normal cognition (CG = 61). In-home, multi-night Sleep Profiler studies were conducted in all participants. Automated algorithms detected NRH, characterized by elevated frontopolar electromyographic power. Between-group differences in NRH were evaluated using Logistic regression, Mann-Whitney *U* and Chi-squared tests.

Results: NRH was greater in the PSD group compared to non-PSD (13.9 ± 11.0% vs. 3.1 ± 4.7%, $P < 0.0001$). The threshold NRH≥5% provided the optimal between-group differentiation (AUC = 0.78, $P < 0.001$). NRH was independently associated with the PSD group after controlling for age, sex, and SSRI/SNRI use ($P < 0.0001$). The frequencies of abnormal NRH by subgroup were PSP = 92%, DLB/PDD = 81%, PD = 56%, MCI = 26%, AD = 17%, and CG = 16%. The odds of abnormal NRH in each PSD subgroup ranged from 3.7 to 61.2 compared to each non-PSD subgroup. The night-to-night and test-retest intraclass correlations were excellent (0.78 and 0.84, both $P < 0.0001$).

Conclusions: In this pilot study, NRH appeared to be a novel candidate sleep biomarker for PSD-related neurodegeneration. Future studies in larger cohorts are needed to confirm these findings, understand the etiology of NRH magnitude/duration, and determine whether it is an independent prodromal marker for specific neurodegenerative pathologies.

Keywords

Sleep hypertonia; Dementia; Biomarker; Prodromal; Neurodegeneration; RSWA; Parkinson

1. Introduction

The World Health Organization has estimated that dementia impacts 50 million individuals worldwide, with an estimated incidence of 10 million new people developing dementia annually, burgeoning to impact an estimated 82 million people by 2030 and 152 million by 2050 [1]. In the U.S. alone, the healthcare costs associated with neurodegenerative disorders are estimated to exceed $250 billion annually as a result of population aging [2].

Early diagnosis and targeted intervention are primary goals in dementia care worldwide [1]. However, available tools that aid in the definition of specific neurodegenerative disorders are currently limited. Reduced β-amyloid and elevated tau proteins in the cerebrospinal fluid predict conversion from mild cognitive impairment (MCI to Alzheimers Disease dementia (AD) [3–5], but are not routine in most memory clinics, and blood-based screening biomarkers for proteinopathies for the full range of neurodegenerative disorders await validation [6].

Polysomnographic assessment of REM sleep without atonia (RSWA) is used to characterize synucleinopathies, with REM sleep behavior disorder (RBD) and isolated RBD (iRBD) indicating the prodromal phase of an eventual manifest disease [7–9]. In a large post-mortem study, 98% of patients with RBD had pathologically proven α-synuclein protein in neurons and/or glial cells [10]. Approximately 70–75% of those diagnosed with iRBD undergo phenoconversion within a 10- to 15-year period with approximately 50% developing a parkinsonism-predominant syndrome [most often Parkinson disease (PD)] and the others developing a dementia-predominant syndrome [i.e., Dementia with Lewy Bodies (DLB) or Parkinson Disease Dementia (PDD)] [9,11]. RBD was also found to occur in up to 88% of patents with multiple system atrophy [12].

Progressive supranuclear palsy (PSP) is characterized as a Parkinsonian syndrome, however the occurrence of RSWA and RBD in is poorly understood. Nomura et al. found that RSWA and RBD were less frequent in PSP patients when compared to a PD cohort [13]. McCarter et al. found that RSWA levels were lower in motor and cognitive phenotypes of PSP, AD and corticobasal degeneration (CBD) compared to the probable synucleinopathy phenotypes of PD, DLB, and Multiple System Atrophy (MSA) [14,15]. Conversely, Sixel-Döring et al. reported RSWA in 95% of PD and 85% of PSP patients with a concurrent RBD diagnosis in 35% and 15% of the cases, respectively [16]. Arnulf et al. also reported similarities in the distributions of RSWA among their PD and PSP cohorts [17].

In our ongoing multi-center research focused on identification of sleep and wake electroencephalographic (EEG) characteristics that differentiate neurodegenerative disorders from healthy aging [18], a novel sleep biomarker, non-REM sleep with hypertonia (NRH) was discovered. The unique distributions of NRH power spectra in the frontopolar EEG had been previously noted and treated as a confounding factor in the accurate, automated staging of sleep. The potential utility of NRH as a sleep biomarker only became apparent during review of the consortium's data set which included patients populations with prodromal or manifest Parkinsonism. Herein, we describe the electrophysiological characteristics of NRH, provide the methods used to quantify NRH, and evaluate whether it could serve as a future biomarker for Parkinsonian spectrum disorders (PSD).

2. Methods

2.1. Participants

A control group of subjects with normal cognition (CG) and patients with neurodegenerative disorders were enrolled in ongoing studies under institutional review board approval at six sites (Table 1). Exclusion criteria included patients with a history of epileptiform activity, open wounds on the forehead, or head circumferences less than 55 cm.

DLB/PDD: Two women and fourteen men (70 ± 5.1 years) were included in this subgroup. Twelve were diagnosed with DLB according to the McKeith criteria [19]. PDD was diagnosed in four patients by combined use of United Kingdom PD Society Brain Bank clinical diagnostic criteria with dementia based on Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Seven patients in this subgroup (44%) were taking

a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) anti-depressant.

PD: Five women and 11 men (67 ± 8.7 years) met either the most recent Movement Disorder Society criteria [20] (n = 14) or United Kingdom PD Society Brain Bank clinical diagnostic criteria for PD (n = 2). None of the PD patients were receiving SSRI/SNRI medications.

PSP: Seven women and six men (70 ± 9.0 years) required one or more clinical features consistent with PSP as described in the Movement Disorder Society criteria [21] or the NINDS-SPSP criteria [22]. Four PSP patients (30.8%) were receiving a SSRI/SNRI.

AD: Six women and 18 men (75 ± 6.8 years) were either diagnosed by DSM-5 criteria applied by a board-certified neurologist with expertise in dementia and movement disorders (n = 16), and/or met the AD criteria described by McKhann et al. [23] (n = 8). Seven AD patients (29.2%) were taking a SSRI/SNRI.

MCI: Ten women and 25 men (71 ± 8.2 years) had a subjective memory complaint evident to the patient and/or their family/caregiver, relatively preserved activities of daily living but with objective cognitive impairment, and a Mini-Mental State Examination (MMSE) score greater than 24. A detailed description of the MCI patients was previously reported [18]. In the MCI subgroup, twelve (34.3%) were being treated with a SSRI/SNRI.

CG: Controls with normal cognition included 32 women and 29 men (65 ± 8.3 years), all had MMSE scores ≥ 29 with no cognitive complaints or history of neurological disorders, dream enactment, or traumatic brain injury. Six in the CG (9.8%) were receiving a SSRI/SNRI.

CG retest: Twenty-six CG subjects (58% women, age: 63 ± 8.7 years) completed a longitudinal in-home retest study with a median lapse of 375 days between the initial test and retest (range: 364–563 days). Two retests were acquired from an 85-year-old woman to confirm changes in NRH, the first 1.5 years after baseline and the second 2.5 years after baseline.

The patients diagnosed with PD, DLB, PDD, or PSP were considered collectively as presumed Parkinsonian spectrum disorders (PSD) (i.e., diagnoses based on well accepted clinical diagnostic criteria without pathologic confirmation), while the AD and MCI patients and CG subjects were characterized as non-PSD.

2.2. Sleep EEG acquisition

In-home sleep recordings were acquired from participants using the Sleep Profiler™ (SP; Advanced Brain Monitoring, Carlsbad, CA; see Fig. 1). For both baseline and longitudinal retest studies, participants were instructed to acquire consecutive nights of data.

The SP acquired three EEG frontopolar signals from AF7-AF8, AF7-Fpz, AF8-Fpz which were labeled as EEG, LEOG, and REOG (left and right electrooculography), respectively.

The exact placement of the sensors relative to the 10–20 system was dependent on head circumference. Pulse rate was acquired using photoplethesmography, snoring level was measured with acoustic microphone, and head movement and head position were derived from a triaxial accelerometer.

The methodology and signal processing associated with the use of three frontopolar EEG signals to stage sleep has been previously described, with its accuracy and reliability found comparable to visually scored PSG [24–27]. The auto-staging, designed to match the American Academy of Sleep Medicine rules for the visual characterization of sleep [28], utilized machine learning algorithms to establish the relationships between the EEG power extracted from the delta (1–3.5 Hz), theta (4–6.5 Hz), alpha (8–12 Hz), sigma (12–16 Hz), beta (18–28 Hz), and electromyography (EMG) (40–128 Hz with a 67 Hz lowpass hardware filter) bands for the staging of each 30-sec epoch. Additional inputs to the algorithms included automated detection of sleep spindles, cortical- and micro-arousals, outputs from cross-correlation of the EOG channels (to help differentiate slow rolling eye movements during stage N1 from phasic rapid eye movements during REM sleep), and the temporal characterization of head movement and snoring. Empirically derived thresholds and rules were then applied to the outputs of the machine learning algorithms to optimize classification accuracy. Based on the probability of a correct classification, an alternative secondary stage was provided to assist with visual inspection and manual editing.

2.3. Visual characteristics of NRH

Fig. 2.a. presents the SP signals and power spectra on a 1-h time scale. Note in the two blocks of NRH the steady burst of EMG and beta power while sigma and alpha power remain relatively unchanged. Fig. 2.b. and c. present the SP signals on a 30-sec time scale with a. the left pane containing NRH with the dashed line highlighting the average EMG power, and b. the right pane showing normal levels of EMG power during non-REM sleep (NREM).

The unique power spectral patterns which characterize NRH were recognized during technical review of the first seven SP recordings made of patients diagnosed with iRBD. The rule-based characterization of NRH was empirically designed using variables extracted from the EEG signal to auto-stage sleep, obtained from recordings of patients with iRBD and recordings which were independent of this study. The generalizability of the NRH rules were visually confirmed in recordings of 10 CG, two DLB, two MCI, one PDD, and one PD which were included in the results.

NRH rules were designed to be applied to all epochs after completion of the standard SP auto-staging algorithms. One set of the standard auto-staging algorithms apply discrete thresholds to the relative EMG power to characterize each NREM stage and REM. Another set of algorithms were designed to differentiate elevated delta power associated with slow wave activity from ocular activity. Thus, it is possible that a NRH block (as described below) includes an epoch(s) which visibly displays the delta and theta wave characteristics of NREM sleep but was initially and incorrectly auto-staged and tallied as Wake, and in the rare occasion REM. To adjust for and accommodate these initial auto-staging errors, NRH

was treated as an independent sleep stage and calculated as a proportion of sleep time, rather than a sub-set of NREM sleep.

Fig. 3 provides a detailed description of the rules developed to detect NRH episodes. The first set of rules (Rules 1.a. through g.) were applied to each 30-sec epoch beginning with a restriction on delta power to exclude epochs which were likely true Wake. Next, rules to detect elevated but steady EMG power in the EEG signal were applied. The relationships between delta, theta, and EMG power were then tested using two regression equations developed with five epochs selected across a range of EEG amplitudes with NRH. One equation used the actual theta/EMG ratio to set the minimum threshold for delta/EMG. The second equation used the actual delta/EMG ratio to set the minimum threshold of theta/EMG power. Epochs with NRH required both delta and theta thresholds to be satisfied. The sigma/EMG power ratio was used to limit epochs with normal sleep characteristics from being recognized as possible NRH.

Rule 2 was applied, using the standard deviation of EMG power across the current, previous, and subsequent 30-sec epochs, to ensure the elevated EMG power was not associated with arousals that caused short duration bursts of EMG activity (e.g., sleep disordered breathing, dream enactment, periodic limb movements, etc.). Further, Rule 3 describes algorithms used to ensure the characteristics of NRH were consistent across at least four epochs within a restricted window. To reduce the need for technician editing during visually detectable elevated EMG power, NRH blocks were extended in each direction to include additional epochs so long as the gap between the block and the previous or subsequent NRH episode met one of the criteria described in Rule 4.

Finally, because EMG is generally elevated after extended periods of Wake, NRH blocks that started within 10-min of elapsed sleep time after sleep onset or immediately after 10-min of being upright were identified with a secondary stripe (for visual confirmation and potential manual editing), but not included in the summation of automated NRH detection. To limit the possibility of NRH being influenced by artifact, periods with elevated skin-electrode impedances were also not included in the computation of percent time NRH.

In 12 patients with suspected iRBD, a strong association between auto-staged NRH derived from simultaneously acquired PSG: Fp1-Fp2 and SP: AF7-AF8 was observed (intraclass correlation = 0.82, $P < 0.0001$). The minor discrepancies were likely explained by power differences attributed to the inter-electrode spacings.

2.4. Data analysis

After auto-staging, the records were manually edited according to described guidelines [24,29]. The proportion of nightly NRH was based on the total duration of auto-detected blocks relative to postedited sleep time (i.e., similar to the quantification of other sleep stages). Spindle duration was computed as the sum of all auto-detected spindle elapsed times. When applicable, sleep metrics were weight averaged based on the sleep times across two nights of data. When three-night baseline studies were acquired, the first two nights were used unless a difference in valid recording time greater than 2-h could be resolved using the third night. Two nights of acceptable data were acquired in 83% (137/165) of

the in-home studies, with two nights recorded in PD = 100%, PSP = 100%, CG = 87%, DLB/PDD = 75%, AD = 75%, and MCI = 71% of the cases. For the in-home studies based on a single night recording: a) less than 4-h was recorded in one of the nights in seven studies, b) less than 4-h of acceptable signal quality was obtained in one of the nights in six records, and c) uninterpretable data was recorded throughout one of the nights in 15 cases.

Mann-Whitney *U* tests were used to assess group differences in the presence of NRH. Multivariate logistic regression was used to assess the association between abnormal NRH and the independent variables of group, age, sex, and SSRI/SNRI use. Receiver operating characteristic (ROC) curves and Chi-squared analysis with two-tailed Fisher Exact probability tests were used to determine group differences in the proportion of cases with abnormal NRH and the odds ratios and 95% confidence intervals (CI) associated with these differences. Intraclass correlations (ICC) were used to measure the strength of association between Night 1 vs. Night 2 and Test vs. Retest.

3. Results

3.1. Distributions of sleep characteristics

The PSD group had lower total sleep duration (5.7 ± 1.6 vs. 6.7 ± 4.8 h, $P < 0.05$) and had poorer sleep efficiency (70.5 ± 0.17 vs. 83.9 ± 0.12%, $P < 0.0001$) as a result of increased sleep latencies (26.0 ± 21.6 vs. 19.5 ± 17.2 min, $P < 0.05$) and wake after sleep onset (120.4 ± 80.8 vs. 55.2 ± 39.1 min, $P < 0.0001$), and more awakenings (4.5 ± 2.0 vs. 3.9 ± 2.5 per hour, $P < 0.01$). The PSD group also had less REM sleep (11.5 ± 9.2 vs. 19.4 ± 7.1%, $P < 0.0001$) and spindle duration (2.7 ± 5.0 vs. 6.2 ± 10.0 min, $P < 0.001$), and greater NRH (13.9 ± 11.0 vs. 3.1 ± 4.7%, $P < 0.0001$). The sleep architecture and sleep continuity measures, stratified by subgroup, are presented in Table 2.

3.2. Frequency of NRH

Fig. 4 presents a box-whisker plot of NRH distributions across the subgroups. NRH was greater in each of the three PSD subgroups when compared to MCI (all $P < 0.005$), AD (all $P < 0.01$), and CG (all $P < 0.01$) subgroups.

Fig. 5 plots the ROC curve differentiating the PSD and non-PSD groups with an area under the curve of 0.78 (95% CI 0.71–0.86). Based on an abnormal NRH threshold of ≥5%, an optimal sensitivity of 0.76 (CI 0.61–0.86) and specificity of 0.81 (CI 0.73–0.87) was achieved.

The frequencies of abnormal NRH in the PSD and non-PSD groups were 76% vs. 19%, respectively ($P < 0.0001$). Abnormal NRH was associated with the PSD group independent of age, sex and SSRI/SNRI use ($P < 0.0001$, odds ratio = 14.3, 95% CI: 6.1–33.5). The proportion of cases having abnormal NRH in each subgroup were PSP = 92%, DLB/PDD = 81%, PD = 56%, MCI = 26%, AD = 17%, and CG = 16%. Based on these distributions, the odds of having abnormal NRH ranged from 3.7 to 61.2 when each of the PSD subgroups were compared to each of the non-PSD subgroups (Table 3).

3.3. NRH reliability

There was a strong concordance between the NRH measured on nights 1 and 2 (ICC = 0.78, $P < 0.0001$) with limited night-to-night variability (Fig. 6.a. and b.). The proportion of recordings with consistently normal or abnormal NRH on both nights was 87% (119/137). The between-night normal/abnormal NRH consistency by subgroup was DLB/PDD = 100%, MCI = 92%, CG = 89% PSP = 85%, AD = 83%, and PD = 69%. Fig. 6.c. and d. show very strong test vs. retest reliability in CG subjects (ICC = 0.84, $P < 0.0001$) with tight distributions around ±5%, the threshold used to identify abnormal NRH. The proportion of studies with consistently normal or abnormal NRH detected during both the test and retest was 85%, with no cases reverting from abnormal to normal.

4. Discussion

The findings from this study suggest NRH may be a novel sleep PSD biomarker. The association between NRH and the PSD group was independent of age, sex and SSRI/SNRI use. The frequency of abnormal NRH was significantly greater in each of the DLB/PDD, PD, and PSP subgroups paralleling previously demonstrated elevations of quantitative RSWA in these phenotypes [14–16,30,31]. NRH also exhibited strong night-to-night and test-retest reliability, with distributions similar to that reported in RSWA [32].

The pathophysiology underlying varying levels of NRH in the Parkinsonian subgroups is unclear. A recent study of spontaneously behaving mice found that the substantia nigra appears to serve a major role in arousal state and motor control [33]. In the Lie et al. study, gamma aminobutyric acid (GABA)-ergic neuronal subpopulations, differentially expressing glutamic decarboxylase 2 and parvalbumin within the substantia nigra pars reticulata (SNr), were found to modulate natural behavioral and motor state transitions between locomotion, nonlocomotory movements and behaviors, quiet wakefulness, and sleep. These neurons were found to have widespread projections interfacing with vital brain regions mediating sleep and motor control in the basal forebrain, thalamus, hypothalamus, midbrain, and pons. The findings suggested that SNr GABAergic neurons may be an integrative center for modulating vigilance state and motor activity during wakefulness and sleep, especially during NREM sleep. Hypertrophic changes within SNr have long been found in DLB and are thought to represent plasticity resulting from damaged SN pars compacta neurons that may result in upstream inhibition of thalamocortical pathways in PD [34].

While the networks involved in NRH manifestation are yet to be determined, concomitant motor activity during wake, NREM and REM sleep, could provide further clarification especially in those with a PSD [35]. Distributions of NRH in the PD group relative to DLB/PDD were similar to those previously observed for RSWA [14]. While NRH manifests as a periodic, sustained increase in muscle tone and excessive fragmentary myoclonus appears as brief <150 ms duration EMG twitches, the proportion of PD patients with these abnormal biomarkers are similar, suggesting a possible overlap of sleep state motor disturbances [36]. Given that the pontomedullary circuit involved in REM sleep is impacted by synucleinopathies, while typically not by primary tau or AD pathologies, the presence of NRH in the absence of RSWA could potentially distinguish PSP, while the absence of both RSWA and NRH may be useful in the characterization of AD pathology. Studies are needed

to further investigate the association between rigidity during wake and increased muscle tone during REM and NREM sleep not only in this study's PSD subgroups, but also in iRBD, MSA and CBS, Huntington's disease, and Multiple sclerosis. The findings could assist in determining whether NRH and/or RSWA are manifestations of proteinopathic-related dysfunctions of the brainstem systems that control muscle tone [17,37].

Previous visual analyses of polysomnographic motor activity in populations with neurodegenerative diseases have focused predominantly on REM sleep muscle activity [8,13–17,30,38–48], although a few previous studies have also shown evidence for elevated NREM phasic muscle activity. NREM sleep muscle activity was previously shown to be higher in PD patients relative to controls [40,41]. Elevated submental EMG was observed in both NREM and REM sleep in iRBD patients when compared to controls, however the amplitude differences were more detectable during REM [49,50]. In a third study, a data-driven algorithmic approach for muscle activity analysis found that the combination of NREM and REM muscle activity improved distinction of iRBD from periodic limb movement disorder patients and controls [51].

Previously we demonstrated that differentially-recorded EEG acquired over the frontalis muscle has unique signal characteristics. For example, the EMG power extracted from the frontalis EEG signal during Wake was 50% greater than simultaneously acquired EMG power from *submentalis recordings*, with 50% less between-subject variability [25]. During sleep, the between-subject variability of frontalis EMG power was two to four times less than *submentalis* EMG power during REM and in all three NREM stages [25].

Discovery of NRH was facilitated by concurrent presentation of the relative power of key frontalis EEG spectral characteristics (i.e., alpha, sigma, beta, and EMG power) viewed on longitudinal time scales not typically utilized for visual sleep staging (i.e., longer time scales of 10-min, 30-min, and 1-h often used for inspection of automated SP scoring and data review versus usual viewing windows of 30-sec, 60-sec, or 120-sec epochs during polysomnography review). A combination of the signal pattern information available with presentation of the power spectra from differentially recorded frontalis EEG and that information typically accessible with the standard PSG-EEG montage may explain why NRH has not been previously reported.

Our study has a number of limitations. First, the automated detection of NRH developed for SP may require threshold modifications for use in PSG-EEG recordings with different electrode locations, sampling rates, and/or low-pass filter characteristics. Because both the beta power (18–28 Hz) and EMG power (>40 Hz) were elevated in the EEG signal, we cannot definitively demonstrate that the hyperactivity was exclusively EMG related or whether NRH may also contain elevated gamma EEG activity. However, it is unlikely that high frequency EEG activity would be the primary source of the NRH signal pattern, given the relatively direct near field proximity of recording sensors to underlying muscle generators, and the significant biological filtering by cerebrospinal fluid, meninges, skull, and scalp of gamma frequency EEG activity generated by the brain.

The accuracy of SP was previously validated in patients with sleep disordered breathing and/or on medications that impact sleep architecture, but not in patients with dementia. In patients with suspected iRBD, however, a comparison between SP inspected sleep staging and simultaneously acquired and manually staged PSG did show substantial agreement (Kappa>0.72) for all stages except N1 [52]. Investigations are underway to assess the interrater agreement in the technical editing of SP studies in patients with neurodegenerative disorders.

While the overall number of records in this pilot study were adequate to support the PSD vs. non-PSD analyses, the subgroup analyses were based on relatively small numbers of cases. The sporadic and limited use of other drugs (e.g., opioid, benzodiazepine, etc.) limited a definitive assessment as to their influence on NRH. Additionally, a small number of records used to confirm the generalizability of the NRH algorithms were included in the results. The diagnostic criteria for PDD, PD, and AD varied between centers (due to differences in the scientific literature that guided development of the protocols when data acquisition began), although each center employed well accepted standard methods used to characterize neurodegenerative disorder groups in previous research. The consortium data set did not include longitudinal information that could be used to assess disease duration, and planned SP longitudinal studies in the PSD patients were cancelled due to the Covid-19 pandemic. Chin EMG was not acquired in a sufficient number of recordings to establish a relationship between abnormal NRH and RSWA, or the proportion of patients in each subgroup with RBD. The proportion of MCI cases with abnormal NRH (i.e., 26%), while likely explained by covert disease progression [53,54], was less than the frequency of RSWA observed in MCI cases [55]. Future studies may benefit from stratification of MCI patients into amnestic and non-amnestic subtypes, since non-amnestic MCI subtypes are more likely to be due to underlying DLB than patients with amnestic MCI [56].

In conclusion, these pilot data served to describe the signal characteristics and establish face-validity for NRH as a sleep biomarker for PSD-related neurodegeneration. NRH appeared to distinguish presumed PSD patients with high sensitivity and specificity and demonstrated consistent reliability. Studies are currently underway with acquisition of chin/arm EMG to understand the relationship between NRH and RSWA. Future studies in larger cohorts are also needed to confirm our findings, investigate the etiology of NRH and how its magnitude/duration might relate to disease severity and the interaction between specific proteinopathies and motor control, and determine the degree to which NRH is an independent prodromal marker for specific PSDs.

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Declaration of competing interest

As shareholders in Advanced Brain Monitoring, Inc. Mr. Levendowski, Ms. Berka and Dr. Westbrook would financially benefit if the SP intellectual property was acquired by a third party. Dr. Boeve has served as an investigator for clinical trials sponsored by Biogen, Alector, and EIP Pharma. He receives royalties from the publication of a book entitled Behavioral Neurology Of Dementia (Cambridge Medicine, 2009, 2017). He serves on the Scientific Advisory Board of the Tau Consortium. Dr. Salat is a consultant to Cyclerion and Amylyx, has a financial interest in Niji Corp and has served as an investigator on research sponsored by Renew Research. Dr. Lee-Iannotti serves as a paid advisor to and speaker for Jazz Pharmaceuticals. Dr Shprecher received research support from the Arizona Alzheimer's Consortium, Abbvie, Acadia, Aptinyx, Axovant, Biogen, Eisai, Eli Lilly, Enterin, Neurocrine, Michael J Fox Foundation, NIH, Nuvelution and Teva; consultant fees from Amneal, Forensis and Neurocrine; speaker honoraria from Acorda, Amneal, Intermountain Healthcare, Neurocrine, Sunovion, Teva and US World Meds. Dr. Mazeika serves as the Medical Director of Advanced Brain Monitoring, Inc. None of the other authors reported financial conflicts.

Abbreviations:

RSWA	REM sleep without atonia

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Fig. 1.
Subject wearing the SP.

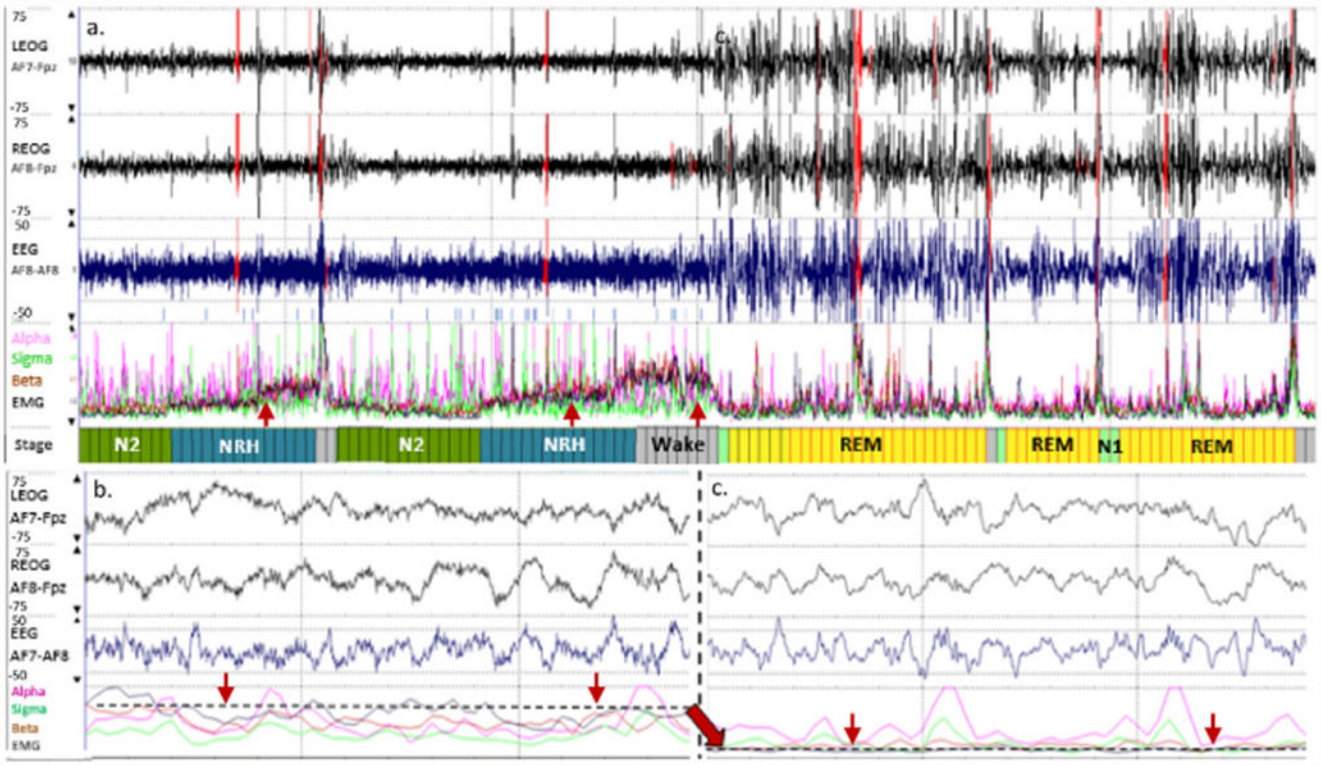

Fig. 2.

a. A 1-h epoch presenting the LEOG, REOG and EEG signals, with the relative EEG power spectral distributions for alpha (pink), sigma (green), beta (brown) and EMG (black). The increase in relative EMG power corresponds with two periods initially auto-staged N2 but then reassigned stage NRH. In the period labeled Wake, the EMG power exceeded the thresholds which allowed it to be auto-staged NRH. b. A 30-sec epoch illustrating NRH with visually apparent fast frequency activity evident in the LEOG, REOG, and AF7-AF8 EEG channels. The dashed lines and arrows highlight the average relative EMG power extracted from the EEG signal in 15-sec panes b) with NRH, and c) without visual evidence of NRH.

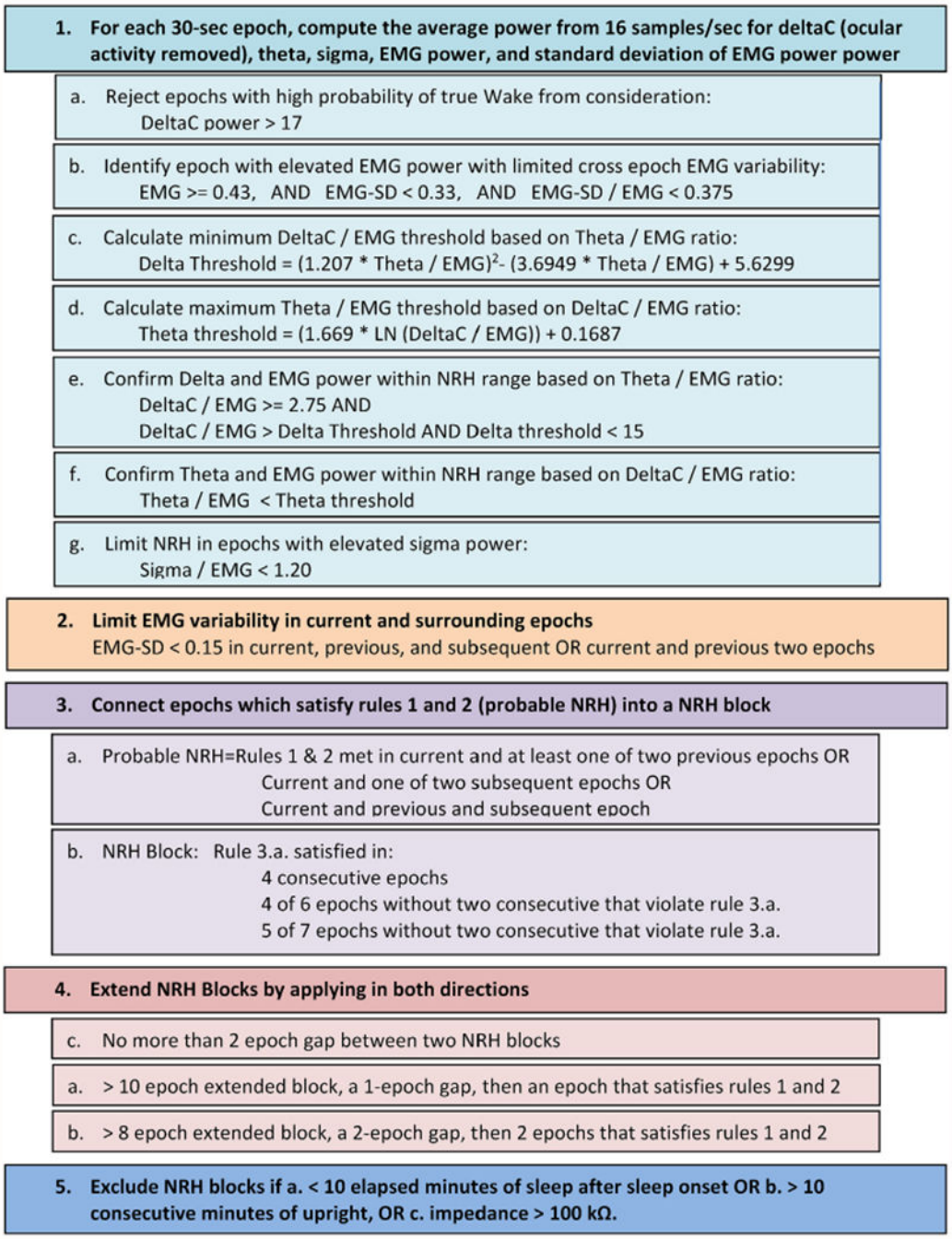

Fig. 3.
Rationale and rules for the automated staging of NRH.

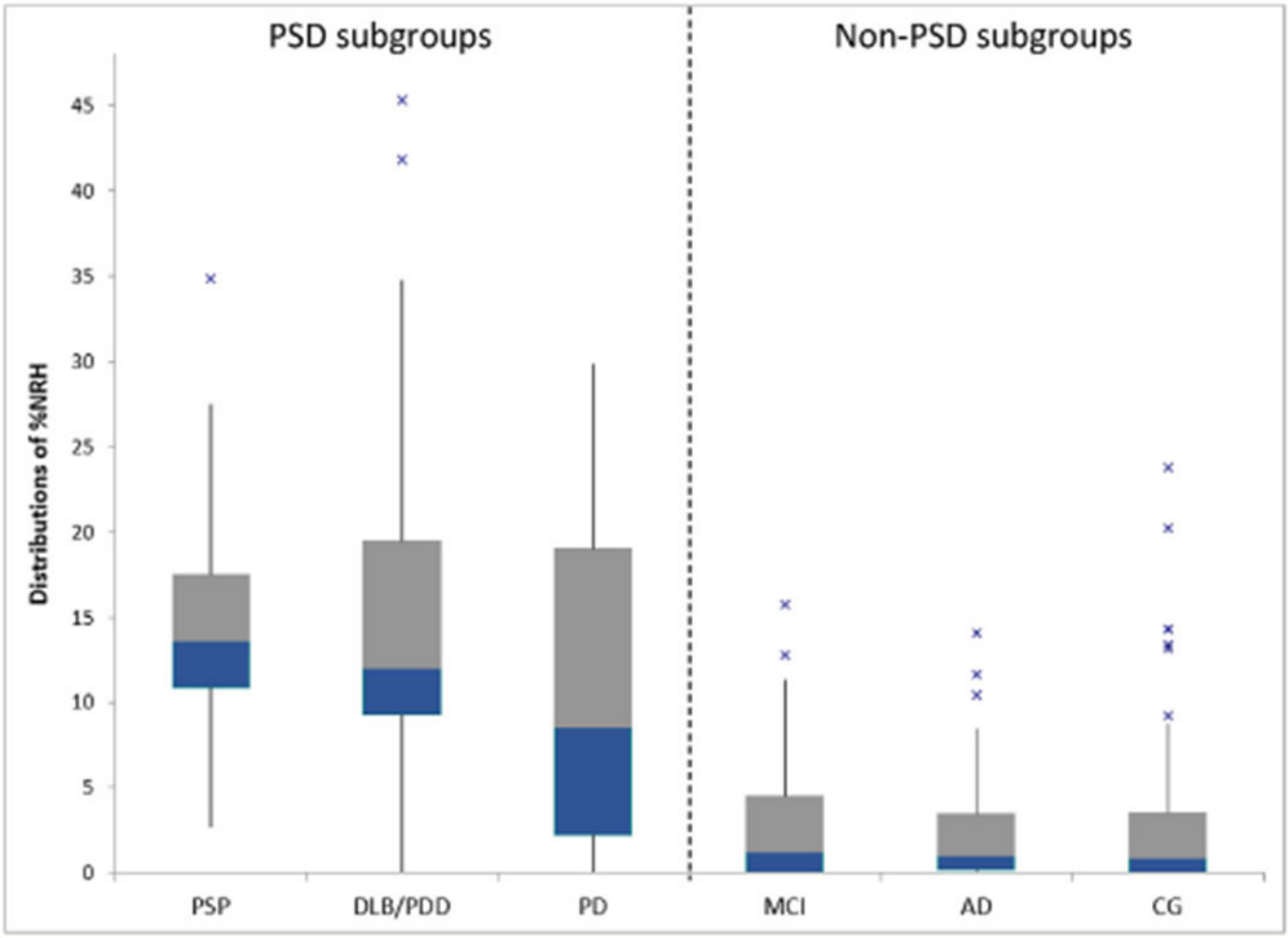

Fig. 4.

Box-whisker plot of %NRH in the PSD (left pane: PSP, DLB/PDD, PD) and non-PSD (right pane: MCI, AD, CG) groups. PSP = progressive supranuclear palsy; DLB = dementia with Lewy bodies; PDD=Parkinson disease dementia; PD=Parkinson disease; MCI = mild cognitive impairment; AD = Alzheimer disease dementia; CG=Control group with normal cognition.

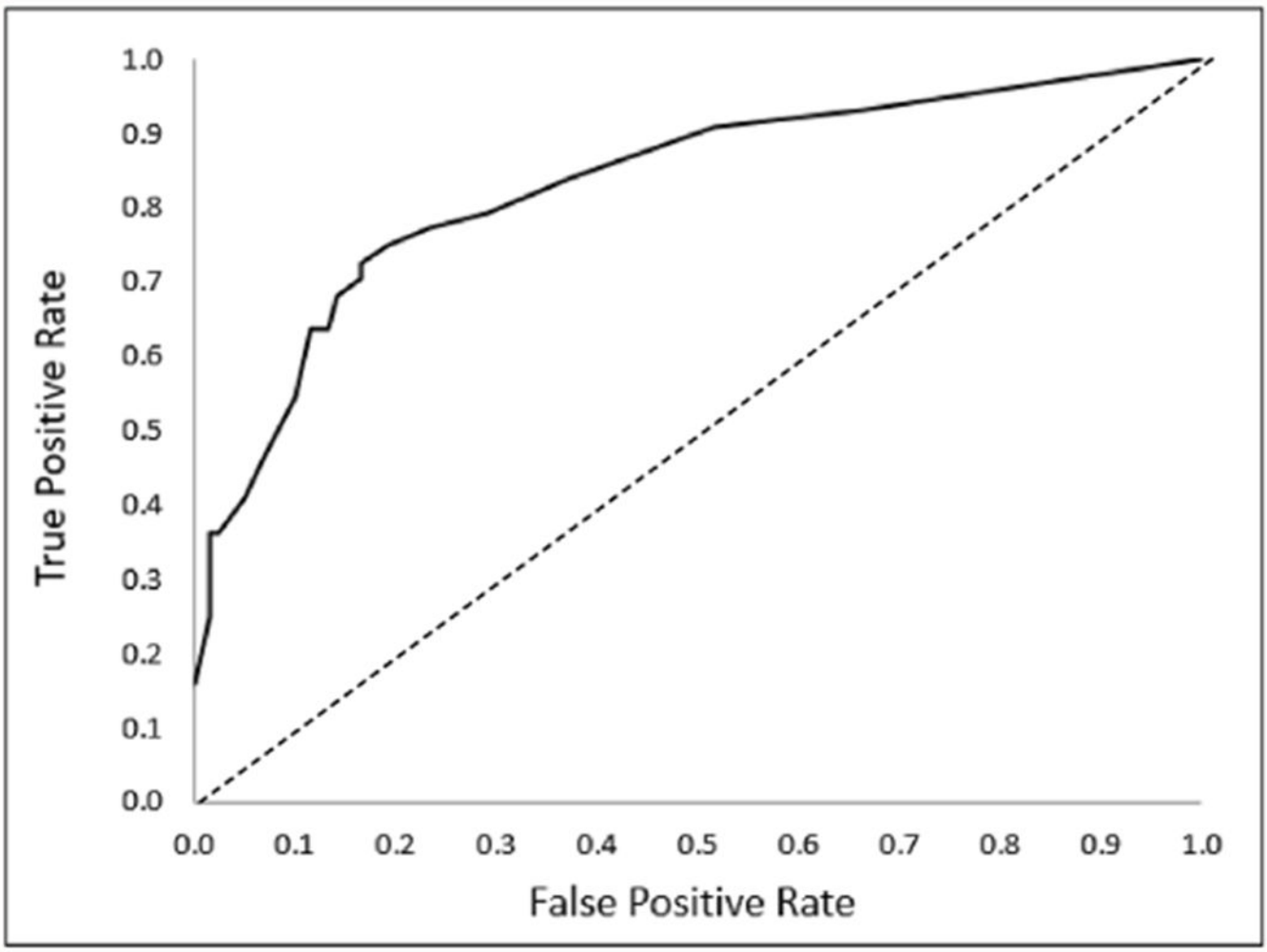

Fig. 5.
Receiver operating characteristics illustrating the diagnostic ability of abnormal NRH to different the PSD and non-PSD groups.

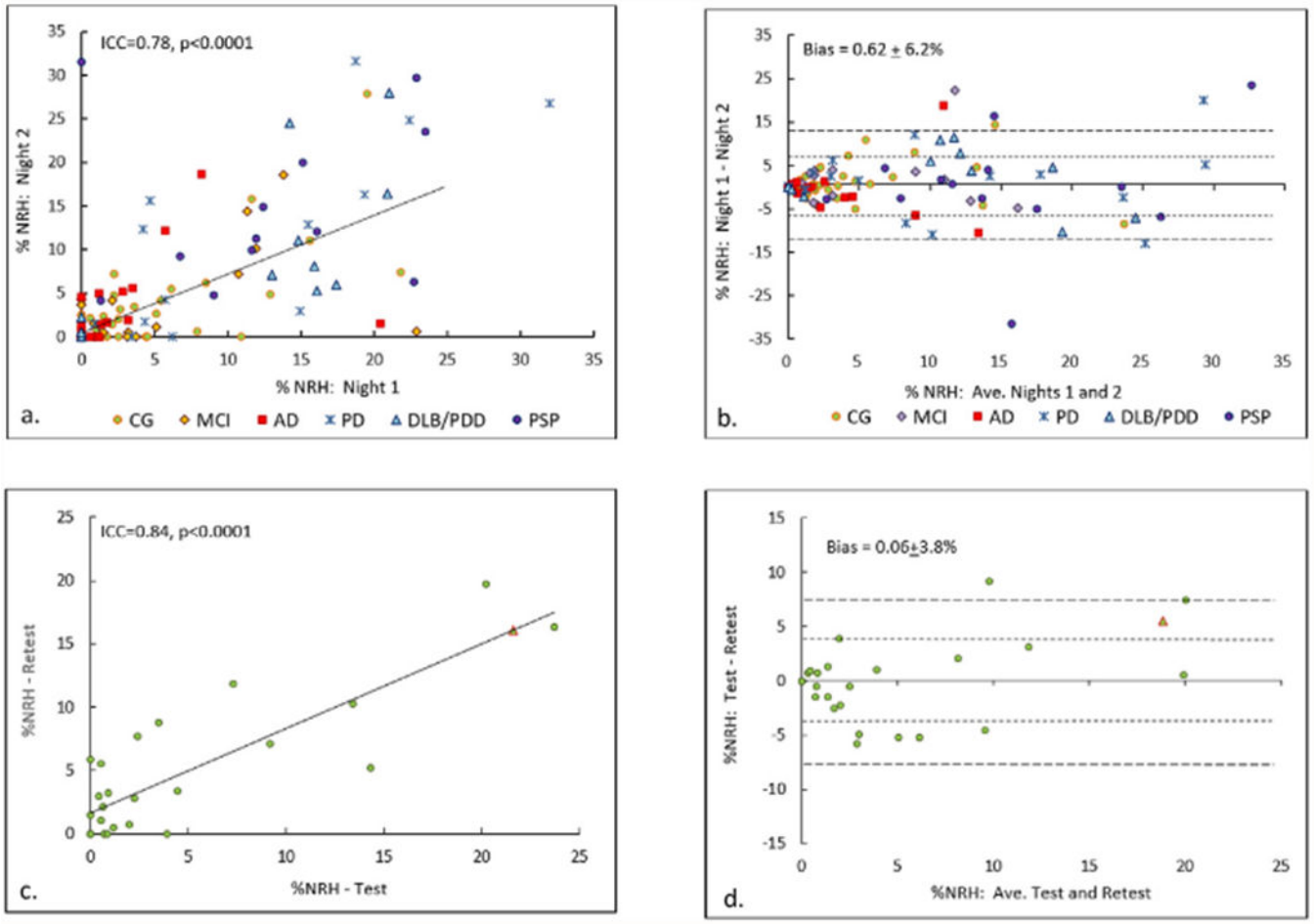

Fig. 6.

Correlation and Bland-Altman plots for %NRH based on night-to-night variability (a. and b.) and one-plus year longitudinal test-retest reliability with the case with two retest results identified ▲ (c. and d.).

Table 1

Sources of sleep recordings by group and site.

	PSD subgroups			Non-PSD subgroups		
	DLB/PDD	**PD**	**PSP**	**AD**	**MCI**	**CG**
Advanced Brain Monitoring						53
Advanced Neurobehavioral Health	5	2		16	20	
Massachusetts General Hospital					10	8
Mayo Clinic	4				4	
University of CA, San Francisco		14	13	1		
VA Puget Sound Healthcare System	7			7	1	
Total	16	16	13	24	35	61

Table 2

Sleep architecture and continuity characteristics.

	PSD subgroups			Non-PSD subgroups		
	DLB/PDD	**PD**	**PSP**	**AD**	**MCI**	**CG**
Sleep Time (hour)	5.8 ± 2.0	6.1 ± 1.1	5.2 ± 1.5	6.3 ± 1.2	6.3 ± 1.4	7.1 ± 6.6
Sleep Efficiency (%)	71.0 ± 18.7	79.9 ± 11.6	58.4 ± 14.1	79.1 ± 0.9	82.8 ± 11.9	86.4 ± 6.7
Stage N1 (% sleep time)	6.5 ± 4.4	6.9 ± 5.1	10.0 ± 12.2	10.4 ± 10.3	6.9 ± 5.0	6.6 ± 4.2
N2	54.0 ± 18.9	49.4 ± 20.8	58.0 ± 21.6	55.4 ± 18.9	53.6 ± 18.7	49.6 ± 14.4
N3	16.5 ± 17.3	14.0 ± 16.2	9.8 ± 12.1	14.8 ± 22.7	18.1 ± 17.6	21.3 ± 20.8
REM	7.5 ± 7.7	18.6 ± 7.6	7.6 ± 7.6	16.6 ± 6.7	18.1 ± 8.6	21.2 ± 5.8
NRH	15.5 ± 13.1	11.1 ± 10.5	15.3 ± 8.8	2.8 ± 4.0	3.3 ± 4.5	3.1 ± 5.1
Spindle duration (min)	1.9 ± 4.9	4.6 ± 6.3	0.8 ± 2.1	3.8 ± 6.8	5.3 ± 9.6	7.9 ± 11.0
Sleep Latency (min)	27.8 ± 26.4	24.7 ± 18.0	25.5 ± 20.6	26.9 ± 23.7	21.9 ± 21.2	14.9 ± 8.0
Wake after sleep onset (min)	107.0 ± 61.7	71.4 ± 56.9	197.1 ± 72.9	77.0 ± 46.6	55.6 ± 40.3	46.5 ± 31.8
Awakenings (event/hour)	5.1 ± 2.7	3.7 ± 0.8	4.8 ± 1.8	4.3 ± 2.6	4.5 ± 3.3	3.4 ± 1.8
Arousal Index (events/hour)	17.9 ± 12.7	16.1 ± 7.9	16.8 ± 16.1	10.9 ± 7.5	14.8 ± 9.7	16.6 ± 8.0

Table 3

Odds ratios of abnormal NRH differentiating each of the PSD subgroups from each of the non-PSD subgroups.

Non-PSD subgroups	PSD subgroups					
	DLB/PDD		PD		PSP	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
AD vs.	21.7 (4.2–113.0)	<0.0001	6.4 (1.5–27.7)	<0.05	60.0 (6.0–601.6)	<0.0001
MCI vs.	12.5 (2.9–54.3)	<0.001	3.7 (1.1–12.9)	0.057	34.7 (3.9–305.5)	<0.0001
CG vs.	22.1 (5.3–92.1)	<0.0001	6.6 (2.0–21.7)	<0.001	61.2 (7.1–515.2)	<0.0001