

# Sleep Disturbances and Their Impact on Cognition in Individuals With Pure Cerebellar Disease

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## Research

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# Abstract

## Background

Individuals with cerebellar ataxia commonly report poor sleep. Our objective was to characterize sleep dysfunction in cerebellar ataxia and study its potential impact on non-motor function.

## Methods

Sleep physiology and behavior were measured in 16 individuals with pure cerebellar ataxia and 16 matched controls. Cognitive function was assessed using the Cerebellar Cognitive Affective Syndrome/Schmahmann Scale (CCAS), and a word-pair learning task. We studied performance on the word-pair task before and after a period of overnight sleep to explore whether sleep-dependent memory consolidation is negatively impacted by cerebellar degeneration.

## Results

Compared to matched controls, individuals with ataxia experienced greater limb movements during sleep ( $p=0.048$ ), and increased sleep fragmentation ( $p=0.009$ ) as measured through polysomnography. Cognitive assessment using the CCAS revealed deficits in executive function in the domains of verbal fluency ( $p=0.011$ ) and cognitive flexibility ( $p=0.048$ ). Individuals with ataxia were also impaired in declarative learning, with poor performance on the word-pair association task during Immediate ( $p=0.021$ ) and Delayed Recall ( $p=0.011$ ) compared to control participants. Poor sleep impacted cognition: increased sleep fragmentation was correlated with lower scores on the CCAS ( $p=0.008$ ) and with immediate recall of the word-pair learning task ( $p=0.001$ ). We found no differences between individuals with ataxia and controls with respect to overnight changes in performance on the word-pair task.

## Conclusions

Sleep integrity is disrupted in individuals with neurodegeneration confined to the cerebellum. Fragmentation of sleep in particular appears to have negative effects on executive function and has practical implications for symptom management.

## Background

Individuals with cerebellar ataxia often seek consultation with their physicians with complaints of poor sleep.<sup>1</sup> The detection and subsequent treatment of the sleep disorders in this population, however, are limited to severe cases of sleep dysfunction.<sup>2</sup> Consequently, sleep disorders may be under-diagnosed or even misdiagnosed in individuals with cerebellar ataxia.<sup>3</sup>

Investigations of sleep physiology in the cerebellar ataxias have focused on spinocerebellar ataxia subtypes SCA1, SCA2 and SCA3 – subtypes associated with extracerebellar pathology in addition to cerebellar atrophy.<sup>4</sup> Studies of sleep in cerebellar ataxias without extracerebellar pathology are limited.<sup>5,6</sup>

One study examined subjective measures of daytime somnolence and sleep quality in individuals with 25 SCA6 in whom neurodegeneration is confined to the cerebellum.<sup>5</sup> Self-reports of daytime somnolence and habitual sleep quality were greater in the SCA6 group compared to control participants. Boesch and colleagues<sup>6</sup> conducted a polysomnographic study in a small sample (n = 5) of individuals with SCA6. They reported periodic limb movements – characterized by episodes of repetitive muscle movements during sleep, such as jerking movements of the limbs or muscle twitches – during sleep in all five individuals. Increased muscle activity during REM sleep and sleep-disordered breathing was also observed in two individuals with SCA6. Therefore, although limited, there is evidence to suggest a role of the cerebellum in sleep physiology and behavior that warrants further investigation.

Clinical and anatomical observations of cerebellar ataxia suggest that the cerebellum is directly involved in modulating higher order cognitive functions.<sup>7</sup> Specifically, poor health-related outcomes in the ataxias are a consequence of debilitating motor deficits associated with cerebellar disease, as well as due to co-morbid cognitive impairments<sup>7</sup> and affective disorders<sup>8,9</sup> known as the Cerebellar Cognitive Affective Syndrome (CCAS).<sup>10,11</sup> A report from Sonni et al. (2014),<sup>12</sup> which used an online battery of instruments to collect subjective information across sleep, cognitive, and affective domains in 176 individuals with cerebellar ataxia, indicates that poor perceived sleep quality and the presence of sleep disorders in individuals with cerebellar ataxia might exacerbate the deficits associated with CCAS.

Sleep plays a crucial role in cognitive processes, such as attention, learning and memory, and emotion processing.<sup>13</sup> Performance on sustained attention tasks, such as the Psychomotor Vigilance Task, is particularly sensitive to sleep loss.<sup>14</sup> Sleep loss also reduces the capacity to acquire *new* information<sup>15</sup> and, conversely, sleep interventions (e.g., the introduction of a mid-day nap) improve learning.<sup>16</sup> Memory consolidation – or the mechanism by which short-term, labile memory traces are strengthened and re-located to long-term neocortical stores – occurs maximally over sleep,<sup>13</sup> with performance on cognitive tasks<sup>17,18,19,20,21</sup> are significantly superior following an interval of sleep relative to an equivalent interval spent awake in healthy adults. This cognitive benefit of sleep is markedly reduced, and in some cases absent, in individuals suffering from chronic sleep loss or sleep-related disorders.<sup>22,23</sup> The impact of poor sleep on cognition has, to date, never been examined in the cerebellar ataxias.

In the current study, we set out to (1) further characterize sleep of individuals with isolated cerebellar degeneration, comparing subjective and objective measures of sleep to that of matched control participants; (2) assess cognitive function in individuals with cerebellar disease, focusing on executive function, visuospatial abilities, and learning; and (3) examine whether sleep-dependent memory consolidation is reduced in individuals with cerebellar disease relative to their healthy counterparts.

## Methods

### Participants

Ataxia Group. Sixteen individuals with cerebellar disease without extracerebellar pathology aged 45 to 75 years were recruited from the Ataxia Unit of Massachusetts General Hospital and from the patient registry maintained by the Coordination of Rare Diseases at Sanford. The study was approved by the Partners Institutional Review Board. Patients were recruited into the study if they had genetically defined ataxic disorders in which imaging confirmed cerebellar volume loss with no brainstem or cerebral hemispheric atrophy, and for whom the known neuropathology is confined largely, if not exclusively, to the cerebellum rather than to brainstem or cerebral hemispheres.

Exclusion criteria included the presence of posterior fossa cysts, cerebellar developmental anomalies such as Joubert syndrome, cerebellar hypoplasia, focal intraparenchymal cerebellar pathology, or co-morbid neurological disorders such as stroke. Individuals with severe visual impairments that may affect performance of vision-dependent cognitive tasks were excluded.

Sleep-affecting medications, such as anti-depressants, benzodiazepines, stimulants and sleep aids, introduce confounds in the analysis of sleep data. Individuals taking such medications followed a safe wash-out protocol prior to the experimental week that was individualized based on their initial dosage. Specifically, in order to avoid side effects from the discontinuation of these medications, we advised patients to gradually decrease the dosage over the course of several weeks – and in some cases, months – prior to participating in the experiment. We provided them with a precise calendar for reference that indicated the dosage to take on each day of their wash-out protocol. We also assisted them in accurately administering the reduced doses by providing empty capsules and dividing the medication into smaller doses and/or helping them to cut their pills into the required dose size. During the week prior to the experiment and during the experiment, all participants had ceased taking sleep-affecting medications.

Control Group. Sixteen healthy controls, matched to the ataxia group based on age, sex, handedness and education, were recruited from the community. To match age, ataxia participants were organized into 5-year age ranges (30–34 yrs, 35–39 yrs, 40–44 yrs, etc.), and the healthy controls were matched based on these groups. Level of education was categorized as: 12 years of education or less (high school diploma or less), 13–16 years of education (college-level education), 17–18 years (Master's degree or similar), > 18 years (higher education).

Healthy status was determined by means of pre-screening procedures and the following exclusion criteria were used: use of sleep-influencing medications including anti-depressants, hypnotics, narcotics, benzodiazepines or herbs such as St. John's wort; history of neurological disease, congestive heart failure, or a myocardial infarction, or a history of stroke, head trauma, or heart surgery; impaired or uncorrected vision (20/30 or less) as assessed with a standard vision chart; known sleep-influencing medical conditions (e.g., asthma, COPD, hypertension if on 3 or more medications, BMI > 30) or a diagnosed sleep disorder; and long or short self-reported sleep (> 11 hrs or < 5.5 hrs).<sup>24</sup>

## Measures

# Assessments of Motor Dysfunction and Neuropsychological Function

**Brief Ataxia Rating Scale (BARS)** is a 5-item clinical rating scale for ataxia that includes one test each for the following functional areas: gait, kinetic function-arm, kinetic function-leg, speech and eye movements.<sup>25</sup> The BARS is a valid instrument with high inter-rater reliability (Cronbach's  $\alpha = 0.90$ ). The BARS is used as an indicator of the extent of cerebellar degeneration in each individual.

**The Cerebellar Cognitive Affective/Schmahmann Scale (CCAS)**<sup>26</sup> is a battery including neuropsychological tests and clinical rating scales designed to detect CCAS.<sup>10</sup> Specifically, the CCAS includes 10 items that assess the following domains: semantic and phonemic verbal fluency, cognitive flexibility, forward and reverse digit span, visuospatial function, verbal recall, abstract reasoning, inhibitory control, and affect.

## Assessments of Sleep and Sleep Behavior

Questionnaire measures of sleep included the following: the **Pittsburgh Sleep Quality Index** to determine sleep quality over the previous 30 days;<sup>27</sup> the **Epworth Sleepiness Scale**, a self-administered questionnaire that provides general level of daytime sleepiness and propensity to fall asleep during certain activities;<sup>28</sup> the **Morningness-Eveningness Questionnaire** to assess whether the participant is inherently more of a "morning person" or an "evening person";<sup>29</sup> the **Stanford Sleepiness Scale**, a 7-point Likert scale with responses range from 1 (feeling active, wide-awake) to 7 (almost in reverie, struggling to remain awake), providing a measure of self-reported sleepiness;<sup>30</sup> and the **Cambridge Hopkins Restless Leg Syndrome Questionnaire**, a validated diagnostic questionnaire used to quantify symptoms of Restless Leg Syndrome.<sup>31</sup>

**Polysomnography** was used to obtain electrophysiological recordings of sleep. An Aura PSG wireless/ambulatory system (Grass Technologies, Astro-Med Inc., West Warwick, RI) montage was applied by the experimenter immediately prior to the participant's bedtime. The montage included bilateral EEG leads (F1, F2, O1, O2, C3, C4, Cz), bilateral EOG leads, two mastoids and one ground electrode, and four EMG leads, including submental, zygomaticus, and bilateral tibial EMG to measure muscle tone in the chin and leg respectively.

The **ApneaLink** (ResMed, San Diego, California) was used to measure sleep disordered breathing. The ApneaLink is a three-channel screening tool, including a nasal pressure transducer to measure airflow and a pulse oximeter to measure oxygen desaturations ( $SaO_2 < 3\%$  is indicative of sleep apnea), and allows for automated scoring.

Participants were provided with an Actiwatch Spectrum actigraph watch (Philips Respironics, Murrysville, PA) to be worn on the non-dominant wrist for one week, providing a continuous recording of day and

night activity levels via an embedded accelerometer, with sensitivity of  $< .01$  g and a sampling rate of 32 Hz. Data collected by this device is stored in 1-min epochs.

## Procedures

The experiment was conducted over the course of 7 days (Fig. 1). On day 1, each participant was administered the Brief Ataxia Rating Scale (BARS) and Cerebellar Cognitive Affective Syndrome (CCAS) Scale, and given the actigraph watch to wear for the following week. Prior to the participant's bedtime, they were fitted with the ApneaLink device – the device was turned on at bedtime and participants were instructed to turn it off immediately following wake onset the following morning.

On the evening of day 6, participants completed the questionnaire packet, which included the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Stanford Sleepiness Scale, Cambridge Health - Restless Leg Syndrome Questionnaire, and the Morningness-Eveningness Questionnaire; and performed the Passive Encoding, Active Encoding, and Immediate Recall phases of the word-pair learning task. During the Passive Encoding phase of the word-pair learning task, each participant was presented with 50 words that were paired together to form 25 word-pairs (e.g. cat-coach, desk-ice).<sup>14</sup> Each word-pair appeared on a computer screen and remained in view for 5 secs before the next word-pair was presented (inter-stimulus interval was 100 ms). Participants were instructed to study and remember the word-pair associations for subsequent recall. The use of a mnemonic strategy was recommended to the participants; for instance, they were advised to “create associations between the words in each pair in order to remember the word pairs. For example, if the words presented are frame-shoe, you might try to picture a framed painting of a shoe in your mind.”

The Active Encoding phase occurred immediately after the completion of the Passive Encoding phase. During this phase, the first word from the 25 word-pairs previously presented appeared on the computer screen one at a time, and the participant was instructed to say the corresponding word out loud. Following the participant's response, the experimenter entered the recalled word into the computer. If the response was incorrect, the correct response was displayed on the computer monitor for 750 ms, thus providing feedback and an opportunity to continue learning the correct associations. The list repeated until performance reached 62% or when the word list had been presented 5 times. The order of items was randomized for each presentation of the list. Twenty mins after the Active Encoding phase, participants performed the Immediate Recall phase, which was identical to the Active Encoding phase, with two exceptions: first, the list of words was presented only once (as opposed to a maximum of 5 times); second, feedback was not presented following an incorrect response (to prevent new learning). The order of items was again randomized for each presentation of the list.

Following the Immediate Recall phase of the word-pair learning task and an hour before their habitual bedtime, the PSG montage was applied. The final phase of the word-pair learning task, the Delayed Recall phase, was conducted the following morning, an hour after the participant awakened (to avoid sleep inertia). Participants first reported their sleepiness (Stanford Sleepiness Scale) before proceeding to the Delayed Recall phase of the word-pair task, which was identical to the Immediate Recall phase.

# Data Analysis

Sleep Patterns and Physiology. Sleep was staged according to the criteria provided by the American Academy of Sleep Medicine.<sup>32</sup> Variables identified were amount of time spent and percent time (percent relative to the whole night) in each sleep stage: non-REM stage 1 (NREM1), NREM2, NREM3 (also known as slow-wave sleep, SWS), and REM sleep.

Actigraphy data were analyzed according to guidelines described in de Jong and colleagues (2016).<sup>33</sup> The following measures were calculated and averaged for overnight and daytime (nap) sleep: total sleep time, sleep onset latency, sleep efficiency, total wake time, and total time spent mobile. Multivariate ANOVAs with Sidak-Bonferroni correction for multiple comparisons were conducted to compare actigraphy measures between individuals with cerebellar ataxia and their matched controls.

Sleep apnea was measured using the ApneaLink device and was characterized by the Apnea-Hypopnea Index (AHI), which was calculated as the number of apneic and hypopneic events occurring per hour of sleep.<sup>34</sup> Severity was categorized as follows: “None/Minimal” if  $AHI < 5$  per hour, Mild:  $AHI \geq 5$ , but  $< 15$  per hour, Moderate:  $AHI \geq 15$ , but  $< 30$  per hour, and Severe:  $AHI \geq 30$  per hour. An ANCOVA with group (Ataxia vs. Controls) and BMI as a covariate was performed to compare AHI between ataxia and control groups. In addition, a chi-squared test was performed to compare the frequency of individuals in each category based on group (Ataxia vs. Controls).

Limb movements were recorded during sleep and scored as per Walters and colleagues (2007).<sup>35</sup> Periodic – as opposed to isolated – limb movements were scored if a minimum of 4 movement events occurred, each separated by 5–90 seconds. Limb movements were additionally scored during REM sleep alone in order to ascertain symptoms of REM sleep without atonia and calculated as an index (number of movements per hour). Since Periodic Limb Movements indices and limb movement indices during REM were non-parametrically distributed in the ataxia and control groups, Mann-Whitney comparisons of independent samples were used to compare values between groups.

Questionnaire and Cognitive Measures. All questionnaire measures (Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Stanford Sleepiness Scale, Cambridge Health - Restless Leg Syndrome Questionnaire, and the Morningness-Eveningness Questionnaire) were scored based on validated criteria. We used a Bonferroni correction for multiple comparisons (number of tests/questionnaire measures = 6;  $\alpha = 0.008$ ). Scores for individuals with pure cerebellar disease and control participants were compared using independent samples *t*-tests. Scores on the Pittsburgh Sleep Quality Index were categorized into “poor sleepers” (Pittsburg Sleep Quality Index  $> 6$ ) and “good sleepers” (Pittsburg Sleep Quality Index  $< 7$ ). A chi-squared test was used to compare frequency of poor vs. good sleepers in ataxia and control groups.

The number of positive symptoms associated with Restless Leg Syndrome, as measured by the Cambridge Hopkins - Restless Leg Syndrome Questionnaire, was calculated (with a maximum possible score of 7). A score  $> 3$  was indicative of possible Restless Leg Syndrome, while a score of 7 indicated

probable Restless Leg Syndrome.<sup>31</sup> The number of individuals with possible vs. probable Restless Leg Syndrome were compared in the ataxia and control groups using a chi-squared test.

Scoring of the Cerebellar Cognitive Affective Syndrome (CCAS) Scale was conducted according to Hoche and colleagues (2018) and the total raw score (maximum of 120) – or the sum of the scores on each item on the test – as well as the number of failed tests (total tests 10) were calculated for each participant. The following categorization was applied for Cerebellar Cognitive Affective Syndrome assessment based on the number of failed tests: “No evidence of CCAS” if 0 failed tests, “Possible CCAS” if 1 failed test, “Probable CCAS” if 2 failed tests, and “Definite CCAS” if 3 or more failed tests. A chi-squared test was conducted in order to compare frequency of ataxia and control individuals assigned to these 3 categories. A multivariate MANOVA with Sidak-Bonferroni correction for multiple comparison was conducted to compare individuals with ataxia and matched controls on the raw scores, number of failed tests, as well as scores on each item of the test.

Performance at encoding of the word-pair association task was compared across groups (Ataxia vs. Controls) by measuring the number of loops required to reach criterion during the Active Encoding phase, as well as accuracy (number of accurately recalled word-pairs) at Immediate Recall. To determine the extent of sleep-dependent processing of the word-pair associates, performance on the word-pair learning task (accuracy at Delayed Recall) post-sleep was compared between groups using an ANCOVA, with Group (Ataxia, Control) as a factor and Immediate Recall (to control for level of initial learning) as a covariate. In order to determine whether sleep-dependent processing of the word-pairs is driven by certain macro and micro architectural aspects of sleep, Spearman correlations (owing to non-parametric distribution of sleep physiological measures) between sleep measures and cognitive measures, including performance *changes* on the word-pair learning task (Accuracy at Delayed Recall – Accuracy at Immediate Recall), were conducted. To correct for multiple comparisons, a Sidak-Bonferroni correction was applied to these correlations.

Relationship between Sleep and Cognition. In order to examine the relationship between sleep physiological measures (actigraphy and polysomnography) and cognitive function, we performed Spearman correlations with a Bonferroni correction for multiple comparisons. For correlations between measures of general cognitive function (scores on the Cerebellar Cognitive Affective Syndrome Scale and measures of learning performance on the word-pair learning task) and sleep, we collapsed ataxia and control groups to increase statistical power. However, to test whether the benefit of sleep on overnight memory consolidation is reduced in ataxia vs. control groups, we performed correlations between overnight change in performance on the word-pair task and sleep within each experimental group separately.

## Results

### Demographics

Sixteen individuals with ataxia were recruited (12 male, 4 female) with a mean age of  $62.13 \pm 8.08$  yrs (range 46 to 76 yrs). Fourteen were right-handed and 2 left-handed. Education level was  $15.94 \pm 2.7$  yrs (high school graduates/12 yrs of education:  $n = 2$ ; college graduates/ 16 yrs:  $n = 11$ ; and post-graduate degrees/16 + yrs:  $n = 3$ ). Genetic diagnoses were: autosomal recessive cerebellar ataxia type 1 (ARCA1;  $n = 2$ ), ARCA3 ( $n = 1$ ), spinocerebellar ataxia type 5 (SCA5;  $n = 1$ ), SCA6 ( $n = 9$ ), and SCA8 ( $n = 3$ ).

Sixteen healthy controls were recruited that were matched by age (mean =  $62$  yrs  $\pm 7.9$  yrs; range 45 to 74 yrs), sex (12 male, 4 female), education ( $16.38 \pm 2.19$  yrs; high school graduates/12 yrs of education:  $n = 4$ ; college graduates/ 16 yrs:  $n = 6$ ; and post-graduate degrees/16 + yrs:  $n = 6$ ).

Independent samples *t*-tests revealed no differences between the ataxia and control groups with respect to age ( $t(30) = 0.111, p = 0.913$ ) and level of education ( $t(30) = -0.504, p = 0.613$ ). Two controls reported occasional melatonin use and were requested to abstain during the week prior to and during the course of the experiment. No participants had known sleep disorders, history of stroke, brain tumor, and neurological or psychiatric conditions. All controls had normal cerebellar motor function as determined by the Brief Ataxia Rating Scale (average score  $0.31 \pm 0.4$ ).

## Questionnaires

Group means and standard deviations for self-reported measures of sleep and sleepiness are in Table 1. Comparisons between groups for questionnaire measures were corrected for multiple comparisons using a Bonferroni correction (number of tests = 6,  $\alpha = 0.008$ ). Ten individuals with ataxia and 4 control participants reported Pittsburgh Sleep Quality Index scores indicative of poor sleep quality (scores  $> 7$ ).<sup>27</sup> The chi-squared test comparing the number of poor and good sleepers in the ataxia and control groups supports a greater incidence of poor sleep in the ataxia group compared to controls ( $\chi^2(1) = 4.571, p = 0.033$ ), which, however, did not reach significance level.

Table 1

Means, standard deviations (SD), and  $p$ -values for comparisons between individuals with pure cerebellar syndrome (Ataxia) and age-, sex-, handedness-, and education-matched controls for questionnaire measures. \*  $p$ -values that indicate significant differences between the ataxia and control groups. Abbreviations: Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Morningness-Eveningness Questionnaire (MEQ), Cambridge-Hopkins Restless Leg Syndrome Questionnaire (CH-RLSq), Stanford Sleepiness Scale (SSS).

Questionnaire	Ataxia		Control		$p$ -value
	Mean	SD	Mean	SD	
PSQI	6.87	4.10	5.06	1.81	0.033
ESS	8.00	4.86	6.13	3.42	0.23
MEQ	59.80	5.25	59.80	5.25	0.63
CH-RLSq	2.56	3.08	1.31	2.41	0.21
Stanford Sleepiness Scale (Evening)	2.85	1.07	1.69	0.63	0.003*
Stanford Sleepiness Scale (Morning)	2.58	1.47	1.6	1.1	0.096

Daytime sleepiness – or the propensity to fall asleep while performing daily activities – was measured using the Epworth Sleepiness Scale. Scores were comparable across groups ( $t(30) = 1.229, p = 0.229$ ); however, 7 individuals with ataxia and 4 controls reported scores on the ESS indicative of excessive daytime sleepiness (Epworth Sleepiness Scale score > 10).<sup>30</sup>

Sleepiness at the time of testing is reported to impact performance on cognitive tasks in older adults.<sup>36</sup> For this reason, self-reported sleepiness was recorded during both the evening and the morning sessions using the Stanford Sleepiness Scale. Compared to their healthy counterparts, individuals with cerebellar ataxia were more sleepy during the morning sessions ( $t(24) = 3.354, p = 0.003$ ) than the evening ( $t(24) = 1.732, p = 0.096$ ). Table 1 displays the means, SDs, and  $p$ -values for comparisons between ataxia and control groups for Stanford Sleepiness Scale measures.

Chronotype was determined using the Morningness-Eveningness Questionnaire, wherein scores < 41 indicate “evening” types, scores between 42–58 “intermediate” types, and scores > 58 “morning” types.<sup>29</sup> The control sample consisted of 9 “evening” types and 7 “morning” types, while all but 3 in the ataxia group – who represented “intermediate” chronotypes – reported being “morning” types. However, there were no significant differences between groups with respect to Morningness-Eveningness Questionnaire scores ( $t(30) = 0.493, p = 0.627$ ).

Cambridge-Hopkins Restless Leg Syndrome symptoms questionnaire scores ranged from 0 to 7 and were reflective of the number of Restless Leg Syndrome symptoms reported. A score > 3 indicated “possible Restless Leg Syndrome,” while a score of 7 indicated “probable Restless Leg Syndrome.”<sup>31</sup> A chi-squared

test comparing probable/possible- vs. “no-Restless Leg Syndrome” across ataxia and control groups also did not reveal any differences between groups ( $\chi^2(1) = 1.247, p = 0.264$ ).

## Evaluation of Cognitive Function

Cerebellar Cognitive Affective Syndrome (CCAS). A MANOVA with a Sidak-Bonferroni correction for multiple comparisons was conducted to compare ataxia and control groups with respect to the total raw score and the number of failed tests on the CCAS. There were no differences between groups with respect to the total number of failed tests on the CCAS ( $F(1,22) = 0.488, p = 0.492$ ), but individuals with cerebellar ataxia had significantly lower raw scores ( $F(1,22) = 6.160, p = 0.021$ ), suggesting subclinical impairments in cognitive function. Individuals with ataxia were impaired relative to controls on tasks of verbal fluency (Fig. 2A;  $F(1,22) = 7.756, p = 0.011$ ) and cognitive flexibility (Fig. 2A;  $F(1,22) = 4.392, p = 0.048$ ), but demonstrated no impairments relative to controls on all other cognitive domains (digit span,  $p = 0.51$ ; visuospatial function,  $p = 0.10$ ; verbal recall,  $p = 0.87$ ; abstract reasoning,  $p = 0.39$ ; inhibitory control,  $p = 0.27$ ; general affect,  $p = 0.47$ ).

A chi-squared test was conducted to compare the frequency of “No CCAS,” “Possible CCAS,” “Probable CCAS,” and “Definite CCAS” across ataxia and control groups. There were no significant between-group differences ( $\chi^2(3) = 1.676, p = 0.642$ ).

Word-Pair Association Task. Participants learned 25 semantically unrelated word pairs in the evening, and the number of presentations to reach the criterion of 64% (at least 16 correct associations), for a maximum of 5 loops, was calculated. Memory accuracy without feedback was probed during the Immediate Recall phase and again following overnight sleep in the Delayed Recall phase. Three individuals with ataxia reported extreme frustration with the task and withdrew from this aspect of the experiment. Therefore, final analyses include 13 individuals with ataxia and 13 matched controls.

An independent samples *t*-test revealed that the number of loops required to reach criterion was comparable between the ataxia and control groups ( $t(24) = 0.492, p = 0.627$ ). However, accuracy was significantly lower for the ataxia group compared to the control group for Immediate Recall (Fig. 2B;  $t(24) = -2.476, p = 0.021$ ) as well as Delayed Recall ( $t(24) = -2.748, p = 0.011$ ). To compare performance on the word-pair task post-sleep relative to pre-sleep performance, one-way ANOVA was performed to compare groups with regard to Delayed Recall accuracy and Immediate Recall accuracy, using Stanford Sleepiness Scale scores from the evening and morning (i.e. sleepiness at the time of testing) as covariates. There were no differences between the ataxia and control groups with respect to Delayed Recall accuracy when Immediate Recall performance and sleepiness during evening and morning sessions were taken into consideration ( $F(1,23) = 0.207, p = 0.654$ ). Although performance on the word-pair task was impaired in individuals with ataxia relative to controls, the effect of sleep in preserving the learned associations appeared to be similar across the two groups.

## Sleep Assessments

Actigraphy was recorded for 7 days for each participant, and habitual sleep-wake patterns were obtained for 14 individuals with ataxia and 14 matched controls (data from 2 individuals with ataxia were excluded due to non-compliance with the actigraphy instructions). The ANOVA with Sidak-Bonferroni correction revealed no significant difference in sleep efficiency between the ataxia group relative to the control group (Ataxia,  $90.13 \pm 4.71\%$ ; Controls,  $92.71 \pm 2.38 \%$ ;  $F(1,25) = 4.068$ ,  $p = 0.055$ ; Table 2). However, compared to the control group, the ataxia group had greater wake after sleep onset (Ataxia,  $42.23 \pm 21.51$  mins; Controls,  $28.51 \pm 8.27$  mins;  $F(1,25) = 4.653$ ,  $p = 0.041$ ) and time spent mobile during the nights (Ataxia,  $8.72 \pm 3.7$  mins; Controls,  $6.3 \pm 1.66$  mins;  $F(1,25) = 5.391$ ,  $p = 0.029$ ).

Table 2

Means, standard deviations (SD), and  $p$ -values for comparisons between individuals with pure cerebellar syndrome (Ataxia) and age-, sex-, handedness-, and education-matched controls for actigraphy measures with respect to both overnight and daytime sleep patterns. \* $p$ -values that indicate significant differences between ataxia and control groups.

Actigraphy Measure	Ataxia		Control		p-value
	Mean	SD	Mean	SD	
<b>Overnight Measures</b>					
Duration	484.01	39.95	475.44	53.34	0.63
Onset Latency	3.03	2.67	2.04	0.95	0.07
Efficiency	90.13	4.71	92.71	2.38	0.06
WASO	42.25	21.51	30.48	10.83	0.04
Mobile Time	8.72	3.70	6.30	1.66	0.03*
<b>Nap Measures</b>					
Duration	33.45	33.18	34.43	38.08	0.94
Onset Latency	0.46	0.75	0.35	0.66	0.69
Efficiency	52.21	47.05	52.50	47.41	0.99
WASO	2.59	3.93	2.99	5.50	0.83
Mobile Time	4.70	5.61	4.37	5.20	0.74

Apnea-Hypopnea Index (AHI) – the number of apneic and hypopneic events occurring per hour – was calculated and compared between ataxia and control groups (see Table 3 for means, SDs, and  $p$ -values associated with the comparison using an ANCOVA between ataxia and control groups, using BMI as a covariate). The chi-squared test revealed no significant differences between ataxia and control groups with respect to assignment into these diagnostic groups of “none/minimal,” “mild,” “moderate,” and “severe” ( $\chi^2(3) = 5.882$ ,  $p = 0.118$ ).

Table 3

Means, standard deviations (SD), and  $p$ -values for comparisons between individuals with pure cerebellar syndrome (Ataxia) and age-, sex-, handedness-, and education-matched controls for physiological measures of sleep. \* $p$ -values that indicate significant differences between ataxia and control groups.

Sleep Measure	Ataxia		Control		p-value
	Mean	SD	Mean	SD	
<b>Sleep Architecture</b>					
Total Sleep Time (mins)	357.15	127.63	431.84	74.62	0.05*
Sleep Onset Latency (mins)	13.81	13.07	9.91	9.95	0.35
Wake After Sleep Onset (mins)	63.50	34.72	53.06	40.19	0.44
Sleep Efficiency (%)	80.73	14.33	87.83	9.22	0.11
NREM Stage 1 (%)	28.49	14.80	23.24	9.29	0.24
NREM Stage 2 (%)	33.89	9.81	34.27	7.77	0.91
Slow-Wave Sleep (%)	21.03	7.50	22.56	7.71	0.57
REM Sleep (%)	17.23	6.00	19.94	4.46	0.16
Sleep Fragmentation Index (Transitions per Hour)	23.88	6.96	17.83	5.20	0.01*
Apnea-Hypopnea Index (# Events per Hour)	11.71	10.57	9.43	8.51	0.53
<b>Spectral Power Density</b>					
Slow Oscillations (0.5-1 Hz)	113.22	52.67	106.64	84.00	0.81
Delta (1–4 Hz)	39.06	21.27	35.97	16.51	0.67
Theta (5–8 Hz)	5.21	2.48	4.16	1.94	0.23
Sigma (11–16 Hz)	2.27	0.95	1.86	0.80	0.24
Slow Sigma (11–13 Hz)	2.97	1.49	2.53	1.23	0.41
Fast Sigma (14–16 Hz)	1.55	0.59	1.17	0.40	0.05*

Group means and standard deviations for physiological measures of sleep can be found in Table 3. A MANOVA with Sidak-Bonferroni correction for multiple comparisons was performed to compare sleep physiological measures between groups. Individuals with ataxia demonstrated reduced total sleep time compared to matched controls (Fig. 3A;  $F(1,30) = 4.084$ ,  $p = 0.05$ ). In addition, individuals with ataxia had

higher sleep fragmentation indices – the number of stage transitions and awakenings per hour – compared to their healthy counterparts (Fig. 3B;  $F(1,30) = 7.773, p = 0.009$ ).

The tibial EMG channels fell off during the night for 2 individuals with ataxia and 1 control; therefore, a final sample size of 13 in the ataxia group and 13 in the control group was used in the statistical analyses. Individuals with ataxia demonstrated greater Periodic Limb Movements per hour compared to controls (Fig. 4; Ataxia, median = 31.8 per hour; Controls, median = 10.3 per hour;  $p = 0.048$ ). There were no differences between groups with respect to limb movements during REM sleep (Fig. 4; Ataxia, median = 2.2 per hour; Controls, median = 2.5 per hour;  $p = 0.488$ ).

## Relationship between Sleep and Cognitive Function

**General Cognitive Function.** In order to examine the relationship between sleep physiological measures and general cognitive function, we performed Spearman correlations, collapsing across groups to increase statistical power. General cognitive function was assessed using the Cerebellar Cognitive Affective Syndrome (CCAS) Scale. In addition, Accuracy during Immediate Recall of the word-pair task was used as a measure of learning. Due to the number of exploratory correlations being performed, a Bonferroni correction for multiple comparisons was applied. With respect to actigraphy, we conducted exploratory Spearman correlations between scores on the CCAS and Immediate Recall accuracy and two actigraphy measures (time spent awake and time spent mobile throughout the night) and one overnight sleep physiological measure (Sleep Fragmentation Index); therefore, the correction resulted in an  $\alpha$  of 0.008 (number of tests performed = 6).

Raw scores on the CCAS Scale were not correlated with time spent awake during the night ( $r_s(21) = -0.421, p = 0.058$ ) or with time spent mobile during the night measured with actigraphy ( $r_s(21) = -0.495, p = 0.023$ ). Likewise, Accuracy at Immediate Recall was not correlated with time spent mobile during the night ( $r_s(20) = -0.559, p = 0.01$ ) or with time spent awake during the night ( $r_s(20) = -0.502, p = 0.024$ ).

With regard to the correlations between Sleep Fragmentation Index and performance on the CCAS and Immediate Recall for the word-pair task, we assumed that the Sleep Fragmentation Index distribution across individuals with ataxia and controls on the experimental night was representative of the true distribution, although likely exacerbated compared to a habitual night owing to the discomfort associated with wearing the PSG montage. Indeed, the Sleep Fragmentation Index determined by one week of actigraphy was significantly correlated with the sleep fragmentation index on the experimental night ( $r(25) = 0.546, p = 0.005$ ). We found negative correlations between the Sleep Fragmentation Index and raw scores on the CCAS (Fig. 5a;  $r_s(26) = -0.528, p = 0.008$ ), as well as Accuracy at Immediate Recall (Fig. 5b;  $r_s(26) = -0.531, p = 0.001$ ), such that greater fragmentation of sleep was associated with poor cognitive performance.

**Sleep-Dependent Memory Consolidation.** We examined the relationship between the change in recall accuracy from pre- to post-sleep (Delayed Recall – Immediate Recall) – reflecting sleep-dependent

memory consolidation – and percent time spent in SWS, given the well-established relationship with SWS and declarative memory consolidation reported in previous studies.<sup>13</sup> In addition, since poor nocturnal sleep and insomnia have been linked with impaired declarative memory consolidation,<sup>17</sup> we also examined the relationship between change in recall accuracy and the Sleep Fragmentation Index. We conducted separate Spearman correlations in the ataxia and control groups to determine whether cerebellar degeneration impacted the relative contributions of these stages of sleep to memory processing. A Bonferroni correction for multiple comparisons was applied (number of tests = 4;  $\alpha = 0.013$ ). There were no significant correlations between change in accuracy and percent time spent in SWS ( $r_s(13) = 0.597, p = 0.04$ ) or with the Sleep Fragmentation Index in the ataxia group ( $r_s(13) = -0.162, p = 0.597$ ). Likewise, overnight performance changes on the word-pair association task were not correlated with SWS ( $r_s(13) = 0.04, p = 0.902$ ) or with the Sleep Fragmentation Index ( $r_s(13) = 0.456, p = 0.117$ ) in the control group.

## Discussion

The goal of the current study was to ascertain whether sleep behavior and physiology are affected in individuals with isolated cerebellar degeneration, and to determine whether these changes in sleep impact cognition function. We report cognitive and sleep-related dysfunction in individuals with cerebellar degeneration compared to matched controls. Poor cognitive performance in certain domains – scores on the Cerebellar Cognitive Affective Syndrome (CCAS) Scale and baseline performance on the word-pair learning task – was found to be correlated with the extent of sleep fragmentation experienced. However, overnight change in memory performance on the word-pair learning task – a measure of sleep-dependent memory processing – was comparable across individuals with ataxia and controls, suggesting that the role of sleep in stabilizing formed memory associations may not be altered in individuals with cerebellar degeneration compared to their healthy counterparts.

## Sleep measures

Actigraphy recording over one week showed that individuals with cerebellar ataxia demonstrated greater wake after sleep onset and greater time spent mobile during the night. These findings were confirmed using polysomnography sleep recordings: sleep was shown to be more fragmented in the ataxia group as reflected by the number of stage transitions per hour – i.e. the Sleep Fragmentation Index. The number of arousals, stage transitions, and awakenings during sleep increase with age and have been associated with age-related cortical thinning, particularly in the lateral orbitofrontal and inferior frontal cortices.<sup>37</sup> Individuals with ataxia, however, demonstrated greater sleep fragmentation than cannot be explained by age-related structural brain changes alone given that their healthy age-matched counterparts did not experience the same levels of sleep fragmentation.

One possible mechanism for increased sleep fragmentation in individuals with cerebellar degeneration is through impaired cerebellar involvement in the neurophysiology of sleep state transitions. Sleep-wake

and sleep stage transitions are orchestrated by subcortical neuronal ensembles that form a “flip-flop” switch.<sup>38</sup> The wake-promoting reticular activating system and the sleep-promoting ventrolateral preoptic nucleus pathway are mutually inhibitory, and the activation (and inhibitory) patterns of the associated cell populations ensure the distinct electrophysiological patterns associated with a wakeful state, as well as with each sleep stage. Anatomical and electrophysiological studies in animal models provide evidence of a cerebellar role in fine-tuning signals responsible for transitions *between* physiological states, by means of its extensive bidirectional connections with neuronal populations involved in wake- and sleep-promotion.<sup>39,40</sup> Damage to the cerebellum may therefore result in inefficient operation of this “flip-flop” switch and, consequently, in greater sleep fragmentation.

Although we found no evidence of sleep-disordered breathing in individuals with pure cerebellar disease – that is, above what would be expected in an aging sample, given the high incidence of obstructive sleep apnea in older adults<sup>24</sup> – we did find greater periodic limb movement indices in individuals with ataxia relative to matched controls. Withdrawal of sedative medications such as benzodiazepines can precipitate Periodic Limb Movement Disorder, however the potentially offending medications were tapered very slowly over the course of weeks or even months in our study, making this an unlikely cause. Periodic limb movement disorder reflects dopaminergic dysfunction resulting from damage to basal ganglia circuits, particularly those involving the ventral striatum.<sup>41</sup> Animal studies demonstrate a direct influence of the cerebellum on striatal function;<sup>42</sup> therefore, cerebellar degeneration could exert deleterious effects on dopaminergic signaling pathways, thus resulting in symptoms of Periodic Limb Movement Disorder. Functional neuroimaging in individuals with the combined disorder of Periodic Limb Movement Disorder – Restless Leg Syndrome indicates a link between cerebellar and thalamic activation and the sensory symptoms associated with the disorder.<sup>43</sup> To this point, administration of dopamine agonists alleviates Periodic Limb Movement Disorder symptoms in individuals with SCA2. The cerebellum therefore seems to engage in the pathophysiology of Periodic Limb Movement Disorder, a conclusion that will need further investigation by means of longitudinal studies and neuroimaging.

## Cognitive measures

Individuals with pure cerebellar disease had significantly lower scores on the CCAS compared to matched controls. Impairments were observed particularly in the domains of verbal fluency and cognitive flexibility, while short-term and long-term memory, abstract reasoning, inhibitory control, and visuospatial abilities were comparable between the ataxia and control groups. Verbal fluency was assessed by means of both semantic and phonemic categories. These tasks recruit cerebral cortical areas involved in attention, memory, and temporal processing, namely, prefrontal (more engaged in phonemic processing) and temporal regions (more heavily involved in semantic fluency).<sup>44</sup> In addition, fluency tasks incorporate cadence of response delivery, awareness of the temporal frame within which the test is operating, and attention shifting to maintain appropriateness of items being listed – all of which engage the cerebellum and cerebro-cerebellar networks.<sup>45,46,47</sup>

In the networks that contribute to cerebrocerebellar functional connectivity, two in particular stand out:<sup>48</sup> the “salience network” which engages the anterior cingulate cortex, subcortical and paralimbic structures to continuously evaluate the salience of incoming stimuli, and the “executive control network” involving frontal and parietal regions that moderate sustained attention and working memory once stimuli have been identified as salient.<sup>49</sup> Cerebellar degeneration might result in compromised activity in these neural networks, resulting in impaired ability to perform tasks of verbal fluency. The current study is consistent with previous reports of deficits in verbal fluency in individuals with cerebellar ataxia relative to controls.<sup>10,50,51,52</sup> The underlying mechanisms leading to these deficits are an area of ongoing study.

Compared to healthy matched controls, individuals with ataxia demonstrated reduced cognitive flexibility measured by the “category switching” task of the CCAS. Participants were instructed to “name a vegetable, and then a profession, and then another vegetable, and so on” for the duration of one minute. Cognitive flexibility places demands on the prefrontal cortex, particularly the ventrolateral prefrontal cortex and the supplementary motor areas.<sup>53</sup> The prefrontal cortex activation subserves sustained attention, response inhibition, working memory, and performance monitoring, all of which operate in concert to enable cognitive set shifting. An important prerequisite for cognitive flexibility is the prior formation of strong context-response associations. This is exemplified by experiential context, such as a category in the case of the category switching task, which evokes an automatic response<sup>54</sup> – a process that is dependent on the cerebellum as contextual cues in tasks involving cognitive flexibility activate fronto-cerebellar pathways. Our findings in ataxia, together with previous studies that have reported impaired mental flexibility in individuals with cerebellar infarcts,<sup>55,56</sup> provide further evidence for a role of the cerebellum in complex cognitive tasks.

Individuals with pure cerebellar disease were no different than healthy controls in the domains of short-term memory (digit span), long-term memory (verbal recall), visuospatial abilities (cube draw and cube copy), abstract reasoning (similarities), or response inhibition (Go/No-Go). Previous studies in individuals with isolated cerebellar disease and extracerebellar pathology demonstrated deficits in these cognitive domains,<sup>57,58,59</sup> and it is possible that the extracerebellar pathology involving cerebral cortex, brainstem, thalamus, and basal ganglia<sup>22</sup> contributed to the deficits. The essentially isolated cerebellar involvement in the current cohort avoids this potential confound and provides further insights into the cerebellum’s role in cognition.

On the word-pair learning task, individuals with cerebellar ataxia as well as controls demonstrated low retrieval accuracy compared to published performance in young adults.<sup>14,60</sup> Age-related changes in retrieval are well described.<sup>61</sup> Older age is associated with under-recruitment and non-specific recruitment of the medial temporal lobe and the prefrontal cortex, reflecting deficits in engaging effortful strategies.<sup>62</sup> Notably, older adults with greater engagement of effortful retrieval strategies show young adult-like performance on episodic memory tasks.<sup>63</sup> In our ataxia group, Immediate Recall, a robust measure of memory retrieval, was lower compared to the age-matched controls, suggesting the importance of cerebellar integrity to episodic memory retrieval. Using neuroimaging, Krause and colleagues (1999)<sup>64</sup>

demonstrated a bilateral increase in BOLD signal during the Encoding phase of a word-pair learning task in the cerebellum, precuneus, and anterior cingulate and prefrontal cortices. Cerebellar activation is greater during tasks that involve effortful recall of recently acquired information, also known as “retrieval effort,”<sup>65,66</sup> while prefrontal and cerebellar-prefrontal functional connectivity have been linked to inhibition of irrelevant information, an important process in memory retrieval.<sup>65</sup> The cerebellum has bidirectional connections with the hippocampus, which is essential for declarative learning,<sup>67</sup> and the cerebellum’s role in hippocampal-dependent learning has been linked to the integration of the contextual aspects of declarative information, helping to maintain online awareness during learning.<sup>68</sup>

Our data show that despite impairments in learning the word-pairs, individuals with ataxia were comparable to healthy controls with respect to sleep-dependent memory processing. Specifically, the ataxia group’s performance on Delayed Recall was impaired relative to controls, but the change in accuracy from Immediate to Delayed Recall was comparable. One explanation for this finding is that both groups demonstrate equivalent age-related impairment in overnight consolidation of word-pairs. However, an alternative explanation is that the observed preservation of memory for the word-pairs learned prior to sleep in individuals with ataxia as well as controls reflects a passive role for sleep in protecting memories from waking interference, rather than an active role of sleep in strengthening and stabilizing the memory traces. To parse the passive and active roles of sleep in associative learning in individuals with pure cerebellar disease, future studies could focus on determining the post-sleep strength of the learned associations using an interference paradigm.<sup>60</sup>

We found a close link between sleep dysfunction and reduced cognitive function in our sample of participants with pure cerebellar syndrome: greater sleep fragmentation was associated with impaired executive function and declarative learning. This is consistent with previous studies that have demonstrated a robust association between sleep fragmentation and diminished performance on numerous tasks, particularly those requiring vigilance and attention (Kingshot et al., 2000<sup>69</sup>; Short and Banks, 2014<sup>70</sup>). Therefore, these findings further emphasize the connection between poor sleep and cognitive function and exemplify its clinical relevance in the context of neurodegenerative disorders. Importantly, impaired sleep can be a clinical marker of neurodegeneration, given that symptoms of disturbed sleep may even precede the onset of the symptoms associated with neurodegeneration by ten or more years.<sup>3</sup> However, the precise etiology of sleep disorders associated with neurodegenerative disease is unknown, and future studies should examine this relationship more deeply.

The current study was the first to our knowledge to examine sleep behavior, physiology, and architecture, while simultaneously determining the impact of poor sleep on cognitive function in individuals with isolated cerebellar disease. Our findings support previous observations of cognitive impairment in individuals with pure cerebellar disease, provide novel evidence of sleep dysfunction in this population, and establish a link between objective measures of sleep physiology and cognitive function in this population. These insights into poor sleep and impaired cognition in individuals with neurodegeneration confined to the cerebellum have practical implications for management. Efforts to improve sleep may

result in improving daytime functioning, self-sufficiency, and general well-being in individuals with cerebellar ataxia.

## Declarations

*Ethics approval and consent to participate:* This study was approved by the Institutional Review Board at the University of Massachusetts #2011-0929 and written informed consent was obtained from all participants.

*Consent for publication:* Not applicable

*Availability of data and materials:* The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

*Competing interests:* The authors have no conflicts of interest with respect to this work to declare.

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Authors' contributions

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## Figures

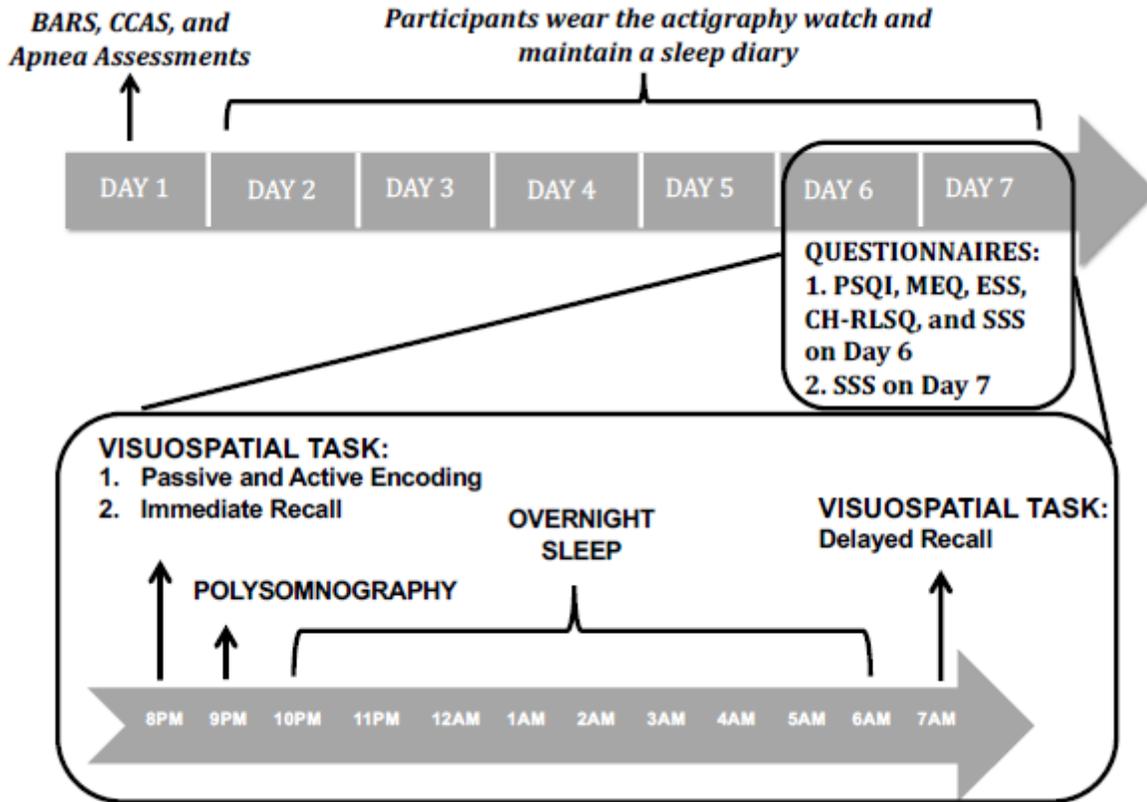


Figure 1

Experimental procedures

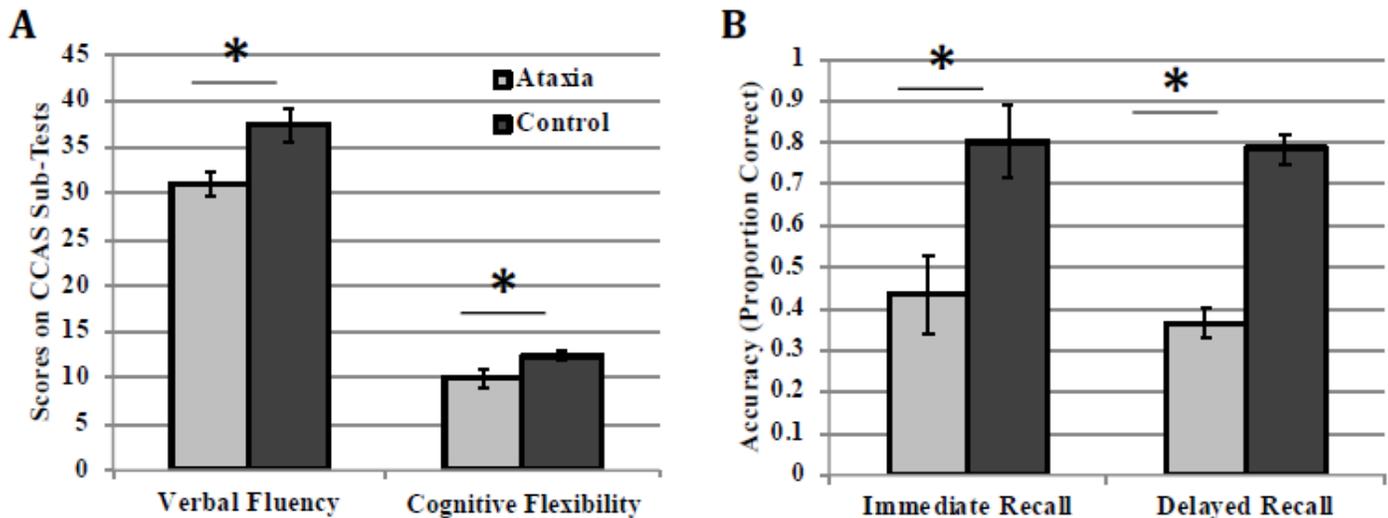


Figure 2

Compared to their age-, sex-, handedness-, and education-matched controls, individuals with pure cerebellar syndrome (Ataxia) demonstrated impairments in A) verbal fluency and cognitive flexibility domains of the Cerebellar Cognitive Affective Syndrome (CCAS), and B) accuracy at Immediate and

Delayed Recall phases of the word-pair association task. \* indicates significant differences between ataxia and control groups

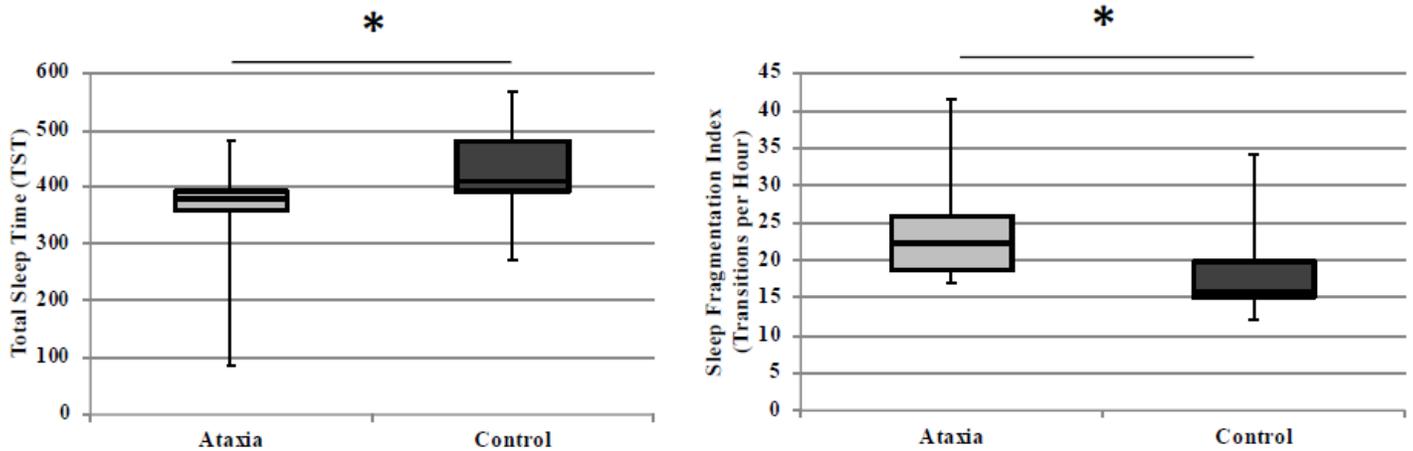


Figure 3

Compared to their age-, sex-, handedness-, and education-matched controls, individuals with pure cerebellar syndrome (Ataxia) had reduced A) Total Sleep Time (TST), and B) Sleep Fragmentation Indices (SFI) – or the number of stage transitions and awakenings per hour of sleep. \* indicates significant differences between ataxia and control groups

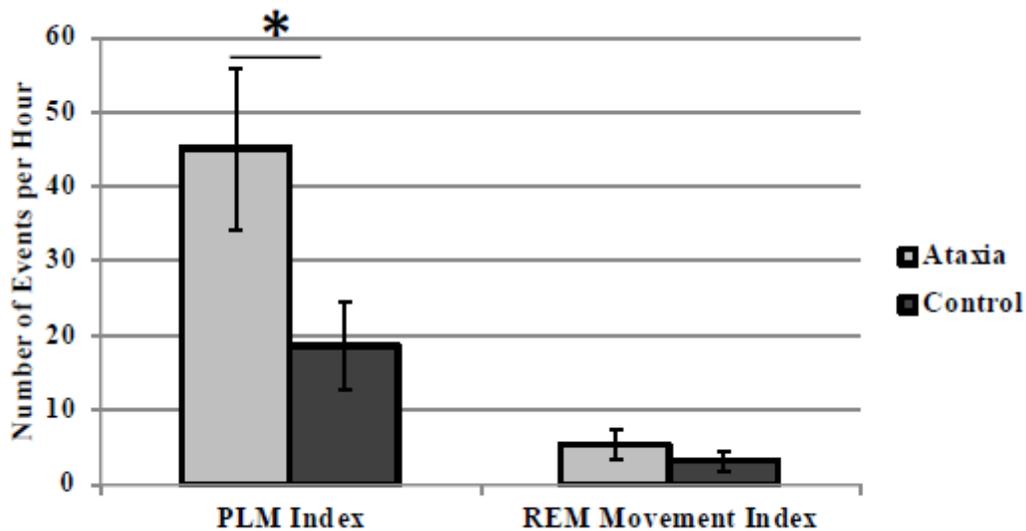
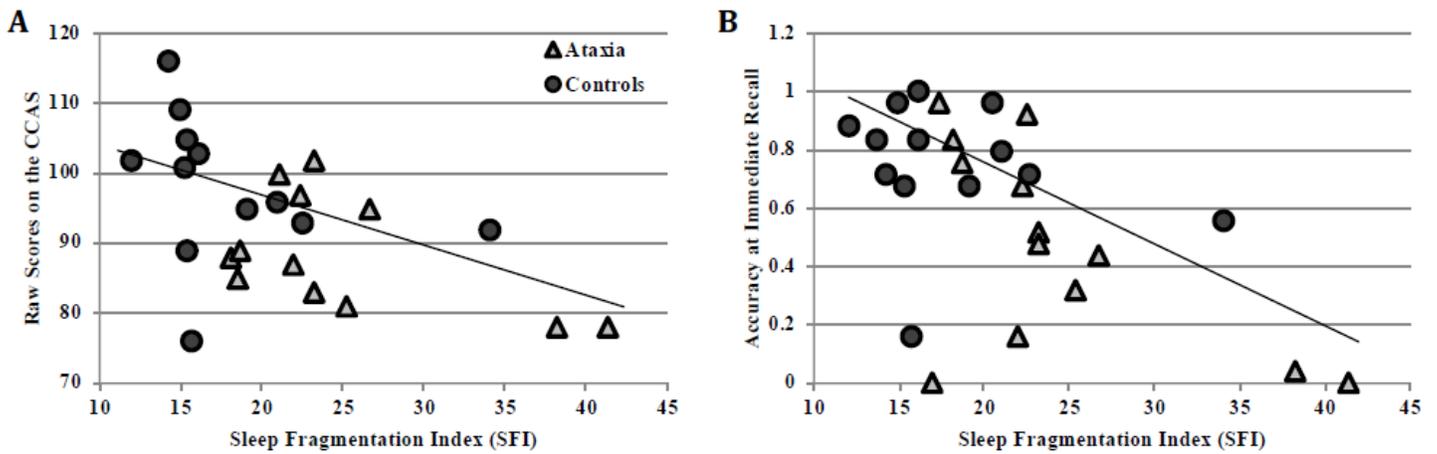


Figure 4

Individuals with pure cerebellar syndrome (Ataxia) demonstrated higher periodic limb movement indices (PLM indices) – a measure of repetitive muscle twitches occurring every 20-40 s – compared to their age-, sex-, handedness-, and education-matched controls. There were no observed differences with regard

to limb movements during REM sleep in particular. \* indicates significant differences between ataxia and control groups.



**Figure 5**

Correlations between sleep measures and cognitive function. Specifically, the relationship between A) the Sleep Fragmentation Index – or the number of stage transitions and awakenings per hour of sleep – and scores on the Cerebellar Cognitive Affective Syndrome (CCAS;  $r_s = -0.528$ ,  $p = 0.008$ ), and B) the Sleep Fragmentation Index and baseline memory retrieval on the declarative word-pair association task ( $r_s = -0.531$ ,  $p = 0.001$ )