

The Effects of Sleep Dysfunction on Cognition, Affect, and Quality of Life in Individuals with Cerebellar Ataxia

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SCIENTIFIC INVESTIGATIONS

Study Objective: Cerebellar ataxia comprises a group of debilitating diseases that are the result of progressive cerebellar degeneration. Recent studies suggest that, like other neurodegenerative diseases, sleep impairments are common in cerebellar ataxia. In light of the role of sleep in mood regulation and cognition, we sought to assess interactions between sleep, cognition, and affect in individuals with cerebellar ataxia.

Methods: A survey of 176 individuals with cerebellar ataxia was conducted. The battery of instruments included a modified International Cooperative Ataxia Rating Scale, Pittsburgh Sleep Quality Index, Restless Leg Syndrome Questionnaire, REM Behavior Disorder Questionnaire, Beck Depression Inventory, Epworth Sleepiness Scale, and a Composite Cognitive Questionnaire.

Results: Fifty-one percent of individuals indicated significant sleep disturbances on the Pittsburgh Sleep Quality Index, 73% of participants had two or more symptoms of restless leg syndrome, and 88% had two or more symptoms of REM behavior disorder. Ataxia severity, based on the modified

International Cooperative Ataxia Rating Scale, predicted scores on the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale and REM Behavior Disorder Questionnaire. Median split analyses revealed that cognitive function appeared to be reduced and depressive symptoms were greater for those individuals with poor subjective sleep quality and severe RLS. Importantly, sleep appears to play a mediatory role between disease severity and depressive symptoms.

Conclusions: These results suggest that disturbed sleep may have detrimental effects on cognition and affect in individuals with cerebellar ataxia. While objective measures are needed, such results suggest that treating sleep deficits in these individuals may improve cognitive and mental health as well as overall quality of life.

Keywords: sleep, cognition, affect, ataxia, cerebellum

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Sleep disturbances are common among individuals with neurodegenerative disorders, and symptoms of disturbed sleep often precede the onset of the symptoms associated with neurodegeneration by ten or more years.¹ This has great implications for furthering the understanding of disease mechanisms and for making earlier diagnoses. Cerebellar ataxia comprises a large group of neurodegenerative disorders that are progressive, debilitating, and irreversible.² Although cerebellar ataxia is a relatively rare disease, it results in significant disability and diminished quality of life for those affected. Sleep disturbances commonly occur in cerebellar ataxia, with higher frequencies reported in the autosomal dominant spinocerebellar ataxias (SCA)—specifically SCA1, SCA2, SCA3 (Machado-Joseph disease), and SCA6—than in the other subtypes.³ The most prevalent among these sleep disturbances are RBD, RLS, periodic leg movement disorder, excessive daytime sleepiness (EDS), insomnia, and obstructive sleep apnea.²⁻⁵

Disordered sleep in cerebellar ataxias may come about through several pathways. Firstly, abnormal motor activity during sleep in individuals with cerebellar ataxia is most likely a result of damage to the well-defined cerebellar motor circuitry.⁶ Likewise, the cyclic motor activities associated with

breathing require sound cerebellar function.^{7,8} There is also evidence pointing toward a direct involvement of the cerebellum in sleep-wake behavior which may be disturbed as a result of the cerebellar degeneration associated with cerebellar ataxias.⁹ Additionally, many forms of ataxia have substantial extracerebellar pathology, particularly in the brainstem,^{7,8} and therefore, in addition to pathways involving cerebellar involvement, brainstem degeneration may also lead to negative

BRIEF SUMMARY

Current Knowledge/Study Rationale: As in the case for numerous neurodegenerative disorders, individuals with cerebellar ataxia often complain of poor sleep. Concurrently, Cerebellar Cognitive Affective Syndrome describes a spectrum of disorders including, cognitive disabilities and emotional dysfunction, that are common in conjunction with cerebellar lesions. In an effort to understand the mechanisms underlying these symptoms, the current study aimed at looking at how poor sleep quality and the presence of sleep disorders may contribute to diminished cognitive abilities and negative affect in individuals with cerebellar ataxia.

Study Impact: This study provides insight into the role of poor sleep in mediating cognitive and affective deficits that markedly reduce quality of life. Results suggest that improving the quality of sleep could result in improved daytime functioning and mood in this population, thus providing novel therapeutic targets for the management of cerebellar ataxia.

outcomes on sleep quality. Degeneration of pontomedullary pathways required for maintenance of REM atonia can cause disorders that are associated with abnormal motor movements during sleep.^{7,8,10,11} Furthermore, degeneration of respiratory centers in the brainstem could adversely affect control of the anatomical structures involved in breathing and ventilation. Therefore, the cerebellum and brainstem structures, together with their projections to the thalamus and cerebral cortex, are involved in regulating various aspects of sleep behavior; damage to any of these structures may result in significant sleep disturbances.

Individuals with cerebellar ataxia are reported to have cognitive deficits such as impairments in learning, language processing, and visuospatial processing, among others.¹²⁻¹⁵ Here, we consider whether sleep may underlie such deficits. Recently, we and others have shown that, during sleep, new memories are transformed into more stable representations and integrated into preexisting memory networks.¹⁶ These sleep-dependent processes are not only important for memory consolidation, but also for providing insight into hidden rules,^{17,18} and for decision making.¹⁹ EDS may also account for impaired cognitive performance in cerebellar ataxia as it has been shown to negatively impact cognitive domains such as attention, memory, motivation and alertness, thus affecting mood, productivity, and quality of life.²⁰⁻²⁴

We have also demonstrated that emotional reactivity is maintained by sleep.²⁵ This role of sleep in emotional processing may contribute to mood regulation. Mosko and colleagues²⁶ reported that a large percentage of individuals with sleep disorders presenting at a sleep clinic also showed depressive symptoms, and in many cases, a major affective disorder. When these individuals were administered the appropriate treatment for their sleep disorder, they subsequently showed improvement in their affect, supporting a link between healthy sleep and regulation of emotion and mood. This is of particular consequence in light of the comorbid sleep disturbances observed in individuals with cerebellar ataxia. Specifically, the cerebellar cognitive affective syndrome describes a spectrum of deficits, including cognitive impairments and impairments in affective processing, ranging from emotional blunting to depression.^{12,13} Although the association between sleep and depression has been observed and reported in various populations,²⁷⁻²⁹ it has yet to be explored in the cerebellar ataxia population. The present study is an effort to bridge this gap in the literature.

To probe the relationship between impaired sleep and cognitive and affective functions in ataxia, we administered a battery of instruments designed to assess sleep, cognition, affect and quality of life, to a large sample of individuals across various subtypes of cerebellar ataxia. We hypothesized that (1) ataxia severity would be related to severity of sleep disturbances, depressive symptomatology, reduced cognitive function and overall reduced quality of life; (2) severity of sleep disturbances would correlate with depressive symptomatology, reduced cognitive function and reduced quality of life; (3) poor sleep quality would mediate the relationship between ataxia severity and reduced cognitive function and depressive symptomatology; and (4) EDS would mediate the relationship between severity of sleep disorders and reduced quality of life.

METHODS

Participants

Participants were recruited from across the United States via advertisements sent to support groups and appearing in the National Ataxia Foundation website and newsletter. Recruitment took place from June 2011 until February 2013. Individuals over 18 years with a diagnosis of cerebellar ataxia, regardless of subtype, were invited to participate. Exclusion criteria included presence of another neurological disorder and/or history of head trauma.

Two hundred fourteen individuals with cerebellar ataxia responded to the survey. Given the limited distribution of the survey (directly targeted to individuals with ataxia), it is assumed that self-reported diagnoses of ataxia and subtype are accurate. There was no compensation for participation, which we assume further reduced dishonest responding.

Procedures

Procedures were approved by the Institutional Review Board of the University of Massachusetts, Amherst. The advertisement contained a URL for the web-based survey. This survey began with a consent form explaining the nature of the research and the enrollment criteria. The survey could be completed by the individuals with ataxia themselves or dictated to a companion or caregiver (given that keyboard responses may be prohibitive to some individuals). Participants were instructed that it would take approximately 60 min to complete all questions and that they could complete this in multiple sessions if they so choose. Participants could skip questions at any time.

Measures

Modified International Cooperative Ataxia Rating Scale

Disease severity was measured by means of a modified International Cooperative Ataxia Rating Scale (ICARS).³⁰ The ICARS is a well-established clinical rating scale used to assess cerebellar symptoms and to determine the extent of impairment. The test-retest reliability of the original ICARS shows a high rate of internal consistency (Cronbach $\alpha = 0.97$).³¹ We modified the ICARS for online administration and for collecting subjective instead of the clinician-reported responses (available upon request). We included 3 questions related to posture and gait functions, 2 questions related to kinetic function, 2 questions related to speech, and 1 question related to oculomotor function.

The Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire used to determine an individual's sleep quality over the previous 30 days,³² and has been shown to be a reliable (Cronbach $\alpha = 0.87$) and valid instrument for the measurement of sleep disturbances, such as primary insomnia, with a high correlation with sleep log data.³³

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a short questionnaire used to measure daytime sleepiness.³⁴ The ESS is a reliable instrument (Cronbach $\alpha = 0.88$)³⁵ and has high sensitivity

(93.5%) and specificity (100%). ESS scores ≥ 10 are indicative of abnormal somnolence relative to the average person.

Restless Leg Syndrome Questionnaire

The Restless Leg Syndrome Questionnaire (RLSQ), designed to determine whether the participant has symptoms of RLS, was developed by sleep clinicians at the Athens Center for Sleep Disorders and is used routinely in their screening procedures.³⁶ Participants are asked whether they experience symptoms such as “creeping, crawling, tingling” feelings in the legs at night that are partially relieved by movement, fidgeting and wiggling of feet and toes. For each question, greater scores indicated increasing severity of the symptom. A caveat of this measure is that reliability and validity measures are not yet available.

REM Behavior Disorder Screening

The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) contains a set of questions that are related to symptoms of RBD. Again, responses were coded such that greater severity was reflected by higher scores. This screening questionnaire has been found to have high sensitivity (96%) and specificity (92%).³⁷

Composite Cognitive Questionnaire

In order to gather information about the individual’s everyday cognitive abilities, we included a Composite Cognitive Questionnaire (CCQ). This survey was a 27-question composite of the Cognitive Failure Questionnaire (CFQ),³⁸ which has been determined to have adequate internal consistency and validity,³⁹ and 5 additional questions from the Information Questionnaire on Cognitive Decline in the Elderly (IQCODE),⁴⁰ used to screen dementia. Careful selection of questions from the 2 questionnaires was conducted in order to minimize time and maximize the breadth. Specifically, one question from the CFQ was removed for potential confound with motor deficits (“Do you drop things”), 2 questions were removed in order to save time (“Do you leave important letters unanswered for days” and “Do you fail to see what you want in a supermarket [although it’s there]”), and questions from the IQCODE were added that were related to the ability to remember phone numbers and dates, to carry out simple math problems, follow stories on the television, and to learn to use new gadgets. Responses for both the CFQ and IQCODE have 5 levels of responses on a Likert scale based on severity of the symptom, such that each question has a possible score ranging from 0 to 4; we added an additional option of “not applicable” that was not scored on the Likert scale, for those participants that did not feel like the question was relevant, resulting in a range of scores from 0 to 108.

Beck Depression Inventory

To assess the prevalence and severity of depressive symptoms in our sample, we included the Beck Depression Inventory (BDI-II).⁴¹ The internal consistency of the BDI-II was found to be acceptable when calculated in a German sample (Cronbach $\alpha = 0.84$).⁴²

Abbreviated Activities of Daily Living Questionnaire

We included a modified, shortened version of the Activities of Daily Living Questionnaire (ADLQ) to assess an individual’s

capacity to carry out self-care activities.⁴³ The original ADLQ has high reproducibility (Lin concordance coefficient = 0.86) and a strong positive correlation with other measures of ability to live independently.⁴⁵ We included 8 of the original 28 questions in the ADLQ, one each regarding ability to use a telephone, shopping, food preparation, housekeeping, laundry, using transport, taking medications, and ability to handle finances.

Demographic Information

Demographic information included date of birth, handedness, level of education, race, ethnicity and whether English was their first language. We also collected information regarding their medical history, namely, if and when they were diagnosed with ataxia and if they were genetically tested for ataxia subtype.

Data Analysis

BDI scores were divided into 3 categories as described by Robinson and Kelley⁴¹: scores of 1-16 characterized the “low depression” group, 17-30 the “moderate depression” group, and > 30 the “significant depression” group. ADLQ was scored according to Johnson and colleagues.⁴⁴ Since we used fewer questions than the original ADLQ, we calculated total percent impairment rather than separate subscales.

Individual component scores of the PSQI were calculated as per Buysse and colleagues,³² and these components were summed to provide a global PSQI score; global PSQI scores ≥ 5 are indicative of significant sleep disturbances. Therefore, global PSQI scores ≥ 5 were considered “poor sleepers” while those < 5 were considered “good sleepers.” Similarly, RBDSQ scores ≥ 6 were characterized as “severe RBD” and scores < 6 were characterized as “mild-to-no RBD.” RLSQ scores < 5 were characterized as “low-to-no RLS” and scores ≥ 5 were “high RLS.” To test the interactions with other measures, the median split scores were subjected to independent samples *t*-tests.

Partial correlational analyses between scores on the modified ICARS and each measure were conducted controlling for age, number of years since disease onset and disease subtype. We report Pearson correlation coefficient, *r*, for each of these analyses.

For all of the above analyses, to correct for multiple comparisons, we used $\alpha = 0.01$ to detect significance. For data that was not normally distributed, we conducted the nonparametric Spearman rank correlations in addition to the Pearson correlation.

We used the Baron and Kenny⁴⁵ method to test whether the interactions between our measures could be explained by the presence of mediators. To this end, we tested the following hypotheses: (1) whether poor subjective sleep quality mediates the relationship between disease severity and depressive symptoms, (2) whether severity of sleep disorders mediates the relationship between disease severity and reduced cognitive functioning, and (3) whether excessive daytime sleepiness mediates the relationship between severity of sleep disorders and reduced quality of life. Significance levels for mediation analyses were set at $\alpha = 0.01$ in order to correct for multiple comparisons as mentioned previously. The Baron and Kenny⁴⁵ approach to mediation analyses describes a mediator as a variable that is not only independently associated with both the

Table 1—Sample characteristics and demographics (n = 176).

Sample Characteristic	%	
Ataxia Subtype	Episodic Ataxia	11.0
	Friedrich's Ataxia	1.7
	SCA1	2.3
	SCA2	9.1
	SCA3	11.0
	SCA5	0.6
	SCA6	8
	SCA7	0.6
	SCA8	5.7
	SCA10	0.6
	SCA14	0.6
Unknown (including idiopathic)	48.8	
Handedness	Ambidextrous	1.1
	Left	11.4
	Right	85.8
	Not reported	1.7
Education	Did not complete High School	2.3
	Completed High School/GED	29.5
	Associates Degree	13.6
	Bachelor's Degree	22.7
	Master's Degree	18.8
	Doctoral Degree	4.0
	Other Professional Schools	7.4
	Not reported	1.7
Ethnicity	Hispanic	5.1
	Non-Hispanic	92.1
	Not reported	2.8
Race	American Indian or Alaska Native	1.1
	African American	2.3
	Asian	3.4
	White	88.6
	Other	2.3
	Not reported	2.3

predictor and the outcome variables, but also accounts for the majority of the variance in the relationship between the two. Therefore, for a variable to be considered as a mediator, the relationship between the predictor and outcome variables as reflected by the regression coefficient must reduce when controlling for the mediator. Additionally, in order to control for age-related changes in sleep and mood, we added age as an independent variable in each step of the model.

Much of the literature related to changes in sleep, cognition and affect in individuals with cerebellar ataxia either focuses on single subtypes, or alternatively, on those subtypes that are characterized by cerebellar pathology either with or without the absence of brainstem involvement.^{2,5,6,10} Thus, to investigate the role of cerebellar subtype, in a final analysis we divided our cohort into two groups based on pathology as per descriptions provided by Schöls and colleagues.⁴⁶ The Cerebellar Pathology group (n = 36) consisted of individuals with diagnosis of SCA 5, 6, 8, 10 or 14 which constitute those subtypes that have pure

Table 2—Summary of neuropsychiatric instruments used and response rate

Measure	Number of Questions	Response Rate (%)
Disease Severity Assessments		
Modified International Cooperative Ataxia Rating Scale (ICARS)	8	78
Daily Living Assessments		
Activities of Daily Living Questionnaire (ADLQ)	8	81
Sleep Assessments		
Pittsburgh Sleep Quality Index (PSQI)	17	56
Epworth Sleepiness Scale (ESS)	8	62
Restless Leg Syndrome Questionnaire (RLSQ)	7	63
REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)	12	40
Cognitive Assessments		
Composite Cognitive Questionnaire (CCQ)	27	84
Affect Assessments		
Beck Depression Inventory (BDI)	21	84

Number of respondents varied for each sample characteristic, as participants chose to leave certain fields blank.

cerebellar pathology without cerebral atrophy. The olivopontocerebellar atrophy group (OPCA; n = 54) consisted of individuals with diagnosis of SCA 1, 2, 3 or 7. Individuals with Friedreich ataxia, episodic ataxia, and unknown (including idiopathic ataxias) were excluded from this analysis. Using independent samples *t*-tests, we compared the 2 groups with relation to scores on all measures. We used an alpha of 0.01 to correct for multiple comparisons.

RESULTS

Sample Characteristics

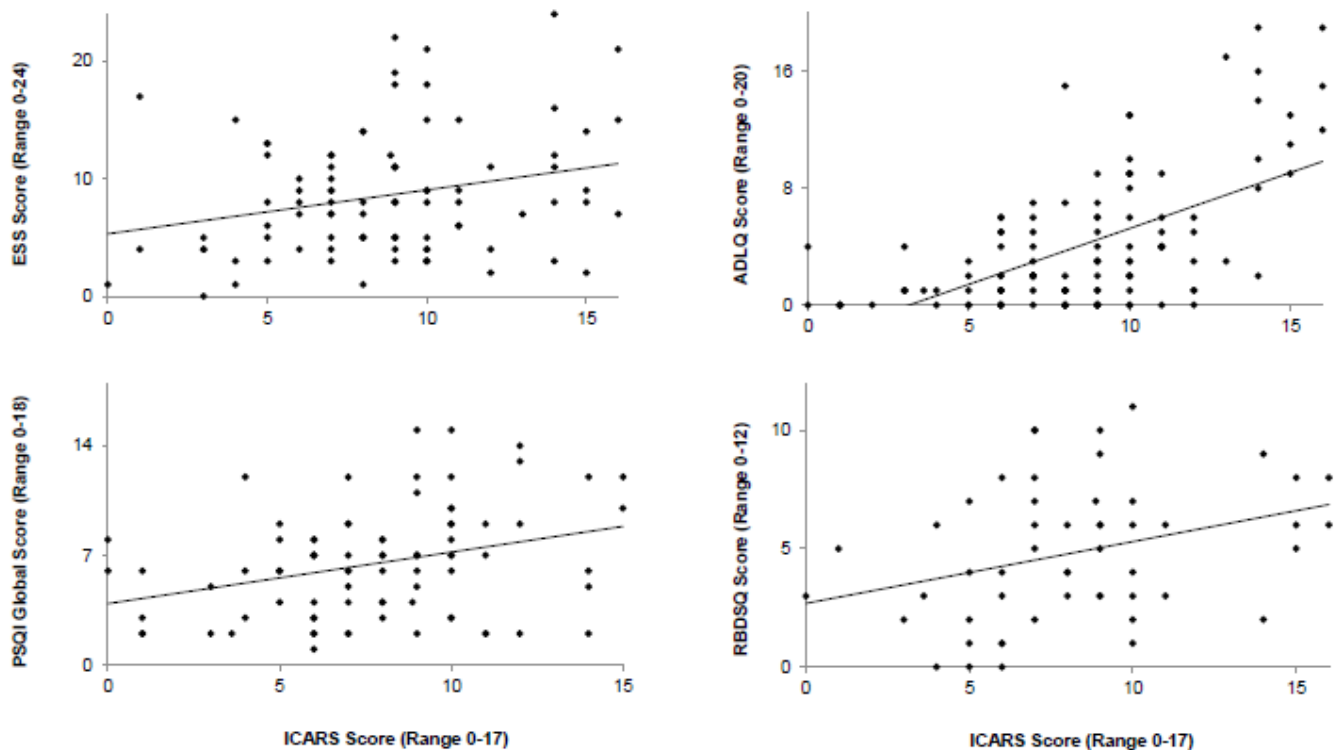
Of the 214 respondents to our survey, we included 176 individuals in our final analyses. Individuals were excluded for the following reasons: ataxia reportedly as a result of toluene exposure (n = 1), history of brain tumor (n = 8), history of epilepsy (n = 4), history of stroke (n = 9), history of head trauma (n = 14), and diagnosis of multiple systems atrophy (n = 2; excluded due to widely distributed pathology). Of those included in the analyses, 5 individuals dictated their responses to their companion or caregiver. One hundred forty-three participants had a genetic test confirming their diagnosis. The age-range of respondents was 19-78 years (M = 53.14, SD 12.44). One hundred sixty-five individuals were native English speakers, 8 were non-native English speakers.

Additional sample characteristics and demographics are summarized in **Table 1**. Given that participants were told they could skip questions, sample size varied across items (**Table 2**).

One hundred thirty-six individuals completed the ICARS. The range of possible scores on the modified version of the ICARS was 0-17. The average score in our sample was 8.4 ± 3.5 . Average scores are broken down by subscale in **Table 3**.

Table 3—Average ICARS scores by subscale

ICARS Subscale	# Questions	Range of Possible Scores	Average	SD
Posture and Gait Disturbances	3	0-8	4.3	2.1
Kinetic Functions	2	0-3	1.4	0.9
Speech	2	0-5	2.1	1.3
Oculomotor Functions	1	0-1	0.6	0.5

Figure 1—Relationship between disease severity and scores on the Epworth Sleepiness Scale (ESS; n = 82), Pittsburgh Sleep Quality Index (PSQI; n = 73), Activities of Daily Living Questionnaire (ADLQ; n = 82) and REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ; n = 45).

All questionnaire data was found to be parametric, with the exception of the ADLQ. In order to ensure robust statistical results, we conducted nonparametric analyses, namely Spearman rank correlations, for comparisons involving this measure.

Sleep

Fifty-one percent of individuals who completed the PSQI (n = 91) had scores that indicated significant sleep disturbances during the past month. Disease severity, measured through the modified ICARS, significantly predicted PSQI scores (n = 73; $r = 0.344$, $p = 0.004$; **Figure 1**). The mean score on the ESS was 8.44 ± 5.06 . Thirty-three percent of individuals that responded to this questionnaire (n = 109) had scores that indicated that they tended to be more somnolent during the day than the average person. Disease severity significantly predicted sleepiness scores on the ESS (n = 82; $r = 0.302$, $p = 0.007$; **Figure 1**).

Prevalence of sleep disorders was high in this cohort; 73% of participants had ≥ 2 symptoms of RLS, and a majority of participants (88%) reported having ≥ 2 symptoms of RBD. Disease severity predicted severity of RBD at near-significance level

(n = 45; $r = 0.363$, $p = 0.018$; **Figure 1**). No significant correlation was found between disease severity and RLSQ scores (n = 83; $r = 0.164$; $p = 0.146$).

Cognitive Measures

One hundred forty-eight participants completed the CCQ. No significant correlation was found between disease severity and cognitive impairment (n = 106; $r = -0.006$; $p = 0.955$).

Mood Measures

Of those who completed the BDI (n = 147), 65% were characterized in the “low depression” group, 30% in the “moderate depression” group, and 5% in the “significant depression” group. Disease severity was correlated with severity of depressive symptoms at trend-level (n = 107; $r = 0.179$; $p = 0.069$).

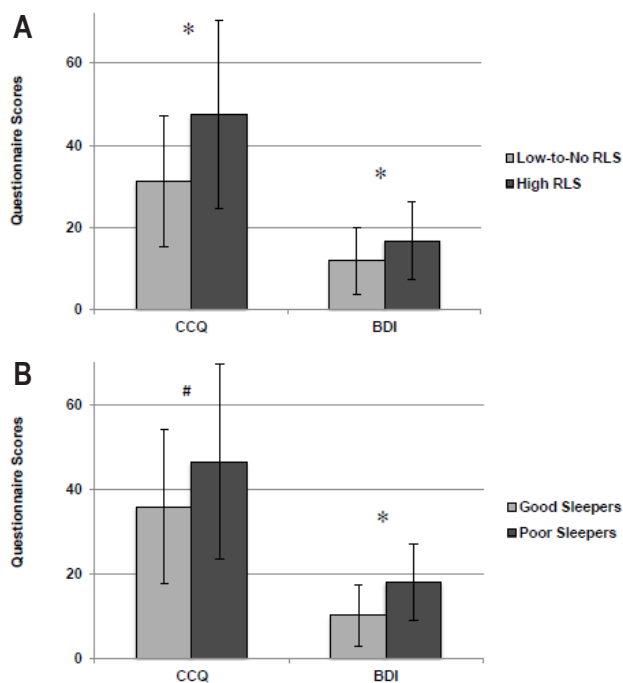
Quality of Life Measures

Average percent impairment for those that completed the ADLQ (n = 142) was 16.8% (SD 18.35). Disease severity significantly predicted the impairment in carrying out daily activities (n = 120; Spearman $\rho = 0.589$, $p < 0.001$; **Figure 1**).

Interactions between Sleep, Cognitive, and Mood Measures

Depression scores on the BDI were not significantly different for the severe RBD group (n = 29) and the mild-to-no RBD group (n = 31; $t_{58} = -1.713, p = 0.095$). However, the low-to-no RLS group (n = 43) had significantly lower scores than the high RLS (n = 52) group on the BDI ($t_{93} = -2.648, p = 0.008$; **Figure 2A**) and the CCQ ($t_{92} = -3.900, p < 0.001$). Using the

Figure 2—Severity of cognitive deficits as measured by the Composite Cognitive Questionnaire (CCQ; range 0-108) and depressive symptoms as measured by the Beck Depression Index (BDI; range 0-84) with relation to (A) restless leg syndrome (RLS) severity: “low-to-no RLS” and “high RLS” groups based on a median split, and (B) Pittsburgh Sleep Quality Index (PSQI) defined “good sleepers” (PSQI < 5) and “poor sleepers” (PSQI ≥ 5).



* $p < 0.01$, # trend-level p-value. Error bars represent standard deviation.

overall PSQI score, “poor sleepers” (n = 50) had significantly higher scores than the “good sleepers” on the BDI (n = 49; $t_{82} = -4.379, p < 0.001$; **Figure 2B**) and CCQ (trend level; $t_{52} = -2.415, p = 0.018$; **Figure 2B**).

ESS scores were significantly correlated with cognitive impairment measured by the CCQ ($\alpha = 0.01, n = 83; r = 0.385, p < 0.001$; **Figure 3**) and RBD severity ($\alpha = 0.01, n = 90$; Pearson $r = 0.426, p < 0.001$; **Figure 3**). ESS scores were correlated with scores on the BDI at trend level ($\alpha = 0.01, n = 90; r = 0.231, p = 0.032$).

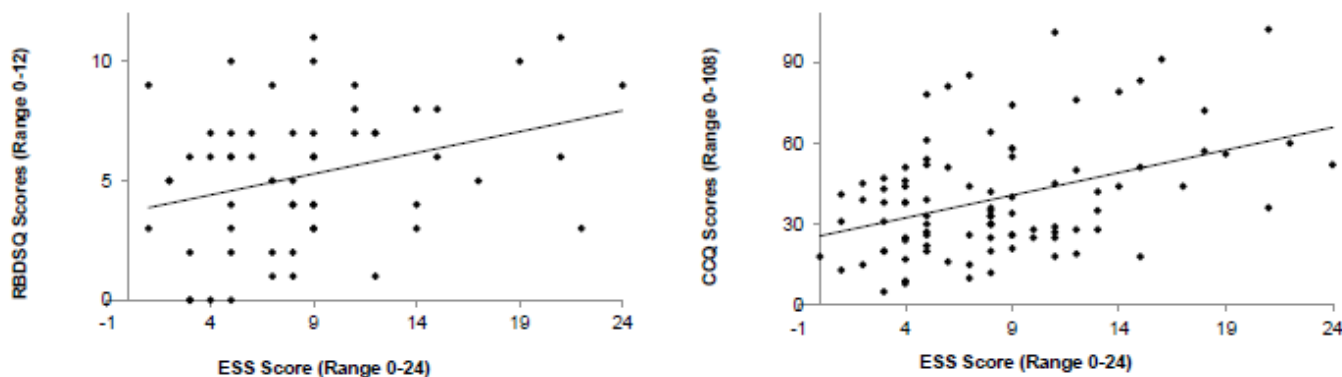
We also found that when controlling for changes in sleep and mood with age, our data supported the model that poor sleep quality plays a mediatory role in the relationship between disease severity and severity of depression, at a clear trend-level. As **Figure 4** illustrates, the standardized regression coefficient for the association between the ICARS and BDI scores decreased from $b = 0.188$ to $b = 0.113$ when controlling for scores on the PSQI, and the association changed to a non-significant one ($p = 0.232$). The other conditions of mediation were also met: disease severity was an independent predictor of depression severity at trend level ($b = 0.188, t_{114} = 2.177, p = 0.032$) and of subjective sleep quality ($b = 0.348, t_{69} = 3.286, p = 0.002$). Additionally, subjective sleep quality was a significant predictor of depression severity while controlling for disease severity ($b = 0.506, t_{69} = 5.518, p < 0.001$).

Our data were not consistent with the mediation model suggesting that the relationship between ataxia severity and cognitive deficits was mediated by poor sleep. Likewise, our data did not support the hypothesis that the relationship between the severity of sleep disturbances and reduced quality of life was mediated by excessive daytime sleepiness.

Cerebellar Pathology vs. Olivopontocerebellar Atrophy

As **Figure 5** illustrates, using an α of 0.01, independent samples t-tests revealed no significant differences between the Cerebellar Pathology and OPCA groups with relation to scores on the PSQI (Cerebellar n = 15, OPCA n = 35, $t_{48} = 0.808, p = 0.423$), ESS (Cerebellar n = 23, OPCA n = 38, $t_{59} = -0.867, p = 0.390$), BDI (Cerebellar n = 29, OPCA n = 45, $t_{72} = 0.764, p = 0.447$), ICARS (Cerebellar n = 30, OPCA n = 40, $t_{68} = -0.340, p = 0.735$), and ADLQ (Cerebellar n = 27, OPCA n = 46, $t_{71} = -1.494, p = 0.140$). However, the two groups significantly differed on scores on the

Figure 3—The relationship between scores on the Epworth Sleepiness Scale (ESS) and those on the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ; n = 57), as well as on the Composite Cognitive Questionnaire (CCQ; n = 93).



RLSQ (Cerebellar n = 24, OPCA n = 36, $t_{58} = -2.815$, $p = 0.007$), where the higher scores were observed in the OPCA group than the Cerebellar Pathology group. Similarly, a trend toward statistical significance was observed for the RBDSQ (Cerebellar n = 12, OPCA n = 21, $t_{31} = -2.054$, $p = 0.048$) and CCQ (Cerebellar n = 29, OPCA n = 43, $t_{70} = -2.029$, $p = 0.046$), and in both cases, the OPCA group had higher scores than the Cerebellar Pathology group.

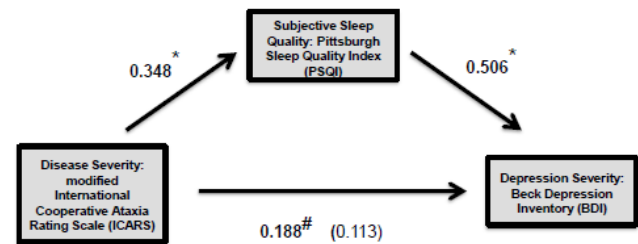
DISCUSSION

We designed an extensive web-based survey to assess sleep, cognition, and mood in a sample of individuals with cerebellar ataxia. Our results revealed that (1) sleep disturbances are prevalent in our cohort of individuals with cerebellar ataxia and the severity of the sleep disturbances is correlated with disease severity; (2) depressive symptoms are also prevalent, and the severity is correlated with disease severity; and (3) the relationship between disease severity and negative affect may be mediated by poor sleep quality.

Fifty-one percent of individuals with cerebellar ataxia reported having disturbed sleep as per the PSQI criteria.³² This suggests a much higher prevalence of disturbed sleep in individuals with cerebellar ataxia compared to the general population: PSQI-measured frequency of sleep disturbances in the general adult population in Japan was 18% to 37% with higher

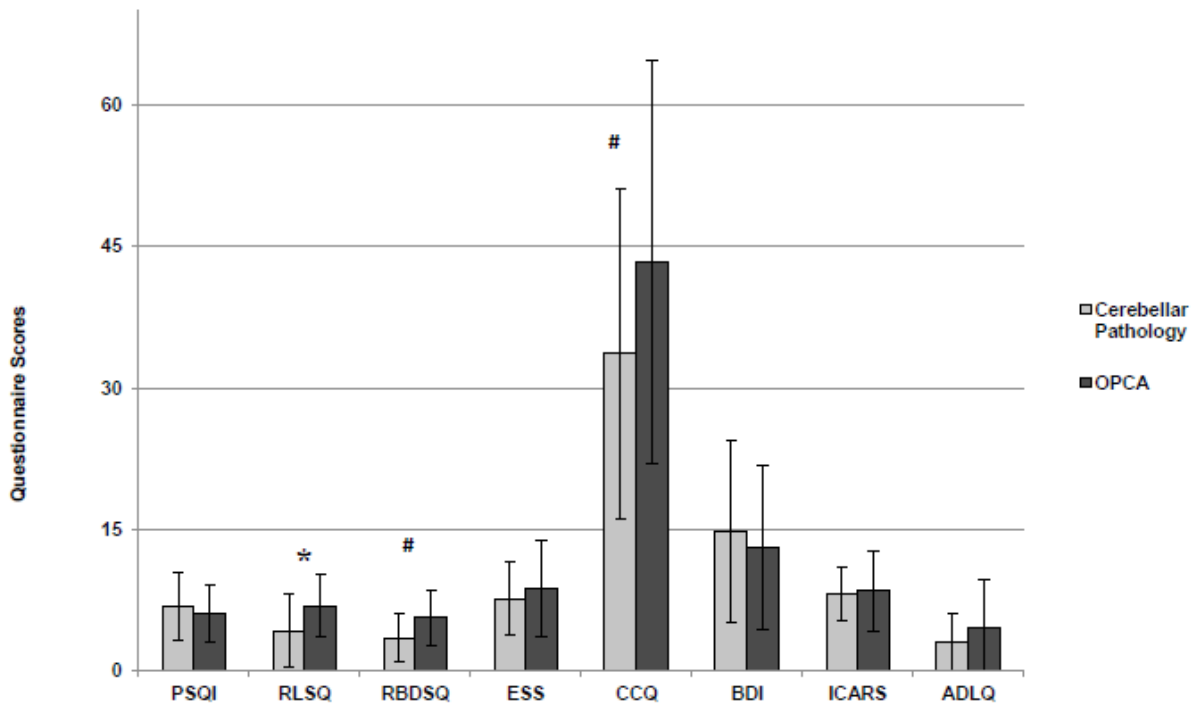
prevalence in the older age groups owing to age-related changes in sleep.⁴⁷ In addition, RBD and RLS prevalence is also high in cerebellar ataxia with 88% of our participants reporting two or more symptoms of RBD and 73% reporting two or more symptoms of RLS. Although the RBDSQ and the RLSQ are not diagnostic tools, these frequencies are considerably higher than the 0.5% prevalence of RBD⁴⁸ and the 7% to 10% prevalence of RLS in the general population.⁴⁹ A growing body of literature shows that individuals with RLS have substantial cognitive

Figure 4—Theoretical model of mediation of the effect of sleep disturbances on depressive symptomatology in cerebellar ataxias.



Age was included as an independent variable in all regression models. * $p < 0.01$, #trend-level p-value. Numbers represent regression coefficient, β as per conditions of a mediation model, β becomes non-significant when accounting for the mediator (in parentheses).

Figure 5—Comparison of scores on the Pittsburgh Sleep Quality Index (PSQI), the Restless Leg Syndrome Questionnaire (RLSQ), the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), the Epworth Sleepiness Scale (ESS), the Composite Cognitive Questionnaire (CCQ), the Beck Depression Inventory (BDI), the modifies International Cooperative Ataxia Rating Scale (ICARS), the Activities of Daily Living Questionnaire (ADLQ) between the “cerebellar pathology” group and the “olivopontocerebellar atrophy (OPCA)” group.



* $p < 0.01$, #trend-level p-value. Error bars represent standard deviation.

deficits compared to healthy age-matched controls.^{50,51} Likewise, our self-report data suggests that severity of sleep disturbances is closely linked with reduced cognitive functioning in cerebellar ataxia, resulting in additional deleterious effects on the patient's well-being.

Furthermore, our participants also reported having EDS; a finding that has been previously reported in various SCA subtypes.^{3,23,24} The average ESS score in our sample (8.67) was considerably higher than that reported in healthy controls (4.86),²³ and 33% had scores ≥ 10 , indicating clinical significance. This is in stark contrast from the 5% to 15% prevalence observed in the general population.⁵² The functional outcomes of EDS are a major health concern, and as indicated by our mediation analyses, may be independent of the comorbid sleep disorders. Although we did not show a correlation between EDS and depressive symptoms or reduced quality of life, we did find that daytime sleepiness was associated with reduced self-reported cognitive functioning. Clinical management of EDS in individuals with cerebellar ataxia is therefore crucial for improving daily functioning, as it may improve health-related perceptions and allow for individuals to be more independent and self-satisfied.

Consistent with the depression literature,²⁷ we found a strong correlation between depression symptoms and subjective sleep quality. However, it is necessary to consider whether sleep mediates negative affect in individuals with cerebellar ataxia; by means of mediation analysis, we found that the relationship between disease severity and depressive symptoms may perhaps be mediated by impaired subjective sleep. Although some of these associations were trending toward significance, consistent with this notion of a mediatory relationship, Franzen and Buysse showed that older adults with insomnia were more likely to develop depression at a later stage in their lives.⁵³ Likewise, Breslau and colleagues performed a large-scale longitudinal study in young adults and reported that sleep disturbances, specifically those associated with insomnia, were reliable predictors of the onset of depression.⁵⁴ Therefore, it is apparent that there is a close, perhaps causal relationship between sleep and depression in ataxia, and this requires further investigation.

We report some differences between the cerebellar ataxia subtypes with predominantly cerebellar pathology and the individuals with olivopontocerebellar atrophy with respect to certain measures, namely, RBD, RLS and cognitive function. However, we did not have statistical power to explore the interactions between the various measures within these subtype groups alone. Nevertheless, it is important to note that the involvement of brainstem components may confer additional risks for developing sleep disorders. Therefore, in future studies, a close examination of disease pathology is necessary in order to understand the underlying mechanisms leading to poor sleep, reduced cognitive function and changes in mood across cerebellar ataxia subtypes.

While the web-based survey allowed for a large population of individuals with cerebellar ataxia, the obvious limitation of this method is the inability to validate diagnoses and obtain objective measures of sleep disturbances. Additionally, subjective reports do not always correlate with objective measures, specifically in the realm of cognitive function,⁵⁵ and therefore our measures are not considered to be diagnostic or

unequivocally conclusive. Finally, our conclusions regarding mediation, while providing support for our theory that sleep disturbances mediate the relationship between disease severity and depressive symptoms, do not prove this direction of effect. Nonetheless, the results here support the need for future objective studies of sleep, cognition and affect.

In conclusion, we have provided subjective evidence for high prevalence of symptoms of sleep disorders, namely RBD and RLS, in a large sample of individuals with cerebellar ataxia. Moreover, we show that poor habitual sleep quality has a substantial impact on the quality of life. Therefore, with objective support of the present results, novel therapeutic measures that target sleep disturbances may be developed in order to improve the quality of life in individuals with cerebellar ataxia.

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