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University of Massachusetts - Amherst

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Sleep, and its relation to non-motor deficits in patients with cerebellar ataxia

A Dissertation Presented

by

AKSHATA SONNI

Submitted to the Graduate School
of the University of Massachusetts in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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Neuroscience and Behavior Program
SLEEP, AND ITS RELATION TO NON-MOTOR DEFICITS IN PATIENTS WITH CEREBELLAR ATAXIA

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AKSHATA SONNI

Approved as to style and content by:

______________________________
Rebecca Spencer, Chair

______________________________
Eric Bittman, Member

______________________________
Julia Choi, Member

______________________________
Jeremy Schmahmann, Member

______________________________
Rebecca Spencer, Graduate Program Director
Neuroscience and Behavior Program

______________________________
John Lopes, Interim Director
Interdepartmental Programs in the Life Sciences, CNS
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To my mom: you were, and are, with me all the time.
ABSTRACT
SLEEP, AND ITS RELATION TO NON-MOTOR DEFICITS IN PATIENTS WITH CEREBELLAR ATAXIA
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AKSHATA SONNI, B.S., UNIVERSITY OF MASSACHUSETTS AMHERST
M.S., UNIVERSITY OF MASSACHUSETTS
Ph.D., UNIVERSITY OF MASSACHUSETTS AMHERST
Directed by: Professor Rebecca M.C. Spencer

The cerebellum is a highly-connected structure, and its involvement in sleep – which is a dynamic process that is modulated by a complex set of neural systems – can come about through a number of neural pathways. We conducted two studies aimed at furthering our understanding of cerebellar involvement in sleep behavior and physiology, as well as measuring the impact of poor sleep on mood and cognition in patients with cerebellar degeneration. First, by means of an online battery including measures of sleep and neuropsychiatric function, we collected data from 176 patients with cerebellar ataxia. We found strong evidence of poor subjective sleep quality, symptoms of movement-related sleep disorders, and excessive daytime sleepiness in this sample. Importantly, poor subjective sleep was associated with both diminished perceptions of cognitive abilities and depression symptomatology. Second, in order to determine whether the benefit of sleep on declarative associative learning, previously observed in healthy controls, was affected by cerebellar degeneration, we compared overnight changes in performance on a word-pair association task between patients with pure cerebellar syndrome and matched-controls. By means of polysomnography recordings, we demonstrated significantly greater fragmentation of sleep and periodic limb movement indices in patients relative to controls. Although patients demonstrated impaired learning of the word-pair association task – which was significantly
correlated with sleep fragmentation – there were no differences between patients and controls with respect to overnight change in accuracy on the word-pair task. Taken together, these findings suggest that inefficient sleep and the presence of sleep disorders in patients with cerebellar ataxia might exacerbate deficits in certain non-motor domains, while other processes – namely those associated with sleep-dependent declarative memory consolidation – remain intact.
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CHAPTER I
GENERAL INTRODUCTION

Luigi Rolando and Marie-Jean-Pierre Flourens were the first to describe the cerebellum as a motor structure that coordinates the timing and execution of movements (Rolando, 1809; Flourens, 1858). Stemming from their work, clinicians described cerebellar disease as an amalgamation of motor deficits, such as incoordination of gait (ataxia) and movements of the extremities (dysmetria), difficulty producing speech (dysarthria), oculomotor symptoms (such as nystagmus), difficulty swallowing (dysphagia), and intention tremors (Fines, Ionita & Lohr, 2002; Manto, 2008). Consequently, a compromised cerebellum – as a result of trauma, exposure to toxins, or inherited genetic mutations – results in debilitating movement disorders known as “cerebellar ataxias” (Diener and Dichgans, 1992).

The first gene mutation associated with a progressive form of cerebellar ataxia was identified almost two centuries after Rolando and Flourens’ classification of cerebellar function (Palau & Espinós, 2006). Today, a number of gene mutations have been identified, and the genetic subtypes are classified based on the mode of inheritance of the associated polymorphisms: autosomal dominant genetic ataxias, or spinocerebellar ataxias (SCA); or autosomal recessive cerebellar ataxias (ARCA), including Friedrich’s ataxia and ataxia-telangiectasia.

The genetic subtypes of cerebellar ataxia are vastly heterogeneous in pathology (Schmahmann & Sherman, 1998). As a result, cerebellar ataxias have been further dichotomized based on the pattern of atrophy observed (Schöls et al., 2004; Manto, 2005): 1) “pure cerebellar syndrome” is characterized by cerebellar atrophy alone, while 2) “cerebellar plus syndrome” presents with extracerebellar pathology – namely degeneration of the brainstem, spinal cord,
thalamus, basal ganglia and cerebral cortex - in addition to damage to the cerebellum itself. In the case of the latter, widespread pathology results in non-motor deficits, such as sleep dysfunction, neuropathy, parkinsonism and dementia.

The hereditary forms of cerebellar ataxia affect 1-4 individuals per 100,000 (Dang and Cunnington, 2010), varying in prevalence based on subtype, race, and geographic location (van de Warrenburg et al., 2002). Due to decreased mobility, difficulty communicating, and inability to perform everyday functions independently, those affected by cerebellar ataxias have significant disabilities and reduced quality of life (Abele and Klockgether, 2007). However, clinical and anatomical observations of patients with cerebellar ataxia suggest that the cerebellum might be involved in modulating higher order cognitive functions (Schmahmann, 1991); specifically, poor health-related outcomes are not only a consequence of the debilitating motor deficits associated with cerebellar disease, but also of co-morbid cognitive impairments (Schmahmann, 1991) and affective disorders (Schmahmann, 1996, 1997). Specifically, patients with cerebellar degeneration have difficulty forming concepts, display generalized intellectual slowing (Kish et al., 1988; Bracke-Tolkmitt et al., 1989), and show attenuated learning curves and increased planning times on cognitive tasks (Grafman et al., 1992; Fiez et al., 1992). In addition, personality changes (Pollack et al., 1995), labile emotional states, and uncharacteristic blunting or heightening of affect (Levisohn et al., 1997) have also been observed in cerebellar ataxias. The cognitive deficits, coupled with mood swings, result in reduced productivity (Tavano et al., 2007), poor health-related perceptions (Schmahmann, 1996, 1997), and low self-sufficiency (Schmahmann, 2004) in this population. Indeed, Schmahmann and Sherman (1998) defined a new clinical entity in order to describe the constellation of deficits associated with
cerebellar ataxia as the “cerebellar cognitive affective syndrome,” now known as the
“Schmahmann Syndrome.”

Sleep is a dynamic physiological state that benefits numerous functions within the
physical (Belloc and Breslow, 1972), cognitive (Walker and Stickgold, 2006), and mental health
domains (Walker, 2009), and consequently, poor sleep has detrimental effects on daytime
functioning (Ramsawh et al., 2009). For instance, low sleep efficiency – or the amount of time
spent asleep relative to time in bed – and inadequate total nocturnal sleep time in adults, are
robustly associated with daytime fatigue and difficulty concentrating on everyday tasks (Alapin
et al., 2000). Furthermore, psychological maladjustment and dysphoria, marked by feelings of
dissatisfaction and anxiety, are heightened in poor, relative to good, sleepers (Broman, Lundh,
and Hetta, 1996). Therefore, it is important to examine the quality of sleep in patients with
cerebellar ataxia, for whom reduced quality of life might be associated, in part, by impaired
sleep.

The relationship between sleep and mood is complex, and even inextricable in some
cases. Mosko and colleagues (1989) reported strong comorbidity between disordered sleep and
major affective disorders, and importantly, observed an improvement in mood following
treatment of the associated sleep disorder. Furthermore, Rosenström and colleagues (2013) used
causality algorithms to demonstrate that sleep problems are more likely to cause dysphoria, than
the reverse. This bi-directional association between sleep quality and health-related outcomes has
particular relevance in clinical populations such as cerebellar ataxia, where quality of life may be
improved by means of targeted sleep interventions.

In addition to its effects on mental health, sleep plays a crucial role in cognitive
processes, such as attention, learning, and memory (Walker and Stickgold, 2006). Performance
on sustained attention tasks, such as the Psychomotor Vigilance Task, is particularly sensitive to sleep loss (Doran, van Dongen and Dinges, 2001), as well as poor habitual sleep quality (Altena et al., 2008). Likewise, sleep loss reduces the capacity to acquire new information (Yoo et al., 2007), while sleep interventions, such as the introduction of a mid-day nap, result in boosting learning (Mander et al., 2011). Furthermore, 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 (Walker and Stickgold, 2006). Specifically, performance on declarative (Gais, Lucas and Born, 2006; Wilson et al., 2012; Sonni and Spencer, 2015) and procedural (Mantua, Baran, and Spencer, 2015; Walker et al., 2002; Wilson et al., 2012) tasks are significantly superior following an interval of sleep relative to an equivalent interval spent awake in healthy adults. Conversely, this cognitive benefit of sleep is markedly reduced, and in some cases absent, in individuals suffering from chronic sleep loss or sleep-related disorders (Bakhaus et al., 2006; Cipolli, Mazzetti and Plazzi, 2013; Kloepfer et al., 2009).

The consequences of poor sleep are numerous, and have significant implications for disease management across a number of neurological conditions. In the case of cerebellar ataxias wherein quality of life is markedly reduced, efforts to improve sleep might result in improving self-sufficiency and general well-being.

A. Evidence of Poor Sleep in Cerebellar Ataxias

Sleep is a heterogeneous state, consisting of four stages, each distinct in its architecture, distribution and function (Iber et al., 2007). The transition between wakefulness - which is associated with beta (12-30 Hz) and gamma (25-100 Hz) frequency bands - and sleep, is marked by the appearance of alpha (8-13 Hz) during restful wake, and then into theta waves (4-7 Hz), indicating a gradual shift into non-rapid eye movement (NREM) stage 1 (N1). Although theta
activity continues into NREM stage 2 (N2), the appearance of K-complexes - a sharp negative peak followed by a positive peak - distinguish N2 from the other NREM stages. In addition, N2 also marks the appearance of high frequency thalamocortical oscillations (sleep spindles; 11-16 Hz). The deepest stage of sleep, NREM stage 3 (N3), is marked by the appearance of low frequency delta waves (0.5-4 Hz), thus giving it the name “slow-wave sleep” (SWS; Rechtschaffen & Kales, 1968). Sleep spindles persist in SWS, occurring periodically against the background delta activity. Finally, REM sleep is paradoxically associated with muscle atonia alongside wake-like EEG components, including alpha, beta and theta waves (Iber et al., 2007).

The distribution and architectural properties of each sleep stage change progressively within a sleep bout, as they are sensitive to the homeostatic drive for sleep (Borbély, 1981; Borbély, 1982), body temperature (Czeisler et al., 1980), and environmental factors.

The last few decades have marked an increase in the number of studies exploring sleep disturbances in cerebellar ataxias. Of these, the majority has focused on the cerebellar plus syndrome, revealing sleep disturbances to be a significant issue in this population (Boesch et al., 2006a; Chi et al., 2013; Schöls et al., 1998; Abele et al., 2001; Dang & Cunnington, 2010). The cerebellar plus syndrome include the subtypes SCA type 1 (SCA1), SCA2, SCA3, SCA7, SCA13 and SCA30 (Schöls et al., 2004). Investigations of sleep quality and behavior however, have concentrated on SCA1, SCA2 and SCA3 – which are the more commonly occurring subtypes - and have revealed greater frequency and severity of sleep disorders compared to healthy controls (Pedroso et al., 2011a). In particular, three major classes of sleep disorders have been identified in patients with cerebellar ataxia: movement-related sleep disorders, sleep-disordered breathing, and excessive daytime somnolence.
Two major, often comorbid, movement-related sleep disorders are periodic limb movement disorder (PLMD) and restless leg syndrome (RLS). PLMD is characterized by episodes of repetitive muscle movements during sleep, such as jerking movements of the limbs or muscle twitches, occurring every 20-40 seconds (Kaplan et al., 1993). It has been reported to be more frequent in patients with SCA2 compared to healthy age-matched controls (Velázquez-Pérez et al., 2011; Tuin et al., 2006; Boesch et al., 2006). RLS is characterized by the uncomfortable, insatiable urge to move the body (Earley, 2003), and Abele and colleagues (2001) found the prevalence and severity of RLS in patients with SCA1, SCA2 and SCA3 to be significantly greater compared to healthy controls. Owing to the role of dopaminergic dysfunction in PLMD and RLS pathophysiology (Ruottinen et al., 2000), the increased frequency of these sleep disorders has been attributed to the varying degrees of striatal degeneration observed in SCA1, SCA2 and SCA3 (Schöls et al., 2004).

In addition to increased risk of sleep disorders such as PLMD and RBD, sleep physiology is also altered in cerebellar plus syndrome: for instance, percent REM was reduced in patients with SCA3 compared to healthy controls, and was negatively correlated with disease severity (Chi et al., 2013). Abnormal motor activity during REM sleep has also been reported in patients with SCA2 (Boesch et al., 2006a; Tuin et al., 2006), SCA3 (Friedman et al., 2003; Pedroso et al., 2011b), and SCA6 (Boesch et al., 2006), reflective of REM sleep behavior disorder (RBD), wherein postural tonus is abnormally maintained during REM sleep (Gugger & Wagner, 2007). These adverse effects on REM sleep physiology in patients with cerebellar ataxia have been linked to dysfunction in the brainstem regulatory pathways that are closely associated with initiating and maintaining REM sleep physiology.
In addition to movement-related sleep disorders, symptoms of sleep-disordered breathing have also been reported in patients with SCA3 (D’Abreu et al., 2010) and SCA6 (Boesch et al., 2006). Sleep-disordered breathing – particularly obstructive sleep apnea (OSA) – which is associated with marked reductions in sleep quality (Punjabi, 2008), is also often accompanied by excessive daytime sleepiness (EDS), defined as the increased propensity to fall asleep (Pagel, 2009). Indeed, greater EDS has been reported in patients with SCA1 (Dang and Cunnington, 2010), as well as SCA6 (Howell, Mahowald and Gomez 2006) compared to healthy controls.

Patients with cerebellar ataxia suffer from damage to neural regions that influence a number of motor and non-motor pathways during sleep and wake. Loss of integrity in these brain regions can produce detriments in a number of physiological domains, including those related to sleep. The characteristic features of each sleep stage are particularly sensitive to immune function, physical and mental fatigue (Spiegel, Lepout and Cauter, 1999; Bryant, Trinder and Curtis, 2004), age (Pace-Schott and Spencer, 2011), and neurological disorders (Raggi & Ferri, 2010). In addition to its restorative properties, sleep is a period of considerable neural processing across various functional domains, and thus sleep disturbances have large implications on health-related outcomes.

B. The Functional Significance of Poor Sleep

Sleep disorders diminish the benefits of sleep on physical, mental, and cognitive health. Owing to these tangible effects of disordered sleep on daytime functioning, individuals often seek consultation with primary care physicians in relation to the downstream effects of poor sleep (Penzel et al., 2007). However, the detection and subsequent treatment of the underlying sleep disorders are limited to severe cases of sleep dysfunction (Kapur et al., 2002); as a result, sleep disorders are still under-diagnosed or even misdiagnosed in the general population, and are to an
even larger extent in patients with neurological disorders that are associated with a spectrum of symptoms (Raggi and Ferri, 2010).

Allen and colleagues (2005) conducted a large-scale, multi-national study of the impact of RLS on quality of life in the general population using a self-reported survey (SF-36) that assessed eight health-related domains (Walters et al., 1995): vitality, health-related perceptions, bodily pain, general physical functioning, mental health, and physical role, emotional role and social role functioning. Compared to healthy individuals, those with RLS scored significantly lower on all eight domains (Allen et al., 2005). In fact, the reduced quality of life reported by individuals with RLS was similar to that of patients with chronic diseases, such as diabetes, rheumatoid arthritis and osteoarthritis. Major affective disorders are also common among individuals suffering from RLS and PLMD, and poor affect may be mediated by diminished functioning within other health-related domains (Picchietti and Winkelman, 2005). Anti-depressant medications in turn exacerbate the symptoms of PLMD, thus perpetuating a vicious cycle that has a significant impact on quality of life.

REM sleep behavior disorder (RBD) is frequent among patients with neurodegenerative disorders, particularly Parkinson’s disease (Raggi and Ferri, 2010). In many cases, RBD precedes the onset of symptoms associated with Parkinson’s disease, and is therefore considered a clinical marker of neurodegeneration (Boeve et al., 2003; Raggi and Ferri, 2010). Patients with Parkinson’s disease and concomitant RBD report greater problems with motility, performing self-care activities, pain, anxiety, and depression compared to those without RBD (Hu et al., 2014). Youn and colleagues (2015) conducted a longitudinal study examining the relationship between RBD and cognitive function in individuals with no evidence of neurodegeneration, and reported progressive impairments across three cognitive domains over the course of 6 years in
the study: executive function, memory, and visuospatial abilities. Therefore, RBD significantly impacts health-related quality of life, and may underlie the development of cognitive impairments.

Sleep-disordered breathing is the most common sleep disorder in the general population, with prevalence increasing with age (Young et al., 1993). The frequent apneic and hypopneic events associated with sleep-disordered breathing result in increased arousals during sleep, greater sleep fragmentation, and reduced sleep efficiency (Morrell et al., 2000). These negative effects on sleep physiology cause reduced daytime functioning as measured by the SF-36 in individuals with OSA (Goncalves et al., 2004). In addition, the subscale of the SF-36 that measures “vitality” is particularly affected by OSA, and is associated with a number of functional limitations, such as the ability to succeed at work and to engage in recreational activities (Moyer et al., 2001). Individuals with sleep-disordered breathing also often report scores on self-rated depression scales that are indicative of mood disorders (Akashiba et al., 2002). Importantly, treatment of sleep-disordered breathing using Continuous Positive Airway Pressure (CPAP) has been found to significantly improve on quality of life, measures of which become more aligned with the general population (Moyer et al., 2001).

EDS has been recognized as a major health concern owing to its detrimental effects on numerous functional domains (El-Ad and Korczyn, 1998). Perhaps the most dangerous effect of EDS on daytime functioning is reduced vigilance, resulting in injuries and motor vehicle accidents (Young et al., 1997). However, EDS also impacts various cognitive domains – such as attention, learning, and memory – as well as mood and health-related perceptions (El-Ad and Korczyn, 1998). Approximately 20% of adults in the United States report excessive sleepiness to be the cause of reduced productivity and quality of life (Pagel, 2009). This statistic is
significantly higher in neurodegenerative populations (Raggi and Ferri, 2010), thus increasing disease burden and reducing quality-adjusted life years (Vergel and Sculpher, 2008).

The relationship between sleep, learning and memory has been investigated extensively over the past few decades. Numerous studies have provided inconvertible evidence to show that memory consolidation – or the process by which newly acquired memories are strengthened, stabilized and committed to long-term neocortical stores – occurs maximally over sleep (Walker and Stickgold, 2006; Diekelmann and Born, 2010). Specifically, these studies have demonstrated that memory for previously learned information is significantly greater following a period of sleep relative to wake. Therefore, given these cognitive benefits of sleep, disruptions to the neurophysiological processes occurring during sleep can have a profound impact on learning and memory.

Poor sleep inarguably affects numerous aspects of daily functioning. The goal of this thesis, therefore, is to not only determine the nature of sleep dysfunction associated with cerebellar ataxias, but to provide – for the first time – the impact of poor sleep on cognitive and affective domains in this population.

C. Aims and Hypotheses

Health-related quality of life is determined by cognitive well-being, mental health, self-perceptions of daytime functioning, and self-sufficiency (Guyatt, Feeny, and Patrick, 1993). The severe motor deficits associated with cerebellar ataxia significantly diminish quality of life, and limit the level of independence an individual can have in their day-to-day activities. Prior to the current studies, the contribution of poor sleep mood and cognition in this population has never before been examined, thus furthering our understanding of the spectrum of non-motor symptoms associated with cerebellar ataxias.
Aim 1: To measure the relationship between self-reported motor and non-motor deficits associated with cerebellar ataxia, and to determine the contribution of poor sleep to non-motor symptomatology in a large sample of patients with cerebellar ataxia.

Aim 1 Hypothesis: Taking into consideration the impact of poor sleep on cognition and mood, the severity of deficits in these non-motor domains in patients with cerebellar ataxia is closely related to sleep quality and the presence of sleep disorders, and are not merely a consequence of reduced functioning in the motor domain.

Aim 2: To determine whether the cognitive benefits of sleep on memory are reduced as a result of cerebellar degeneration.

Aim 2 Hypothesis: Taking into consideration animal studies that have demonstrated cerebellar connectivity with brain regions involved in sleep physiology, sleep will be disrupted in patients with pure cerebellar syndrome – without extracerebellar pathology – negatively impacting daytime cognitive function and sleep-dependent memory processing.
CHAPTER II

THE EFFECTS OF SLEEP DYSFUNCTION ON COGNITION, AFFECT, AND QUALITY OF LIFE IN INDIVIDUALS WITH CEREBELLAR ATAXIA

Sleep disturbances are a common complaint among patients with neurodegenerative disorders (Raggi & Ferri, 2010), and consequently, interventions, medications and therapies targeted at improving sleep represent an important approach to disease management. Research in this area has primarily focused on synucleinopathies such as Parkinson’s disease, Multiple Systems Atrophy, Alzheimer’s disease and Dementia with Lewy Bodies. The goal of this study was to gather evidence of sleep dysfunction across a large sample of patients with cerebellar ataxia, including the pure cerebellar and cerebellar plus syndromes. Additionally, the diverse sample allowed us to compare sleep quality across the two cerebellar syndromes, which differ with respect to pathology and health-related outcomes. Furthermore, in order to determine the impact of poor sleep on cognition and mood, the relationship between sleep, cognitive function, and symptoms of depression and anxiety were assessed. Therefore, this study provided valuable insight into the consequences of poor sleep in patients with cerebellar ataxia.

A. Title page of published manuscript:

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

Akshata Sonni¹ B.S.; Lauri B. F. Kurdziel¹ M.S.; Bengi Baran² M.S.; Rebecca M. C. Spencer¹,² Ph.D.

¹Neuroscience and Behavior, University of Massachusetts, Amherst MA; ²Department of Psychology, University of Massachusetts, Amherst MA

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Short title: Sleep, cognition and affect in cerebellar ataxia
B. Abstract

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.

**Key Words:** sleep, cognition, affect, ataxia, cerebellum

**C. Introduction**

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. 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. 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. The most prevalent among these sleep disturbances are RBD, RLS, periodic leg movement disorder, excessive daytime sleepiness (EDS), insomnia, and obstructive sleep apnea.

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. Likewise, the cyclic motor activities
associated with breathing require sound cerebellar function.\textsuperscript{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.\textsuperscript{9} Additionally, many forms of ataxia have extracerebellar pathology, particularly in the brainstem,\textsuperscript{7,8} and therefore, in addition to pathways involving cerebellar involvement, brainstem degeneration may also lead to negative 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16} These sleep-dependent processes are not only important for memory consolidation, but also for providing insight into hidden rules,\textsuperscript{17,18} and for decision making.\textsuperscript{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.\textsuperscript{20-24}

We have also demonstrated that emotional reactivity is maintained by sleep.\textsuperscript{25} This role of sleep in emotional processing may contribute to mood regulation. Mosko and colleagues\textsuperscript{26}
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 and depression.\textsuperscript{12,13} Although the association between sleep and depression has been observed and reported in various populations,\textsuperscript{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.

D. Methods

1. 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.

2. 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.

3. Measures

a. Modified International Cooperative Ataxia Rating Scale

Disease severity was measured by means of a modified International Cooperative Ataxia Rating Scale (ICARS). 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 $\alpha = 0.97$). 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 ocular function.

**b. 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, 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.

**c. Epworth Sleepiness Scale**

The Epworth Sleepiness Scale (ESS) is a short questionnaire used to measure daytime sleepiness. The ESS is a reliable instrument (Cronbach $\alpha = 0.88$) and has high sensitivity (93.5%) and specificity (100%). ESS scores ≥10 are indicative of abnormal somnolence relative to the average person.

**d. 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. 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.
**e. 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%).

**f. 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), which has been determined to have adequate internal consistency and validity, and 5 additional questions from the Information Questionnaire on Cognitive Decline in the Elderly (IQCODE), 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.

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

**h. 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. The original ADLQ has high reproducibility (Lin concordance coefficient = 0.86) and a strong positive correlation with other measures of ability to live independently. 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.

**4. 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.

**5. Data Analysis**

BDI scores were divided into 3 categories as described by Robinson and Kelley: 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. 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, and these components were summed to provide a global PSQI score; global PSQI scores $\geq 5$ 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 Kenny\textsuperscript{45} 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 Kenny\textsuperscript{45} approach to mediation analyses describes a mediator as a variable that is not only independently associated with both the 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.\textsuperscript{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.\textsuperscript{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 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.

\textbf{E. Results}

\textbf{1. 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.

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.

2. 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; Fig. 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; Fig. 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 =
No significant correlation was found between disease severity and RLSQ scores (n = 83; r = 0.164; p = 0.146).

3. 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).

4. 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).

5. 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 ρ = 0.589, p < 0.001; Fig. 1).

6. 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; Fig. 2A) and the CCQ (t_{92} = −3.900, p < 0.001). Using the 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; Fig. 2B) and CCQ (trend level; t_{52} = −2.415, p = 0.018; Fig. 2B).

ESS scores were significantly correlated with cognitive impairment measured by the CCQ (α = 0.01, n = 83; r = 0.385, p < 0.001; Fig. 3) and RBD severity (α = 0.01, n = 90;
Pearson $r = 0.426$, $p < 0.001$; Fig. 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.

7. Cerebellar Pathology vs. Olivopontocerebellar Atrophy

As Figure 5 illustrates, using an $\alpha$ 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 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 RBSQ (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.

F. 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 RBD\(^{48}\) and the 7% to 10% prevalence of RLS in the general population.\(^{49}\) A growing body of literature shows that individuals with RLS have significant cognitive 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. The average ESS score in our sample (8.67) was considerably higher than that reported in healthy controls (4.86), and 33% had scores ≥10, indicating clinical significance. This is in stark contrast from the 5% to 15% prevalence observed in the general population. 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, 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. 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. 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, 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 significant 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.

Acknowledgements
This work was funded in part by NIH R01 AG040133. We extend our appreciation to the National Ataxia Foundation for facilitating the distribution of advertisements.
G. Figures

**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 Behavior Disorder Questionnaire (RBDSQ; n = 45).
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.
Figure 3. The relationship between scores on the Epworth Sleepiness Scale (ESS) and those on the REM Behavior Disorder Questionnaire (RBDSQ; n = 57), as well as on the Composite Cognitive Questionnaire (CCQ; n = 93).
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 Behavior Disorder Questionnaire (RBDSQ), the Epworth Sleepiness Scale (ESS), the Composite Cognitive Questionnaire (CCQ), the Beck Depression Inventory (BDI), the modified 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.
## H. Tables

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

<table>
<thead>
<tr>
<th>Sample Characteristic</th>
<th>%</th>
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<tbody>
<tr>
<td><strong>Ataxia Subtype</strong></td>
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<tr>
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<td>Friedrich's Ataxia</td>
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<tr>
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<td>Left</td>
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<td>Right</td>
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<tr>
<td>Not reported</td>
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<td>Did not complete High School</td>
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<td>Completed High School/GED</td>
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<td>Other Professional Schools</td>
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<tr>
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<tr>
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<tr>
<td>Not reported</td>
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Table 2. Summary of neuropsychiatric instruments used and response rate

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<th>Measure</th>
<th>Number of Questions</th>
<th>Response Rate (%)</th>
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<tr>
<td><strong>Disease Severity Assessments</strong></td>
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<tr>
<td>Modified International Cooperative Ataxia Rating Scale (ICARS)</td>
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<tr>
<td><strong>Daily Living Assessments</strong></td>
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<tr>
<td>Activities of Daily Living Questionnaire (ADLQ)</td>
<td>8</td>
<td>81</td>
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<tr>
<td><strong>Sleep Assessments</strong></td>
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<tr>
<td>Pittsburgh Sleep Quality Index (PSQI)</td>
<td>17</td>
<td>56</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale (ESS)</td>
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<td>62</td>
</tr>
<tr>
<td>Restless Leg Syndrome Questionnaire (RLSQ)</td>
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<td>63</td>
</tr>
<tr>
<td>REM Behavior Disorder Screening (RBD-S)</td>
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<td>40</td>
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<tr>
<td><strong>Cognitive Assessments</strong></td>
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<td></td>
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<tr>
<td>Composite Cognitive Questionnaire (CCQ)</td>
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<td>84</td>
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<tr>
<td><strong>Affect Assessments</strong></td>
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<td></td>
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<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>21</td>
<td>84</td>
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Number of respondents varied for each sample characteristic, as participants chose to leave certain fields blank.
Table 3. Average ICARS scores by subscale

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<th>SD</th>
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<tr>
<td>Kinetic Functions</td>
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<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Speech</td>
<td>2</td>
<td>0-5</td>
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<td>1.3</td>
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<tr>
<td>Oculomotor Functions</td>
<td>1</td>
<td>0-1</td>
<td>0.6</td>
<td>0.5</td>
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I. References


CHAPTER III

SLEEP PHYSIOLOGY, SLEEP DISORDERS, AND SLEEP-DEPENDENT MEMORY

CONSOLIDATION IN PATIENTS WITH PURE CEREBELLAR SYNDROME

A. Introduction

The cerebellar plus syndromes are associated with damage to the brainstem, basal ganglia and cerebral cortex – however, the impact of cerebellar damage alone on sleep remains principally unexplored. An evaluation of sleep quality in the pure cerebellar syndromes is limited, with only two investigations of sleep in SCA6 (Howell, Mahowald and Gomez, 2009; Boesch et al., 2006b).

Howell, Mahowald and Gomez (2006) examined subjective measures of daytime somnolence and sleep quality in 25 individuals diagnosed with SCA6, and compared them with healthy age-matched controls. Self-reports of both, daytime somnolence and habitual sleep quality, were significantly greater in the SCA6 group compared to their healthy counterparts. Given these findings, the authors stressed the importance of considering the cerebellum’s role in sleep behavior and hypothesize that poor subjective sleep quality might even be driven by underlying sleep disorders associated with cerebellar damage. Indeed, there are a number of ways in which cerebellar damage alone could result in the disrupted sleep, particularly with relation to the three major classes of sleep disorders observed in the cerebellar plus syndromes – namely movement-related sleep disorders, sleep-disordered breathing, and excessive daytime sleepiness.

The basal ganglia and the cerebellum work in concert to produce motor behaviors (Middleton and Strick, 2000), and therefore damage to either system can lead to movement-related sleep disorders. Specifically, the basal ganglia and the cerebellum send signals to, and
receive afferents from, the primary motor cortex in order to coordinate motor behaviors (Kornhuber, 1974). The cerebellar and basal ganglia circuits were thought to operate independently (Percheron et al., 1996); more recently however, a pathway by which the cerebellum directly influences striatal function has been labeled in rats (Ichinohe, Mori, and Shomoura, 2000) and in non-human primates (Hoshi et al., 2005). Loss of cerebellar integrity therefore, could perhaps produce symptoms of movement-related sleep disorders owing to the intimate involvement of the cerebellum in multiple motor circuits, despite the lack of direct striatal or cerebral involvement. In line with this, two studies have demonstrated RLS during sleep in patients with pure cerebellar syndrome (Schöls et al., 2004; Boesch et al., 2006b). Additionally, frequent PLMs have been observed in patients with SCA6 (Boesch et al., 2006b) – a pure cerebellar syndrome not associated with extracerebellar pathology.

Cerebellar degeneration, and the subsequent loss of functional connections between the cerebellum and the brainstem, might negatively impact numerous aspects of REM sleep behavior. The markers of REM sleep – theta waves, rapid eye movements, and muscle atonia – are regulated by two independent excitatory pathways arising from the “REM-ON” region located in the midbrain (Fuller, Saper & Lu, 2007; Hishikawa & Shimizu, 1995): the first involves activation of nuclei within the basal forebrain to regulate electrophysiological aspects of REM sleep, while the second projects to the ventromedial medulla to induce muscle atonia. Afferents from the cerebellum, particularly the fastigial nuclei, directly influence activity within these REM-ON nuclei (Kiernan, 2009; Fuller, Saper and Lu, 2007), which are consequently sensitive to cerebellar degeneration. Indeed, abnormal motor activity during REM sleep has also been reported in patients with SCA6 (Boesch et al., 2006b), reflective of REM sleep behavior.
disorder (RBD), suggesting either a direct or indirect involvement of cerebellum in REM sleep pathology.

The cerebellum is also involved in the regulation of crucial autonomic functions (Macey et al., 2002). Of particular importance with relation to sleep behavior, is the cerebellum’s role in the anatomical and physiological aspects of respiration. Under-stimulation or over-stimulation of the deep cerebellar nuclei – which communicate with the brainstem respiratory centers – might result in an increased risk for sleep apnea (Martin & Booker, 1878; Kiernan, 2009). There is some evidence to show that the cerebellum controls the muscles of the upper airways involved in the mechanical aspects of breathing (Macey et al., 2008). Consequently, cerebellar degeneration might impact the control of muscles of the pharynx, leading to the apneic and hypopneic events associated with obstructive sleep apnea (OSA). Symptoms of sleep-disordered breathing have been reported in patients and SCA6 (Boesch et al., 2006b) might therefore come about as a consequence of respiratory dysfunction associated with cerebellar damage.

As a “well-informed” structure that receives cross-modal information regarding the internal and external status of the body (Kiernan, 2009), the cerebellum may be involved in fine-tuning the wake- and sleep-promoting signals, much like it does with relation to the timing and execution of motor movements. Cunchillos and de Andrés (1982) quantified the amount of time spent awake, drowsy, in SWS, and in REM sleep in cerebellectomized cats. They reported that, compared to intact animals, the cerebellectomized cats spent significantly less time awake and in SWS, and greater time in REM sleep and in a state of drowsiness.

Wakefulness and SWS represent physiological states that are activated by antagonistic neural pathways (Fuller, Saper & Lu, 2007): the wake-promoting reticular activating system (RAS; Magoun, 1952), and the sleep-promoting pathway originating in the ventrolateral preoptic
area (VLPO; Sherin et al., 1996; McGinty & Szymusiak, 2000) act in a mutually inhibitory manner. In contrast, REM sleep is a unique stage of sleep that it is associated with activation of one branch of the wake-promoting pathway as well as the sleep-promoting signal (VLPO-mediated pathway; Sherin et al., 1996; McGinty & Szymusiak, 2000). Cunchillos and de Andrés’ (1982) observations in cerebelloctomized cats suggest a role of the cerebellum in orchestrating these sleep stage transitions, with cerebelloctomy having two major consequences: first, the incomplete activation of the sleep pathway, resulting in increased drowsiness and reduced SWS; second, the simultaneous activation of the wake and sleep pathways, resulting in increased REM sleep. Therefore, excessive sleepiness in cerebellar ataxias may not merely be a consequence of a comorbid sleep disorder, but rather of a compromised role of the cerebellum in modulating sleep-wake states, as purported in animal models (Cunchillos and de Andrés, 1982). The role of the cerebellum in sleep-wake transitions has not been tested in humans, and requires further investigation.

To date, there has been only one polysomnographic (PSG) study in patients with pure cerebellar syndrome: Boesch and colleagues (2006b) conducted PSG in a small sample (n = 5) of individuals with SCA6. They reported periodic leg movements (PLMs) during sleep in all five patients in the study; furthermore, two out of the five patients had a PLM index indicative of a sleep disorder. Evidence of increased muscle activity during REM sleep, as well as sleep-disordered breathing, was observed in two patients as well. Therefore, as an important step in the determination of cerebellar contribution to sleep behavior, this pilot study begs for further exploration of sleep in a larger sample of individuals with pure cerebellar syndrome.

Sleep-dependent declarative memory consolidation in patients with cerebellar degeneration has never been investigated; such an examination is of particular importance as the
cognitive deficits reported in this population (Schmahmann and Sherman, 1998) may be mediated, at least in part, by poor sleep. The age of onset of the pure cerebellar syndrome subtypes, not associated with extracerebellar pathology, varies between 30 and 60 years (Schöls et al., 2004), but individuals are generally diagnosed in their later years. Therefore, an examination of sleep-dependent declarative memory consolidation in a population of diagnosed, genetically confirmed patients with a pure cerebellar syndrome involves a comparison with a healthy age-matched population, including middle-aged and older adults.

1. Sleep-Dependent Memory Processing Across the Lifespan

Sleep facilitates memory consolidation – the process by which newly acquired memories are strengthened, stabilized and committed to long-term neocortical stores (Walker and Stickgold, 2006). Sleep-dependent memory consolidation studies in young adults have demonstrated that memory for recently acquired declarative information is superior following an interval of sleep, relative to an equivalent interval spent awake. For instance, memory for related (Gais and Born, 2004) and unrelated (Wilson et al., 2012) word pairs was greater when learning was followed by overnight sleep compared to when learning was followed by an equivalent interval of daytime wake. Likewise, visuospatial memories are better recalled post-sleep than post-wake (Rasch et al., 2007; Rudoy et al., 2009; Sonni and Spencer, 2015). This benefit of sleep is not limited to overnight sleep; in fact, a mid-day nap has been demonstrated to have similar positive effects on word-pair recall and visuospatial memory (Tucker et al., 2006).

Declarative learning relies on the hippocampus (Tulving & Markowitsch, 1998), which acts as a temporary store of information and combines various features of a single event, thus providing contextual relevance (Eichenbaum, 2000). It has been proposed that consolidation of declarative memories might involve a three-stage process initiated by the hippocampus: first,
hippocampal memories are replayed in order to induce long-term potentiation (LTP) of memory traces (Kandel, 2001); second, potentiated memory traces are transferred to appropriate neocortical stores (Roediger et al., 2007); third, consolidated memories become hippocampus-independent, such that successful recall is neocortically-driven and is less reliant on hippocampal activation (Takashima et al., 2006).

During sleep, the transfer of hippocampal-dependent declarative memories to neocortical stores is facilitated by a number of electrophysiological events. Memory traces in the hippocampus are reactivated, such that greater hippocampal reactivation is associated with larger performance benefits post-sleep (Peigneux et al., 2004). Widespread cortical slow oscillations during SWS orchestrate temporal synchrony between hippocampal “sharp-wave ripples” and thalamocortical spindles, thus acting as a physiological mediator for the hippocampal-neocortical dialogue that underlies declarative memory consolidation (Buzsáki, 1996; Siapas & Wilson, 1998). In addition, hippocampal theta rhythms that occur during REM sleep induce LTP of these recently acquired memories (Cantero et al., 2003).

The stabilization of declarative memories during sleep is a dynamic process that relies on more than one aspect of sleep physiology. However, aging is associated with structural and functional changes in the brain regions responsible for generating the necessary EEG waveforms for memory processing (Pace-Schott and Spencer, 2011), and consequently, the relationship between sleep and declarative memory consolidation changes with age.

Healthy aging is associated with marked changes in sleep physiology, the most notable of which are the reduction in time spent in SWS (Ancoli-Israel, 2008), and the reduction in spectral power density of SWS (Sonni and Spencer, 2015). However, despite these alterations in SWS physiology – a stage of sleep closely associated with declarative memory consolidation in young
adults (Rasch, Gais and Born, 2007; Marshall et al., 2006; Peigneux et al., 2004; Plihal and Born, 1997; Sonni and Spencer, 2015) – sleep-dependent consolidation of autobiographical memories (Aly and Moskovitch, 2010) and memories for unrelated word-pairs (Wilson et al., 2012) appears to be preserved in older adults. Given the lack of sleep-dependent gains on procedural tasks in older adults (Spencer et al., 2006; Wilson et al., 2012), the preserved benefit of sleep on declarative learning in aging has been suggested to reflect a passive protection of sleep from waking interference, as opposed to active memory consolidation (Wilson et al., 2012).

Active memory consolidation over sleep involves the strengthening and stabilization of the memory traces, thus rendering memories resistant to subsequent interference (Ellenbogen et al., 2006). Evidence of such active memory consolidation has been seen in young adults on a word-pair learning task (Ellenbogen et al., 2006) and on a visuospatial learning task (Diekelmann et al., 2011; Sonni and Spencer, 2015). Recently, active memory consolidation, by means of greater resistance to interference following a period of sleep relative to wake, was reported in older adults using a visuospatial task (Sonni and Spencer, 2015). Interestingly, this benefit of sleep was dependent on time spent in REM sleep early in the night – and not SWS as in the case for young adults - suggesting greater reliance on REM-dependent memory processing in aging. This shift is perhaps reflective of compensatory mechanisms for sleep-dependent declarative memory consolidation in aging, and is concurrent with a decrease in SWS, and an increase in REM sleep, early in the night. The current study aims to determine whether the presence of sleep disorders, and the changes in sleep physiology associated with cerebellar degeneration, adversely affect these sleep-related cognitive processes.

2. The Current Study
The goals of the current study were to determine whether, and to what extent, the following domains were affected by cerebellar degeneration: (1) sleep behavior, physiology and architecture, (2) cognitive function, including executive function, visuospatial abilities, learning, and memory, and (3) the cognitive benefits of sleep on declarative learning. To achieve these goals, we conducted actigraphy and physiological recordings of sleep in patients with pure cerebellar syndrome and in age-, sex-, handedness-, and education-matched controls. Participants were tested on a battery of cognitive tests, while learning and memory were additionally probed using a declarative word-pair association task. In order to determine whether sleep-dependent memory consolidation was reduced in patients relative matched-controls, we tested participants on a word-pair association task before and after a period of sleep. Finally, we examined the relationship between sleep and cognitive function in patients and matched-controls in order to determine whether benefits of sleep on cognition were reduced as a result of cerebellar degeneration.

The word-pair association task was specifically selected as a probe of sleep-dependent declarative memory consolidation for two reasons. First, word-pair learning is a robust probe of declarative memory processing that receives a benefit of overnight sleep (Plihal and Born, 1999; Ellenbogen et al., 2006; Wilson et al., 2012). Second, previous work in older adults has demonstrated a sleep benefit for the word-pair association task (Wilson et al., 2012). Sleep-dependent consolidation of visuospatial information, on the other hand, has been shown to be preserved in high-performing older adults only – those with learning curves similar to young adults (Sonni and Spencer, 2015) – and was therefore deemed inappropriate for use in a patient sample, where cognitive impairments have previously been reported.

B. Methods
1. Participants

a. Patient Group

Sixteen patients with pure cerebellar syndrome between the ages of 45 and 75 years were recruited from a patient database maintained by Dr. Jeremy Schmahmann at Massachusetts General Hospital and approved by the Partners Institutional Review Board, as well as from the patient registry maintained by Coordination of Rare Diseases at Sanford (CoRDS). Recruitment was limited to pure cerebellar syndromes, wherein atrophy is confined to the cerebellum. The following ataxia subtypes met these inclusion criteria:

1. **Spinocerebellar ataxia type 5 (SCA5)**, is a slow progressing form of ataxia with mean age of onset in the third decade (Bürk et al., 2004; Dupré et al., 2007). SCA5 is characterized by pathogenic variants in the *SPTBN2* gene causing atrophy in the cerebellar vermis and cerebellar hemispheres.

2. **Spinocerebellar ataxia type 6 (SCA6)**, an autosomal dominant cerebellar ataxia, with mean age of onset is 43-52 years (Gomez, 1998). SCA6 is a slow progressing polyglutamine disorder, with expanded CAG repeats observed in the gene *CACNA1A*. Degeneration is limited to Purkinje cells; however, damage to the granular cell layer has also been observed (Gomez et al., 1997; Sasaki et al., 1998).

3. **Spinocerebellar ataxia type 8 (SCA8)**, is an autosomal dominant form of cerebellar ataxia, with age of onset varying from 1 to 73 years (Ayhan et al., 2001). SCA8 is a slowly progressing polyglutamine disorder that is characterized by trinucleotide repeat expansions in two overlapping genes: *AYXN8OS* and *ATXN8*. MRI and CT scans in patients with SCA8 have indicated atrophy in the cerebellar hemisphere and vermis (Day et al., 2000; Ikeda et al., 2000; Schölts et al., 2004).
4. **Spinocerebellar ataxia type 28 (SCA28)**, an autosomal dominant form of cerebellar ataxia that, unlike SCA6 and 8, has a young-adult onset, with mean age of onset at 24 (± 15) years (Brussino et al., 2011; Rossi et al., 2014). SCA28 is caused by mutations in the gene *ATP3L2*, inherited in an autosomal dominant manner and resulting in degeneration of the superior vermis (Maltecca et al., 2009). Unlike SCA6 and 8, SCA28 is not a polyglutamine disorder and is therefore, not associated predominantly by the presence of trinulceotide repeat expansions; at present, mutational hotspots within the *ATP3L2* gene have been identified, and further research is ongoing to determine the precise location and nature of the causative mutations.

5. **Autosomal recessive cerebellar ataxia type 1 (ARCA1)**, also known as *SYNE1*-related ARCA, is associated with a mean age of onset of 31 years with highest prevalence in the French-Canadian population (Dupré et al., 2007). ARCA1 is a slow progressing form of ataxia that is characterized by mutations in the *SYNE1* gene that are inherited in an autosomal recessive manner, causing diffuse cerebellar atrophy (Fogel et al., 2013).

Exclusion criteria included the presence of Dandy Walker cysts, other cerebellar developmental anomalies such as Joubert syndrome, cerebellar hypoplasia, focal intraparenchymal cerebellar pathology, or co-morbid neurological disorders such as stroke. Furthermore, individuals with severe visual impairments that were prohibitive to performing the cognitive task were excluded.

Since sleep-affecting medications introduce numerous confounds in the analysis of sleep data, patients with pure cerebellar syndromes that were on sleep-affecting medications – such as anti-depressants, benzodiazepines, stimulants and sleep aids - were requested to follow a
medication wash-out protocol prior to the experimental week. Medications were slowly and safely reduced over a recommended period of time (determined on an individual basis) leading up to the experiment. During the week prior to the experiment and during the course of the experiment, participants ceased all sleep-affecting medications.

**b. Control Group**

Sixteen healthy controls were recruited from the community, and matched to patients based on age, sex, handedness and education. Patients with pure cerebellar syndrome enrolled into the study 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 age categories. Level of education was categorized as such: twelve years of education or less (High School diploma or less), 13-16 years of education (college-level education), 17-18 years (Masters degree or similar), > 18 years (higher education). Patients and controls were matched for education based on these categories.

Participants were required to have unimpaired, or corrected vision (20/30 or less) as assessed with a standard vision chart, in order to accurately perform the cognitive tasks. In addition, healthy status was determined by means of pre-screening procedures and the following exclusion criteria were used:

1. Use of sleep-influencing medications including anti-depressants, hypnotics, narcotics, benzodiazepines or herbs such as St. John’s wort. Unlike in the case of patients with pure cerebellar syndrome, for whom symptoms of depression and anxiety are often a result of the incorporation of the cerebellum into those neural pathways engaged in emotional modulation (Schmahmann 1991, 1996) – and which are therefore inextricable from the motor deficits – control participants with symptoms of
depression or anxiety were excluded owing to the lack of information regarding their neuropsychiatric history.

2. History of neurological disease, congestive heart failure, or a myocardial infarction, or a history of stroke, head trauma, or heart surgery.

3. To accurately perform the behavior task, participants must have unimpaired, or corrected vision (20/30 or less) as assessed with a standard vision chart.

In addition to these screening procedures, 4 out of the 16 controls were recruited from the “Midlife and Older Adult Database” maintained in Dr. Rebecca Spencer’s lab (approved by the UMass IRB). These participants were additionally screened against:

4. Have known sleep-influencing medical conditions (e.g., asthma, COPD, hypertension if on 3 or more medications, BMI>30) or a sleep disorder, such as insomnia, OSA, RLS, RBD, PLMD, parasomnia, or a circadian rhythm disorder.

5. Long or short self-reported sleep (> 11 hrs or < 5.5 hrs), which are signs of a sleep disorder and, particularly high sleep quantity in an older adult, generally poor health and might reflect the presence of an underlying neurological disorder (Ancoli-Israel, 2009). For this reason, we required that participants sleep on average 5.5-11 hrs/day.

2. Measures

a. Assessments of Motor Dysfunction and Neuropsychological Function

1. Brief Ataxia Rating Scale (BARS), 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 (Schmahmann et al., 2009). 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 patient.

2. **The Cerebellar Cognitive Affective Syndrome/Schmahmann Syndrome Rating Scale (CCAS-RS)**, a battery (Hoche et al., *in press*) including neuropsychological tests and clinical rating scales that designed to detect the non-motor deficits associated with cerebellar disease, collectively described as the cerebellar cognitive affective syndrome (Schmahmann syndrome; Schmahmann and Sherman, 1998). The syndrome is characterized by deficits in executive function, linguistic processing, spatial cognition, and affect regulation. The beta version of CCAS-RS, designed to be administered by an experimenter or clinician either at bed-side or in an office, includes 10 items that assess the following domains: verbal fluency, cognitive flexibility, memory span, visuospatial function, verbal recall, abstract reasoning, inhibitory control, and affect. Hoche and colleagues (*in press*) tested the efficacy of this battery in a sample of 77 patients with cerebellar disease, and found that it was able to detect cognitive deficits that were missed when using other cognitive batteries such as the Mini-Mental State Exam (Royner and Folstein, 1987) or the Montreal Cognitive Assessment (Nasreddine et al., 2005). The CCAS-RS is therefore a powerful clinical assessment of CCAS in patients with cerebellar disease.

*b. Subjective Assessments of Sleep and Sleep Behavior*

1) **Pittsburgh Sleep Quality Index (PSQI)** to determine sleep quality over the previous 30 days (Buysse et al., 1989). The PSQI includes questions probing subjective sleep quality, sleep latency, sleep duration, sleep efficiency, disturbances during sleep, the use of sleep-affecting medications, and daytime somnolence; it has been determined to be a reliable
(Cronbach’s $\alpha=0.87$) and valid instrument for the measurement of sleep disturbances (Backhaus et al., 2002).

2) **Epworth Sleepiness Scale (ESS)**, a self-administered questionnaire that provides general level of daytime sleepiness, and their propensity to fall asleep during certain activities (Johns, 1991). The instrument has been shown to be reliable ($r = 0.82$) and have high internal consistency (Cronbach’s $\alpha=0.88$; Johns, 1992).

3) **Morningness-Eveningness Questionnaire (MEQ)**, to assess whether the participant is inherently more of a “morning person” or an “evening person” (Horne & Ostberg, 1976). This questionnaire has been demonstrated to show high levels of correlation with objective measures of individual chronotype (such as oral temperature). The test-retest reliability of the instrument is acceptable (Cronbach’s $\alpha=0.80$; Kerkhof, 1984), and has been validated in young and older adult samples (May and Hasher, 1998).

4) **Stanford Sleepiness Scale (SSS)**, 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 (Hoddes et. al., 1973). The SSS has been shown to correlate strongly with other visual analog scales that assess subjective fatigue (Lee, Hicks, and Nino-Murcia, 1991).

5) **Cambridge Hopkins Restless Leg Syndrome Questionnaire (CH-RLSq)**, a validated diagnostic questionnaire used to quantify symptoms of restless leg syndrome (RLS) present in a patient (Allen et al., 2009). The questionnaire determines which if the following diagnostic features are present: the presence of recurrent, uncomfortable feelings in the legs; worsening of discomfort at rest; temporary relief from discomfort with continuous movement; worsening of discomfort in the evening and at night; lack of
relief from discomfort as a result of simply changing leg position; discomfort that is never due to muscle cramps.

6) **A Sleep-Time Diary**, a questionnaire administered in the morning to gather information regarding bedtime, sleep duration and quality the night before.

7) **A Wake-Time Diary**, a questionnaire to assess daytime activities such as exercise, naps and caffeine or alcohol consumption over the course of the day.

c. **Objective Measures of Sleep and Sleep Behavior**

1. **Polysomnography** (PSG; Aura PSG wireless/ambulatory system, Grass Technologies, Astro-Med Inc., West Warwick, RI) was used to obtain electrophysiological recordings of sleep. Participants were tested in their home to minimize discomfort and maximize sleep quality (Doering et al., 2008). The PSG montage was applied immediately prior to the participant’s bedtime: the montage included bilateral EEG leads (F1, F2, O1, O2, C3, C4, Cz); bilateral EOG leads to record eye movements, 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.

2. **ApneaLink** (ResMed, San Diego, California) will be 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 (SaO2 < 3% is indicative of sleep apnea), and allows for automated scoring. The resulting Apnea-Hypopnea Index (AHI) has been extensively validated against PSG (Erman et al., 2007; Ng et al., 2009). Apneas are nasal-cannula airflow cessations lasting > 10 s, while hypopneas are abnormal respiratory events with at
least 30% reduction in thoraco-abdominal movement or airflow compared to baseline lasting > 10 s.

3. **Actigraphy** (AW2, MiniMitter, Bend, OR) was worn on the participant’s non-dominant wrist, providing a continuous recording of day and night-time activity levels via an embedded accelerometer, with sensitivity of <0.01 g and a sampling rate of 32 Hz. Data collected by this device is stored in 1-min epochs. Participants were instructed to wear the actigraph for 1 week, previously validated as adequate time for capturing habitual activity levels (Cochrane et al., 2012). During this time, participants maintained sleep hygiene: they were instructed to maintain a bedtime no later than 2:00 AM, abstain from alcohol or recreational drugs, and minimize caffeine intake. Participants were also given sleep and activity logs to be completed each day (to ensure accuracy of actigraphy data).

**3. Procedures**

The experiment was conducted over the course of 7 days (Figure 6). On day 1, following informed consent procedures, height and weight was recorded for all participants. Each participant was then administered the BARS and CCAS/Schmahmann Syndromme-RS. Participants were given an actigraph watch and trained on using the event marker button, to be pressed when going to bed (for a nap or overnight sleep), on awakening, and before and after taking the watch off the wrist (e.g. before and after a shower). Prior to the participant’s bedtime, they were fitted with the ApneaLink device, and were instructed to turn it off immediately following wake onset the following morning.

On the evening of day 6, participants completed the Sleep-Time Diary and the SSS before performing the word-pair association task. For the word-pair association task, participants were
introduced to 25 semantically unrelated word pairs (Wilson et al., 2012). During the “Passive Encoding” phase of the experiment, each participant was presented with 50 words that were paired together to form 25 word-pairs (e.g. cat-coach, desk-ice). Each word-pair appeared on a computer screen and remained in view for 5 seconds, before the next word-pair was presented (inter-stimulus interval was 100ms). 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 in your mind a framed painting of a shoe.”

The “Active Encoding” phase occurred immediately after the completion of the 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 pair associate 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. 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.

Following the Active Encoding phase, participants were requested to respond to questionnaires for 20 minutes (PSQI, MEQ, ESS, CH-RLSQ), after which they performed the “Immediate Recall” phase. The Immediate Recall phase 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. The order of items was again randomized for each presentation of the list.
Following behavioral testing and an hour before their habitual bedtime, the PSG montage was applied. The final session was conducted the following morning, an hour after the participant awakened (to avoid sleep inertia). Participants first reported their sleepiness (SSS) and completed the Wake-Time Diary. They then proceeded to the “Delayed Recall” phase of the word-pair task, which was identical to the Immediate Recall phase.

a. Statistical Analyses

i. Sleep Physiology and Behavior

Sleep staging was performed according to the criteria described by the American Academy of Sleep Medicine (Iber et al., 2007). EEG spectral power analysis was conducted using BrainVision Analyzer 2.0 (Brain Products, Munich, Germany). Raw data was segmented to include NREM (N2 + SWS) and REM sleep separately, and low (0.3 Hz) and high (35 Hz) pass filters were applied. Semi-automatic artifact rejection was then performed and further segmented into 4 s bins. Spectral power density (µV²/Hz) was calculated over the frontal and central derivations in the sigma (11-16 Hz), slow oscillation (0.5-1 Hz), delta (1-4 Hz) ranges during NREM sleep, and theta range (5-8 Hz) range during REM respectively; this was conducted by means of a Fast-Fourier transform analysis with a 10% Hanning window with no overlap (Marshall et al., 2006). Actigraphy data was analyzed as per de Jong and colleagues (2016), and the following measures were calculated and averaged for overnight and daytime (nap) sleep: total sleep time, sleep onset latency, sleep efficiency, total wake time, total time spent mobile. Multivariate ANOVAs with Sidak-Bonferroni correction for multiple comparisons were conducted to compare sleep measures between patients with pure cerebellar syndrome 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 (Ruehland et al., 2009). Participants were categorized into the following categories based on the AHI values: “None/Minimal” if AHI < 5 per hour, Mild: AHI ≥ 5, but < 15 per hour, Moderate: AHI ≥ 15, but < 30 per hour, and Severe: AHI ≥ 30 per hour.

An ANCOVA with group (Pure Cerebellar Syndrome vs. Controls) with BMI as a covariate was performed to compare AHI between patient and control groups. In addition, a chi-squared test was performed in order to compare the frequency of individuals in each category based on group (Patients vs. Controls).

Limb movements were recorded during sleep and scored as per Walters and colleagues (2007). 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 (RSWA). Since PLM indices and limb movement indices during REM Sleep were non-parametrically distributed in patients and matched controls, Mann-Whitney comparisons of independent samples were used to compare values between patients and controls.

**ii. Questionnaire and Cognitive Measures**

All questionnaire measures (ESS, Johns, 1991; SSS, Hoddes et al., 1973; and MEQ, Horne and Ostberg, 1976; PSQI, Buysse et al., 1989) were scored based on validated criteria and scores for patients with pure cerebellar syndrome and matched-controls were compared using independent samples $t$-tests. Scores on the PSQI were categorized into “poor sleepers” (PSQI >6) and “good sleepers” (PSQI < 7) and a chi-squared test was used to compare frequency of poor vs. good sleepers in patient and control groups.
The number of positive symptoms associated with RLS, as measured by the CH-RLSq, was calculated (with a maximum possible score of 7). A score > 3 was indicative of possible RLS, while a score of 7 indicated probable RLS (Allen et al., 2009). Patient and control groups were compared with relation to the number of individuals with possible vs. probable RLS using a chi-squared test.

Scoring of the CCAS-RS were conducted as per Hoche and colleagues (in press) and the total raw score – or the sum of the scores on each item on the test – as well as the number of failed tests were calculated for each participant. The total number of tests on the CCAS-RS is 10, while the maximum raw score possible is 120. The following categorization was applied for CCAS 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 patients and controls assigned to these 3 categories. A multivariate ANOVA with Sidak-Bonferroni correction for multiple comparison was conducted to compare patients 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 learning task was compared across groups (Patients, Control) with relation to number of loops required to reach criterion during the Active Encoding phase, as well as accuracy (number of accurately recalled word-pair associates) 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 (Patients, 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-pair associates 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.

C. Results

1. Sample Descriptives

Table 4 displays descriptive information for each patient and control. Sixteen patients (12 male, 4 female) with pure cerebellar syndrome were recruited for the study. The age of the patient sample ranged from 46 to 76 yrs, with an average age of 62.13 ± 8.08 yrs. Of the 16 patients, 14 were right-handed and 2 left-handed. The average number of years of education was 15.94 ± 2.7 yrs, and consisted of the following distribution: high school graduates (12 yrs of education; n=2), college graduates (16 yrs; n=11), and graduates with higher education degrees (16+ yrs; n=3).

The sample included the following subtypes: 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). Severity of motor dysfunction – including gait, kinetic function of the limbs, speech and oculomotor function – was assessed using the Brief Ataxia Rating Scale (BARS). Appropriate medication tapers were implemented for those patients that were taking sleep-affecting medications that could not be discontinued abruptly.

Sixteen age-, sex-, handedness-, and education-matched controls were recruited for the study (age range 45-74 yrs; average age 61.81 ± 7.9 yrs; 12 male, 4 female; 14 right-handed, 2 left-handed; average number of years of education 16.34 ± 2.19 yrs). While sex and handedness
were matched 1:1, independent samples \( t \)-tests revealed no differences between the patients and controls with respect to age (\( t(30) = 0.111, p = 0.913 \)) and level of education (\( t(30) = -0.504, p = 0.613 \)).

Among the controls, there was no reported use of sleep-affecting medications, except for two participants that stated occasional melatonin use; these two participants were requested to refrain from melatonin during the week prior to and during the course of the experiment. In addition, none of the participants had any known sleep disorders, and reported no history of stroke, brain tumor, and neurological or psychiatric conditions. All control participants displayed healthy motor function as determined by the BARS (average score 0.31 ± 0.4).

2. Questionnaires

Group means and standard deviations are displayed in Table 5. Habitual sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). Ten patients and 4 control participants reported PSQI scores indicative of poor sleep quality (scores > 7; Buysse et al., 1989). A chi-squared test comparing the number of poor and good sleepers among the patients and controls revealed that more patients reported being poor sleepers than controls (\( \chi^2 (1) = 4.571, p = 0.033 \)).

Daytime sleepiness – or the propensity to fall asleep while performing daily activities – was measured using the Epworth Sleepiness Scale (ESS). ESS scores were comparable across patients and controls (\( t(30) = 1.229, p = 0.229 \)); however, 7 patients and 4 controls reported scores on the ESS indicative of excessive daytime sleepiness (EDS; ESS score > 10; Hoddes et al., 1973).

Chronotype was determined using the Morningness-Eveningness Questionnaire (MEQ), wherein scores < 41 indicate “evening” types, scores between 42-58 “intermediate” types, and scores > 58 “morning” types (Horne and Ostberg, 1976). The control sample consisted of 9
“evening” types and 7 “morning” types, while all but 3 patients – who represented “intermediate” chronotypes – reported being “morning” types. There were however, no significant differences between groups with respect to MEQ scores ($t(30) = 0.493, p = 0.627$).

Restless Leg Syndrome (RLS) symptomatology was determined using the Cambridge-Hopkins RLS symptoms questionnaire (CH-RLSq): scores ranged from 0 to 7, and were reflective of the number of RLS symptoms reported. A score > 3 indicated possible RLS, while a score of 7 indicated probable RLS (Allen et al., 2009). An independent samples $t$-test comparing the full range of CH-RLSq scores (0 to 7) showed no significant differences between the patients and controls ($t(30) = 1.279, p = 0.211$). A chi-squared test comparing probable/possible- vs. no-RLS across patients and controls also did not reveal any differences between groups ($\chi^2 (1) = 1.247, p = 0.264$).

3. Evaluation of Cognitive Function

a. The Cerebellar Cognitive and Affective Syndrome Rating Scale (CCAS-RS)

The CCAS-RS includes assessments of cognitive function across a number of domains, as well as an evaluation of affect by the experimenter (Hoche et al., in press). Raw scores on the CCAS-RS range from 0-120, representing the full range of responses for each item on the scale: low scores were indicative of poor cognitive function. In addition, each item on the scale was given a pass/fail categorization based on response criteria, and the total number of failed tests was also calculated (up to a maximum of 10).

Means, standard deviations and $p$-values associated with CCAS-RS scores are displayed in Table 6. A MANOVA with a Sidak-Bonferroni correction for multiple comparisons was conducted in order to compare patients and controls with respect to the total raw score and the number of failed tests on the CCAS-RS. In addition, raw scores for each of the following
domains were also compared across groups: verbal fluency, cognitive flexibility, digit span, visuospatial function, verbal recall, abstract reasoning, inhibitory control, and general affect.

Although there were no differences between patients and controls with respect to the total number of failed tests on the CCAS-RS ($F(1, 22) = 0.488, p = 0.492$), the controls had significantly higher raw scores compared to patients ($F(1, 22) = 6.160, p = 0.021$), suggesting subtle impairments in cognitive function as a result of cerebellar degeneration. With regard to the sub-domains of the test, the greatest impairments in patients compared to controls were observed for verbal fluency (Figure 7a; $F(1, 22) = 7.756, p = 0.011$) and cognitive flexibility (Figure 7a; $F(1, 22) = 4.392, p = 0.048$).

A chi-squared test was conducted in order to compare the frequency of “No CCAS,” “Possible CCAS,” “Probable CCAS,” and “Definite CCAS” across patient and controls groups. There were not significant differences between the two groups with respect to these categorizations ($\chi^2 (3) = 1.676, p = 0.642$).

**b. Performance on the Word-Pair Association Task**

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

Since sleepiness at the time of testing has been shown to impact performance on cognitive tasks, especially in older adults (Ohayon and Vecchierini, 2005), self-reported sleepiness was recorded during both, the evening and the morning, sessions using the SSS.
Paired samples $t$-tests revealed that SSS scores did not differ between evening and morning sessions for either the patients ($t(12) = 0.697, p = 0.499$) or the controls ($t(12) = 0, p = 1.000$). However, the patients were significantly more sleepy compared to the controls during the morning ($t(24) = 3.354, p = 0.003$), but not evening ($t(24) = 1.732, p = 0.096$) sessions. Table 5 displays the means, SDs, and $p$-values for comparisons between patients and controls for SSS measures.

An independent samples $t$-test revealed that the number of loops required to reach criterion was comparable between patients and controls ($t(24) = 0.492, p = 0.627$). However, accuracy was significantly lower for patients compared to controls at Immediate Recall (Figure 7b; $t(24) = -2.476, p = 0.021$), as well as Delayed Recall (Figure 7b; $t(24) = -2.748, p = 0.011$). Since we were interested in looking at performance on the word-pair association task post-sleep relative to pre-sleep performance, a one-way ANOVA was used to compare groups with regard to Delayed Recall accuracy, with Immediate Recall accuracy, and pre- and post-sleep sleepiness scores (SSS) as covariates. There were no differences between patients and controls with respect to Delayed Recall accuracy when sleepiness during both, evening and morning sessions, was accounted for in addition to Immediate Recall ($F(1,23) = 0.207, p = 0.654$). Therefore, although performance on the word-pair association task was markedly impaired in patients relative to matched-controls, the effect of sleep in preserving the learned associations appeared to be similar across the two groups. Table 7 displays the means, SDs, and $p$-values associated with comparisons between patients and controls for performance measures on the word-pair association task.

4. Sleep Assessments

a. Actigraphy
Actigraphy was recorded for 7 days for each participant, and habitual sleep-wake patterns were obtained for 14 patients and 14 matched-controls (data from 2 patients were excluded due to non-compliance with the actigraphy instructions). Data for overnight sleep, as well as for nap behavior, were obtained and compared between groups. Means, standard deviations and \( p \)-values for all actigraphy measures can be found in Table 8.

The average duration of the overnight sleep bouts was comparable between patients (7.92 ± 0.89 hrs) and controls (8.07 ± 0.67 hrs; \( F(1,25) = 0.343, p = 0.563 \)). Likewise, there were no differences between groups with respect to latency to sleep onset (Patients, 3.03 ± 2.67 mins; Controls, 2.04 ± 0.95 mins; \( F(1,25) = 1.316, p = 0.262 \)). However, sleep efficiency was reduced in the patients relative to the controls at near-significance level (Patients, 90.13 ± 4.71 %; Controls, 92.71 ± 2.38 %; \( F(1,25) = 4.068, p = 0.055 \)); this was due to significant wake after sleep onset (WASO; Patients, 42.23 ± 21.51 mins; Controls, 28.51 ± 8.27 mins; \( F(1,25) = 4.653, p = 0.041 \)) and time spent mobile during the nights (Patients, 8.72 ± 3.7 mins; Controls, 6.3 ± 1.66 mins; \( F(1,25) = 5.391, p = 0.029 \)). There were no differences between patients and controls with respect to any of the measures related to nap behavior.

**b. Sleep Apnea Assessment**

Participants wore the ApneaLink device for one night: the device included an effort sensor, pulse oximetry, and a nasal cannula. The Apnea-Hypopnea Index (AHI) – the number of apneic and hypopneic events occurring per hour – was calculated and compared between patients and controls. Additionally, owing to the greater risk for developing sleep-disordered breathing with increasing Body Mass Index (BMI), height and weight information was used to calculate BMI for each participant, and applied as a covariate in the comparison.
A total of 14 patients and 14 controls were included in the analysis of AHI values (2 patients complained of discomfort from the nasal cannula and chose not to participate in that aspect of the experiment). An independent samples t-test showed no differences in BMI between the patient (27.29 ± 4.91) and control (26.72 ± 4.23) groups \((t(26) = 0.330, p = 0.744)\). An ANCOVA comparing AHI values across the patient and control groups, with BMI as a covariate, revealed no significant differences between groups \((F(1,25) = 28.175, p = 0.582)\).

Participants were categorized in the following manner based on their AHI value (Ruehland et al., 2009). AHI < 5 per hour as no/minimal sleep apnea, AHI ≥ 5 per hour but < 15 per hour as mild sleep apnea, AHI ≥ 15 per hour but less than 30 per hour as moderate sleep apnea, and AHI ≥ 30 per hour as severe sleep apnea. A chi-squared test revealed no significant differences between patients and controls with respect to assignment into these diagnostic groups \((\chi^2(3) = 5.882, p = 0.118)\). Table 9 displays means, SDs, and \(p\)-values associated with AHI measures.

c. Polysomnography

Sleep Architecture: Polysomnography (PSG) was conducted during the last night of the experimental week for each participant; the PSG montage included EEG, EOG, submental EMG and tibial EMG. Group means and standard deviations for physiological measures of sleep can be found in Table 9. A MANOVA with Sidak-Bonferroni correction for multiple comparisons was performed to compare sleep physiological measures between groups. Patients had significantly reduced total sleep time (TST) compared to matched-controls (Figure 8a; \(F(1,30) = 4.084, p = 0.05)\). However, there were no observed differences between patients and controls with respect to sleep efficiency \((F(1,30) = 2.776, p = 0.106)\), sleep onset latency \((F(1,30) = 0.905, p = 0.349)\), or percent time spent in either N1 \((F(1,30) = 1.441, p = 0.239)\), N2 \((F(1,30) = 0.905, p = 0.349)\), or with a level
0.014, \( p = 0.905 \), SWS \( (F(1,30) = 0.324, p = 0.573) \), or REM sleep \( (F(1,30) = 3.623, p = 0.07) \).

However, we observed evidence of disrupted sleep in patients relative to controls. Specifically, patients had significantly higher sleep fragmentation indices (SFI) – the number of stage transitions and awakenings per hour – compared to their healthy counterparts (Figure 8b; \( F(1,30) = 7.773, p = 0.009 \)).

**EEG Spectral Power:** Spectral power density – calculated as the Fourier transform the EEG signals, with a unit of \( \mu V^2/Hz \) – for the following frequency bands were averaged across all the frontal and central derivations: slow oscillations during NREM sleep (0.5-1 Hz), delta during NREM sleep (1-4 Hz), theta frequency during REM sleep (5-8 Hz), slow sigma during NREM sleep (11-13 Hz), and fast sigma during NREM sleep (14-16 Hz).

Spectral power density was compared across patient and control groups using a MANOVA with a Sidak-Bonferroni correction for multiple comparisons (means, standard deviations and \( p \)-values for all frequency bands can be found in Table 8). Patients and controls were comparable with regard to spectral power density for all frequency bands, with the exception of fast sigma power density: patients demonstrated significantly greater fast sigma power density averaged over the frontal and central derivations compared to their healthy counterparts (Figure 9; \( F(1,25) = 4.038, p = 0.05 \)).

**Limb Movements during Sleep:** Limb movements during sleep were detected by means of bilateral tibial EMG, and the following measures were calculated: (1) the periodic limb movement index (PLMI), which is the number of repetitive muscle movements (occurring every 20-40 s) during sleep per hour, and (2) limb movement index during REM sleep, calculated as the total number of movements occurring per hour of REM sleep. Mann-Whitney comparisons of independent samples were used to compare the patient and control groups owing to the non-
parametric distribution of values across samples. The tibial EMG channels fell off during the night for 2 patients and 1 control; therefore, a final sample size of 13 patients and 13 controls was used in the statistical analyses.

Patients demonstrated significantly greater periodic limb movements per hour compared to controls (Figure 10; Patients, Mdn = 31.8 per hour; Controls, Mdn = 10.3 per hour; $U = 46, p = 0.048$). There were no differences between patients and controls with respect to limb movements during REM sleep (Figure 10; Patients, Mdn = 2.2 per hour; Controls, Mdn = 2.5 per hour; $U = 71, p = 0.488$).

d. Interactions between Sleep, Motor, and Non-Motor Function
Spearman correlations were performed in order to examine the relationship between severity of motor symptoms (BARS) and – where differences between patients and controls were found – sleep and cognitive measures. The patient and control groups were collapsed for the purpose of these correlations to increase statistical power.

The relationship between severity of motor dysfunction, as measured through the BARS, and the following sleep physiological measures was calculated using Spearman rank correlation coefficients, owing to the differences observed between patients and their matched-controls: frontal fast sigma power density during NREM sleep, sleep fragmentation index (SFI), and periodic limb movement index (PLMI). In addition, the relationship between motor dysfunction (BARS) and cognitive function was measured by means of Spearman rank correlation coefficients for two cognitive measures: raw scores on the CCAS/Schmahmann Syndrome-RS, and Immediate Recall accuracy on the word-pair association task as a measure of learning abilities. Due to the number of exploratory correlations being performed, a Sidak-Bonferroni correction for multiple comparisons was applied to all tests (number of tests = 5; $\alpha = 0.01$).
Scores on the BARS – wherein greater scores were indicative of greater severity of motor deficits – were positively correlated with sleep fragmentation indices (Figure 11; $\alpha = 0.01; r_s(32) = 0.447, p = 0.01$), but not with fast sigma power density during NREM sleep ($\alpha = 0.01; r_s(28) = 0.409, p = 0.031$) or with periodic limb movement indices ($\alpha = 0.01; r_s(26) = 0.334, p = 0.095$).

There was a robust negative correlation between scores on the BARS and those on the CCAS/Schmahmann Syndrome-RS (Figure 12; $\alpha = 0.01; r_s(24) = -0.556, p = 0.005$), indicating that those with greater motor dysfunction also suffered from greater cognitive deficits. However, there was no significant correlation between the BARS and accuracy at Immediate Recall ($\alpha = 0.01; r_s(26) = -0.440, p = 0.02$).

**e. Relationship between Sleep and Cognitive Function**

In order to examine the relationship between sleep measures and cognitive function – namely raw scores on the CCAS/Schmahmann Syndrome-RS and accuracy at Immediate Recall – we performed Spearman correlations, collapsing across patient and controls groups to increase statistical power. Due to the number of exploratory correlations being performed, a Sidak-Bonferroni correction for multiple comparisons was applied to all tests (number of tests for each cognitive measure = 5; $\alpha = 0.01$).

The measures of habitual sleep behavior included the following: ESS, PSQI, and actigraphy measures. Spearman correlations demonstrated that neither scores on the CCAS/Schmahmann Syndrome-RS, nor accuracy at Immediate Recall were correlated with daytime sleepiness as measured through the ESS ($\alpha = 0.01; \text{CCAS-RS, } r_s(23) = -0.058, p = 0.793; \text{Immediate Recall, } r_s(26) = -0.059, p = 0.775$), or with habitual sleep quality on the PSQI ($\alpha = 0.01; \text{CCAS-RS, } r_s(23) = -0.007, p = 0.975; \text{Immediate Recall, } r_s(26) = -0.126, p = 0.547$).
With regard to the actigraphy measures, significant differences between patients and controls were found for sleep efficiency, time spent awake, and time spent mobile during the night (see “Actigraphy” section above). The CCAS/Schmahmann Syndrome-RS was not correlated with sleep efficiency \( (\alpha = 0.01; r_s(21) = 0.156, p = 0.499) \), with time spent awake during the night \( (\alpha = 0.01; r_s(21) = -0.421, p = 0.058) \), or with time spent mobile during the night \( (\alpha = 0.01; r_s(21) = -0.495, p = 0.023) \). Accuracy at Immediate Recall was significantly correlated with time spent mobile during the night \( (\alpha = 0.01; r_s(20) = -0.559, p = 0.01) \), but not with sleep efficiency \( (\alpha = 0.01; r_s(20) = 0.279, p = 0.234) \) or with time spent awake during the night \( (\alpha = 0.01; r_s(20) = -0.502, p = 0.024) \).

Although the physiological measures of sleep represent a single night’s events, we conducted correlations between SFI and performance on the CCAS/Schmahmann Syndrome-RS and during Immediate Recall for the word-pair association task. These correlations were conducted under the presumption that the SFI distribution observed across patients and matched-controls on the experimental night – although likely scaled compared to a habitual night owing to the discomfort associated with wearing the PSG montage – was representative of the true distribution. Indeed, the fragmentation index as determined by one week of actigraphy was significantly correlated with the SFI on the experimental night \( (r(25) = 0.546, p = 0.005) \). Due to the number of exploratory correlations being performed, a Sidak-Bonferroni correction for multiple comparisons was applied to all tests (number of tests = 3; \( \alpha = 0.017 \)). We found strong negative correlations between SFI and raw scores on the CCAS/Schmahmann Syndrome-RS (Figure 13a; \( \alpha = 0.017; r_s(26) = -0.528, p = 0.008 \)), as well accuracy at Immediate Recall (Figure 13b; \( \alpha = 0.017; r_s(26) = -0.531, p = 0.001 \)), such that greater fragmentation of sleep was associated with poor cognitive performance.
Finally, we examined the relationship between the change in recall accuracy from pre- to post-sleep (Delayed Recall – Immediate Recall) – reflective of the extent to which memories of the word-pairs were consolidated over sleep – and percent time spent in SWS and REM sleep, and SFI. We conducted separate Spearman correlations in patients and controls, in order to determine whether cerebellar degeneration impacted the relative contributions of these stages of sleep to memory processing. Due to the number of exploratory correlations being performed, a Sidak-Bonferroni correction for multiple comparisons was applied (number of tests for each sleep stage = 4; $\alpha = 0.013$). There were no significant correlations between change in accuracy and percent time spent in SWS ($\alpha = 0.013$; $r_s(13) = 0.597, p = 0.04$), in REM sleep ($\alpha = 0.013$; $r_s(13) = 0.208, p = 0.495$), or with SFI in patients ($\alpha = 0.013$; $r_s(13) = -0.162, p = 0.597$).

Likewise, overnight performance changes on the word-pair association task was not correlated with SWS ($\alpha = 0.013$; $r_s(13) = 0.04, p = 0.902$), in REM sleep ($\alpha = 0.013$; $r_s(13) = -0.187, p = 0.540$), or with SFI ($\alpha = 0.013$; $r_s(13) = 0.456, p = 0.117$) for controls.

D. Discussion

The goal of the current study was to ascertain how sleep behavior and physiology are affected by cerebellar degeneration, and to determine whether these changes in sleep impact sleep-dependent declarative memory consolidation. In order to accomplish this, actigraphy, polysomnography and sleep apnea procedures were conducted in 16 patients with pure cerebellar syndrome and 16 age-, sex-, handedness-, and education-matched controls. In addition, performance on a word-pair association task was evaluated before and after a period of overnight sleep to determine whether the benefit of sleep on declarative memory was reduced in patients relative to controls.

Our specific predictions were that relative to their healthy counterparts, patients with pure cerebellar syndrome would (1) have reduced sleep quality owing to the presence of sleep
disorders and changes in the electrophysiological properties of sleep, (2) demonstrate deficits in cognitive processing across executive function, learning, and memory domains, (3) show reduced sleep-dependent memory consolidation. The study revealed both, cognitive and sleep-related, dysfunction in patients with cerebellar degeneration compared to matched-controls. However, overnight change in memory performance on the word-pair association task was comparable across patients and controls. Below is a discussion of each prediction in light of the empirical data, providing mechanisms for the observed effects.

1. Sleep

In order to measure sleep dysfunction associated with cerebellar degeneration in the absence of extracerebellar pathology, we assessed sleep-wake behavior using actigraphy and sleep physiology using polysomnography in patients with pure cerebellar syndrome and in age-, sex-, handedness-, and education-matched controls. We found a distinct reduction in sleep quality as a result of cerebellar degeneration, the severity of which was greater in patients with more severe motor deficits.

The electrophysiological aspects of sleep are mediated by sub-cortical and cortical regions of the brain (Schwartz and Roth, 2008). However, cerebellar activity during sleep – first observed by Marchesi and Strata (1970) – is increasingly considered to be a functional, stage-specific occurrence, and a consequence of extensive cerebellar connectivity with neural regions and pathways crucial to sleep (Canto et al., 2017). We examined overnight total sleep time (TST), the relative distribution of sleep stages – N1, N2, SWS and REM sleep – and the spectral power density of the EEG during NREM and REM sleep in patients with pure cerebellar syndrome and in matched-controls.

a. Sleep Behavior, Physiology, and Architecture
Sleep-wake patterns were determined using actigraphy, and found no observed differences between patients and matched-controls for the following measures: overnight sleep duration, sleep onset latency, number of naps, and nap duration. However, patients with pure cerebellar syndrome demonstrated lower overnight sleep efficiency as a result of greater wake after sleep onset (WASO). This reduction in the quality of sleep was confirmed using polysomnography, which revealed that sleep was significantly more fragmented in patients than controls, as reflected by the Sleep Fragmentation Index (SFI), a measure of the number of arousal, awakenings and stage transitions per hour. 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 (Joo et al., 2013). Patients with pure cerebellar syndrome in the current study however, demonstrated greater sleep fragmentation than would be expected merely as a result of age-related structural changes in the brain, and the degree of sleep fragmentation was robustly correlated with the severity of the associated motor deficits.

One possible mechanism for increased sleep fragmentation as a result of cerebellar degeneration is through impaired cerebellar involvement in the neurophysiology of sleep state transitions. Sleep-wake and sleep stage transitions are orchestrated by a number of sub-cortical cell populations that form an elegant “flip-flop” switch (Saper, Chou, and Scammel, 2001). Specifically, the wake-promoting reticular activating system and the sleep-promoting VLPO pathway are mutually inhibitory, and the activation (and inhibitory) patterns of the associated cell populations are crucial to ensuring the distinct electrophysiological patterns associated with a wakeful state, as well as with each sleep stage. Early animal studies have provided evidence of a role of the cerebellum in fine-tuning the signals responsible for transitions between
physiological states, by means of its extensive bilateral connections with a number of the cell populations involved in wake- and sleep-promotion (Ito, 1982; Cunchillos and de Andrés, 1982). Although such connectivity between the cerebellum and the sleep-wake centers of the brain has not been mapped in humans, thus requiring further investigation, damage to the cerebellum could perhaps result in the inefficient operation of the “flip-flop” switch, and consequently, in greater sleep fragmentation.

We observed greater spectral power density in the fast sigma frequency range (14-16 Hz), which is reflective of fast spindle activity (Doran, 2003), over the frontal and central derivations in patients with pure cerebellar syndrome relative to matched-controls. Slow and fast spindles not only differ in topology and frequency, but also in source and function (Mölle, et al., 2011). While slow spindles have been associated with coupling between cortical regions, fast spindles have been linked with modulation of thalamocortical coupling. Therefore, fast spindles not only play a role in memory processing – the synchronized activity of hippocampal ripples and thalamocortical coupling during slow oscillations provide a mechanism for hippocampal-neocortical transfer of memories (Siapas and Wilson, 1998) – but also in sleep continuity (Bessett et al., 1998; Dang-Vu et al., 2010; Dijk, 1995). The specific functions of slow and fast spindles are actively under investigation, and differential roles for these electrophysiological events are yet to be clearly defined; however, greater fast spindle activity in patients relative to controls in the current study might indicate more active sleep maintenance mechanisms at play.

b. Sleep Disorders

Although we found no evidence of sleep-disordered breathing in patients with pure cerebellar syndrome – that is, above what would be expected in an aging sample, given the high
incidence of OSA in older adults (Ancoli-Israel, 2009) – we did find significantly greater periodic limb movement indices (PLMI) in patients relative to matched-controls.

There is strong evidence in the literature to suggest that PLMD is a dopaminergic dysfunction disorder, and is a result of damage to basal ganglia circuits, particularly those involving the ventral striatum (Abele et al., 2001). Animal studies have demonstrated a direct influence of the cerebellum on striatal function (Hoshi et al., 2005); therefore, cerebellar degeneration could exert deleterious effects on dopaminergic signaling pathways, thus resulting in symptoms of PLMD. Indeed, functional MRI in patients with the combined disorder of PLMD-RLS indicated a robust link between cerebellar and thalamic activation and the sensory symptoms associated with the disorder (Bucher et al., 1997). Furthermore, administration of dopamine agonists has shown to result in the alleviation of PLMD symptoms in patients with spinocerebellar ataxia type 2. These past findings, taken together with those of our current study, point toward a distinct role of the cerebellum in the pathophysiology of PLMD, and require deeper investigation by means of longitudinal studies and neuroimaging.

It is important to note here that withdrawal from sedative medications – such as benzodiazepines – can produce PLMD symptomatology. However, although the use of such sleep-affecting medications was discontinued in the current study for a number of patients, it is unlikely the reason for the appearance of symptoms if PLMD: medications were gradually tapered over the course of weeks, and even months in some cases, in order to minimize such withdrawal effects.

2. Cognitive Function

In order to elucidate the cognitive deficits associated with cerebellar degeneration, we compared performance on the Cerebellar Cognitive Affective Syndrome/Schmahmann Syndrome Rating
Scale (CCAS/Schmahmann Syndrome-RS; Hoche et al., *in press*) as well as on a word-pair association task, between patients with pure cerebellar syndrome and age-, sex-, handedness-, and education-matched controls. We demonstrate deficits on a number of cognitive measures, and moreover, these deficits were strongly correlated with the severity of motor deficits displayed (BARS scores). These findings suggest that loss of cerebellar integrity impacts both, motor and cognitive domains, in a dose-dependent manner.

*a. Assessment of CCAS/Schmahmann Syndrome*

We used a neuropsychological battery, the CCAS/Schmahmann Syndrome-RS (Hoche et al., *in press*), to examine cognitive function and general affect in patients with pure cerebellar syndrome and in matched-controls. Patients with pure cerebellar syndrome scored significantly lower on the CCAS/Schmahmann Syndrome-RS compared to matched-controls; moreover, greater cognitive deficits were observed in patients with more severe motor deficits. These findings indicate that cerebellar degeneration leads to dysfunction in motor and non-motor pathways, with increasing negative effects on both domains as disease progresses. Indeed, one study used functional connectivity MRI and demonstrated unequivocal functional connections between the cerebellum, the prefrontal and parietal cortices of the human brain (Allen et al., 2005), a neural network that is consequently disturbed as a result of cerebellar pathology (Stoodley and Schmahmann, 2009).

Specific cognitive impairments were observed 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 patients and controls. Verbal fluency was assessed by means of a test for semantic fluency – wherein participants were asked to list as many animals as they could in one minute – as well as for phonemic fluency, wherein
participants were asked to list as many words as they could in one minute that began with the letter “F.” Performance on these tasks relies on a number of neural regions, such as those involved in attention, memory, and temporal processing. Both, semantic and phonemic, fluency tests engage prefrontal and temporal regions of the brain, although phonemic fluency is more reliant on the former, while semantic fluency on the latter (Baldo et al., 2006). In addition, both components of verbal fluency – where the cadence of response delivery, awareness of the temporal frame within which the test is operating, and attention shifting in order to maintain appropriateness of items being listed, are all crucial to task performance – require engagement of the cerebellum and the cerebro-cerebellar neural networks (Diamond, 2000; Schmahmann, 2004; Buckner, 2013).

The functional connectivity between the cerebellum and the cerebral cortex forms two pathways through which the cerebellum contributes to higher functions (Stoodley, 2012): 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 (Seeley et al., 2007). Consequently, 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 cerebellar patients relative to controls (Leggio et al., 2000; Stoodley and Schmahmann, 2009), and future research could focus on the specific underlying mechanisms leading to such deficits.

Compared to healthy matched-controls, patients with pure cerebellar syndrome in the current study also demonstrated reduced cognitive flexibility, as measured by the “category
switching” task: participants were instructed to “name a vegetable, and then a profession, and then a vegetable, and so on” for the duration of one minute. Similar to verbal fluency, cognitive flexibility is an executive function that relies on the prefrontal cortex, particularly the ventrolateral PFC and the supplementary motor areas (SMA; Zuk et al., 2014). PFC activation is crucial for sustained attention, response inhibition, working memory and performance monitoring, all of which must occur in concert in order to successfully perform a cognitive set shift task. In addition, an important pre-requisite for cognitive flexibility is the prior formation of strong context-response associations, such that an experiential context – a category in the case of the category switching task – evokes an automatic response (Bartolo et al., 2009). This process has been shown to be dependent on the cerebellum; more specifically, activation of fronto-cerebellar pathways as a result of contextual cues has been observed in tasks involving cognitive flexibility. Our current findings in patients with degenerative cerebellar disease – together with previous studies that have reported impaired mental flexibility in patients with cerebellar infarcts (Malm et al., 1998; Hokkanen et al., 2006) – thus provide further evidence for a role of the cerebellum in complex cognitive tasks.

Patients with pure cerebellar syndrome in the current study did not show reduced cognitive function relative to healthy controls in the following domains: 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 patient samples that include both, patients with pure cerebellar syndrome as well as those with extracerebellar pathology, have demonstrated deficits in the abovementioned cognitive domains (Kish et al., 1988; Bracke-Tolkmitt et al., 1989; Grafman et al., 1992). However, the cerebellar plus syndromes involve structural alterations in the cerebral cortex, brainstem, thalamus, and
even the basal ganglia (Schös et al., 2004); therefore, based on these prior studies, it remained unclear how cerebellar degeneration contributed to the constellation of cognitive deficits observed. The current helps to disentangle cognitive function across these domains with relation to “pure” cerebellar pathology.

**b. Learning and Memory**

Learning and memory were assessed using a declarative word-pair association task. During the Encoding phase of the task, participants were presented with 25 semantically unrelated word-pairs, and were asked to recall the word associations until criterion was reached, or until they had been tested on all word pairs 5 times. In addition, memory for the word pairs was tested during the Immediate Recall phase, which took place 20 minutes after the Encoding phase.

Tulving (1985 a,b; Tulving et al., 1994) described two stages in episodic memory formation: the encoding phase involves the acquisition and subsequent incorporation of novel information, while memory retrieval phase involves the process by which previously stored memories are accessed. In the current study, the number of loops required to reach criterion during the Encoding phase represented a measure of acquisition, while memory retrieval was measured by means of accuracy at Immediate Recall.

The number of loops required to reach criterion did not differ between patients with pure cerebellar syndrome and their healthy counterparts. The lack of observable group differences was likely due to low statistical power owing to a small effect size. There are two possible reasons for this: first, although a continuous variable, the range of responses associated with the number of loops was rather limited (0 to 5) and therefore, did not elicit variability in data; second, group differences were further diminished owing to attenuated learning curves in the control group, an observation that is consistent with the older adult literature (Vakil and Agmon-
Ashkenazi, 1997; Davis et al., 2003). Therefore, although the number of loops completed during the Encoding phase was comparable between groups, this does not necessarily reflect unimpaired learning in patients relative to controls. Indeed, patients with pure cerebellar syndrome demonstrated significantly lower accuracy at Immediate Recall – a robust measure of memory retrieval soon after learning – compared to healthy controls.

Considering patients with pure cerebellar syndrome in the current study – and consequently, the matched-controls – represent an aging sample, it is important to take into account age-related changes in retrieval effort. De Brigard and colleagues (2013) reported distinct differences in young and older adults with respect to activation of the neural regions that control relational memory processing, the process by which unrelated items or contexts are linked. Specifically, aging is associated with both, under-recruitment and non-specific recruitment, of the medial temporal lobe (MTL) and the PFC, reflective of deficits in engaging effortful strategies in older age (Glisky et al., 2001). In fact, older adults with greater engagement of effortful retrieval strategies show young adult-like performance on episodic memory tasks (Nyber et al., 2017). Given these documented changes in episodic memory formation with age (De Brigard et al., 2013), it is unsurprising to see that both patients and matched-controls in the current study demonstrated low retrieval accuracy on the word-pair association task compared to young adults in previous studies (Ellenbogen et al., 2006; Wilson et al., 2012). In addition, patients with pure cerebellar syndrome demonstrated significantly reduced retrieval abilities compared to the matched-controls, thus emphasizing the importance of cerebellar integrity to episodic memory retrieval.

In a study using whole-brain fMRI, Kraus and colleagues (1999) demonstrated a bilateral increase in the BOLD signal during the Encoding phase of the word-pair association task –
above that associated with minimal cognitive effort – in the cerebellum, precuneus, and anterior cingulate and prefrontal cortices. Although the specific role of the cerebellum in the computational aspects of episodic memory formation are yet unknown, cerebellar activation has been purported to be greater during tasks that involve the effortful recall of recently acquired information, also known as “retrieval effort” (Schacter et al., 1996; Desgranges et al., 1998). For instance, activation of prefrontal regions as well as cerebellar-prefrontal functional connectivity have been linked to inhibition of irrelevant information, which is an important process in memory retrieval (Schacter et al., 1996).

In addition to its involvement in optimizing effortful retrieval strategies (Schacter et al., 1996), the cerebellum has also been shown to have numerous bidirectional connections with the hippocampus, which is essential for declarative learning (Eichenbaum, 2001). Interestingly, the cerebellum’s role in hippocampal-dependent learning has been linked to the integration of the contextual aspects of declarative information, and its role has been described as one that helps maintain online awareness during learning (Yu and Krook-Magnuson, 2015). Although the precise contributions of the cerebellum to episodic learning is poorly understood, there is growing evidence to show that there are numerous pathways through which the cerebellum influences hippocampal responses. Adding to this literature, the current study is the first to provide direct evidence of impaired declarative learning as a result of isolated cerebellar degeneration in humans.

Three patients with pure cerebellar syndrome demonstrated extreme frustration towards the word-pair association task, and chose to withdraw from that particular aspect of the experiment. This observation perhaps points towards attentional challenges faced by patients with cerebellar degeneration, and might provide additional support for the involvement of the
cerebellum in executive function by means of its connectivity with the prefrontal cortex and anterior cingulate cortex – crucial areas of the attention network (Kraus et al., 1999). Another possible explanation for this effect is that the simultaneous execution of a motor task (speaking, pointing) and a cognitive task (recall of word-pair associations) could have introduced a specific form of dual-task interference, known as cognitive-motor interference (Plummer et al., 2013). Cognitive-motor interference is associated with over-activation of the neural regions associated with the motor and cognitive components of this task – such as the cerebellum and prefrontal cortices respectively (Wu et al., 2013). Wu and colleagues (2013) suggested that the cerebellum, which is directly involved in executive networks and in dual motor-cognitive task processing, is responsible for integrating the motor and cognitive networks. Patients with cerebellar degeneration would therefore, be particularly vulnerable to cognitive-motor interference, resulting in learning impairments, and in extreme cases, in the incapacity to perform the word-pair association task.

3. The Relationship between Sleep and Cognition

a. Impact of Sleep Quality on Cognition

We found a close link between sleep dysfunction and reduced cognitive function in our sample of patients with pure cerebellar syndrome, wherein both, poor habitual sleep quality and sleep fragmentation, were 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; Short and Banks, 2014). Therefore, these findings further emphasize the connection between poor sleep and cognitive function, and additionally, exemplify its clinical relevance in the context of neurodegenerative disorders.
**b. Sleep-Dependent Memory Processing**

Although aging is associated with a reduction in the benefit of sleep on non-declarative learning (Bottary et al., 2016; Wilson et al., 2012), sleep-dependent declarative memory consolidation is preserved in older adults (Sonni and Spencer, 2015; Wilson et al., 2012). Therefore, in the current study, we used a declarative word-pair association task in order to examine overnight changes in memory accuracy in patients with pure cerebellar syndrome and in healthy matched-controls. We predicted that sleep-dependent declarative memory consolidation would be reduced in patients relative to controls. However, the data from the current study show no differences in overnight performance changes between patients and matched-controls, suggesting that the benefit of sleep in stabilizing learned associations is preserved in patients with pure cerebellar syndrome.

For patients and matched-controls, we found no correlations between sleep physiological measures and post-sleep memory performance. This is likely a result of age-related changes in the neural reorganization of memory traces occurring over sleep. Specifically, Baran and colleagues (2016) compared post-nap and post-wake performance on a word-pair association task in young and older adults: using fMRI, they demonstrated that following sleep-dependent memory processing in young adults, successful memory retrieval was associated with time spent in SWS over the nap, as well as hippocampal disengagement during retrieval. This is consistent with the theory of systems consolidation, or the process by which declarative memories become increasingly more hippocampal-independent as they become more committed to the neocortex (Dudai, 2004). In contrast, older adults were more reliant on hippocampal-PFC connectivity post-sleep, and furthermore, showed no association between nap physiology and post-sleep performance at retrieval (Baran et al., 2016). Therefore, these findings indicate that the trajectory
of memory consolidation – with respect to the neural ensembles engaged at each step of memory processing – varies with age.

Our data show that despite significant impairments in learning on the word-pair association task relative to matched controls, patients with pure cerebellar syndrome demonstrated a similar benefit of sleep to controls. Therefore, although performance at Delayed Recall was markedly lower in patients relative to controls, the change in accuracy from Immediate to Delayed Recall was comparable across groups. One possible explanation for this result is that the observed preservation of memory for the word-pair associations learned prior to sleep in patients – and perhaps even in controls – is reflective of a passive role of sleep in protecting memories from waking interference, rather than an active role of sleep in strengthening and stabilizing the memory traces.

In order to determine whether preserved memory performance post-sleep was reflective of the passive role of sleep in protecting memories from waking interference, Sonni and Spencer (2015) used interference prior to recall to test the strength of learned visuospatial information following overnight sleep. They found that, compared to wake, sleep strengthened and stabilized the memories such that they were less susceptible to interference, thus providing support for an active role of sleep in declarative memory consolidation in aging. Although such an interference paradigm as been conducted in a young adult sample for the word-pair association task, a similar exploration has never been conducted in an aging sample. Therefore, in order to parse the passive and active role of sleep in associative learning in patients with pure cerebellar syndrome, future research could focus on determining the post-sleep strength of the learned associations. Such an examination would allow us to determine whether sleep-dependent processing of
associative learning is preserved in aging and in the presence of cerebellar degeneration, and to elucidate the mechanisms underlying such processes.

**E. Limitations and Future Directions**

Given the rarity of pure cerebellar disease, our sample size of 16 patients and 16 matched-controls was small, and we did not have the statistical power to detect differences between groups that might have had smaller effect sizes. The small sample size – and consequent lack of statistical power – was particularly evident in our exploratory analyses looking at the interactions between motor, sleep, and non-motor measures. To increase statistical power, the patient and control groups were collapsed: although Spearman rank correlations were used owing to the non-parametric distribution of variables across the 2 groups, it is important to note that the distribution, especially with respect to BARS scores, were vastly different across groups.

Although an earnest effort was made to reduce confounds and to equate patient and control groups in as many ways as possible, there were still some sources of variability that were unaccounted for. For instance, more stringent screening criteria could have been employed for controls in order to ensure healthy cognitive status; a number of controls failed items on the CCAS/Schmahmann Syndrome-RS, which is indicative of early signs of dementia (Hoche et al., *in press*), thus making it difficult to detect cognitive deficits specific to pure cerebellar syndrome.

Another source of variability was the heterogenous nature of the patient group. Although recruitment was limited to those with genetically confirmed subtypes that have been classified as “pure” cerebellar diseases, we did not have recent neuroimaging data to determine what specific cerebellar structures were affected and to what extent. The neuroanatomy of the cerebellum is complex, and cerebellar structures are associated with differential involvement in the various
motor and non-motor pathways (Schmahmann, 2013). Therefore, in addition to increasing the variability of the patient, we also lacked the ability to make more detailed assessments of the role of the cerebellum in cognitive function.

The in-home design for conducting the sleep recordings had two major advantage: first, it provided participants the comfort of their home, thus allowing them to sleep as they ordinarily would, and; second, it prevented effortful travel for patients with severe motor deficits. However, since participants were not monitored through the night, the in-home design resulted in loss of data owing to both, conscious and unconscious, removal of sleep-recording probes at night.

To further simplify the sleep-recording procedures that the participants were required to follow and to minimize discomfort, the sleep apnea assessment and the polysomnography recordings were conducted on two separate nights. PLMs are conventionally not scored following a respiratory event; however, without the two devices being time-locked, we were unable to parse the PLMs based on whether they occurred after an apneic or hypopneic event.

Performance on the word-pair association task was tested in the evening prior to the participant’s bedtime, and again the following morning, thus introducing the possibility of circadian influences on cognition. However, a strong attempt was made to reduce the variability in task performance owing to such time-of-day effects. First, sleepiness at the time of testing (as measured by the SSS) was included as covariates in the ANOVA used to compare pre- and post-sleep performance on the word-pair associations task: such an approach resulted in the differences between patients and matched-controls with respect to accuracy at Delayed Recall to become non-significant. The interpretations were consequently modified accordingly. Second, the MEQ was used to gather information about each patient and control’s chronotype, and we found no differences in morningness/eveningness between the groups. Therefore, although
circadian differences in task performance likely exist, those differences would apply to the two groups equivalently since both groups were tested under the same experimental conditions. Future studies can eliminate confounds due to circadian effects by using a nap paradigm.

Four of the sixteen matched-controls were pre-screened against sleep disorders. Although this number is small, their inclusion in the dataset might have nonetheless biased the results. Finally, without the inclusion of a “wake” group that performed the word-pair association task before and after a period of wake – as opposed to a period of overnight sleep – we were unable to compare the effect sizes associated with the sleep benefit in patients and matched-controls. Future studies could include such a comparison group in order to further elucidate the differences in offline memory processing over wake and sleep in patients with pure cerebellar syndrome compared to healthy matched-controls.

F. Conclusions

Although sleep behavior and physiology have previously been examined in patients with cerebellar ataxia, such studies have predominantly focused on the cerebellar plus syndromes. Two studies in the pure cerebellar syndromes – specifically, SCA6 – provided support for the theory that cerebellar degeneration alone results in sleep disturbances: however, of these, one study lacked objective measures of sleep physiology (Howell, Mahowald, and Gomez, 2006), while the other was conducted in a small sample of patients belonging to the same family (Boesch et al., 2006).

The current study was the first, to the best of our knowledge, to simultaneously (1) examine sleep behavior, physiology, and architecture, and (2) determine the impact of poor sleep on cognitive function in patients with pure cerebellar syndrome relative to age-, sex-, handedness-, and education-matched controls. We tested 16 patients and 16 matched-controls on
measures of executive function across a number of domains; in addition, we tested the participants on a declarative word-pair association task before and after a period of overnight sleep in order to explore whether the cognitive benefits of sleep are negatively impacted by cerebellar degeneration. Finally, we examined the relationship between sleep measures and cognitive function to assess whether deterioration in sleep quality was associated with cognitive deficits.

Our data show that sleep is significantly impacted by cerebellar degeneration, providing evidence of changes in sleep physiology and the presence of sleep disorders in patients relative to controls. Specifically, patients with pure cerebellar syndrome demonstrated excessive limb movements during sleep, and significantly greater fragmentation of sleep. Furthermore, the severity of the sleep disturbances was closely linked to the severity of motor deficits reported. These findings therefore, point toward a potential common underlying neural pathway – or pathways – involving the cerebellum that mediate motor and sleep-related domains.

With respect to cognitive function, patients with pure cerebellar syndrome demonstrated deficits in executive function, particularly in the domains of verbal fluency and cognitive flexibility. Furthermore, they displayed significant impairments in declarative learning as evident by their poor performance on the word-pair association task during Encoding and Immediate Recall relative to controls. The extent to which cognitive function was impaired was robustly correlated with the severity of motor deficits experienced, thus providing additional support for the role of the cerebellum in higher-level cognitive function.

Finally, we report a strong link between poor sleep and cognitive function: poor sleep quality – as determined by increased sleep fragmentation – was correlated with diminished cognitive function. Therefore, the current study supports previous findings of cognitive
impairments in patients with pure cerebellar syndrome, provides additional evidence of sleep
dysfunction, and establishes the first link between objective measures of sleep physiology and
cognitive function in this population. In conclusion, the current study is an important step toward
determining the role of the cerebellum in sleep, further elucidating the functional relevance of
this structure across numerous aspects of daily functioning.
CHAPTER IV
GENERAL DISCUSSION

Through years of clinical experience with somnolent patients suffering from encephalitis lethargica, Constantin von Economo developed a theory of sleep in 1929 (Von Economo, 1929); in his theory, he deviated from the hitherto popular belief that sleep was a period when the brain was disconnected, or isolated, from the rest of the body. Von Economo was instead determined to describe the function of sleep, convinced that it reflected more than a loss of consciousness and represented an active physiological state. Indeed, sleep sub-serves functions such as emotional processing and mood regulation (Mauss, Troy and Lebourgeois, 2012), as well as cognition (Walker & Stickgold, 2006). Therefore, in addition to its restorative properties, sleep is a period of considerable neural processing across various functional domains, and sleep disturbances have large implications on health-related outcomes.

With growing evidence of cerebellar involvement in non-motor function (Stoodley, 2012; Schmahmann & Sherman, 1998), it is no longer accurate to consider sleep disturbances to be “non-cerebellar” symptomatology. The cerebellum is a highly connected structure, and its involvement in sleep – which is a dynamic process that is modulated by a complex set of neural systems – can come about through a number of pathways that directly, or indirectly, influence sleep behavior. In order to augment our understanding of cerebellar involvement in sleep behavior and physiology, and to shed light on the impact of poor sleep on the quality of life in patients with cerebellar degeneration, we conducted two studies, each contributing novel findings that speak to a spectrum of sleep-related symptoms in this population.
The last few decades have marked an increase in the number of studies exploring sleep disturbances in cerebellar ataxias. Of these, the majority has focused on the cerebellar plus syndrome, revealing sleep disturbances to be a significant issue in this population (Boesch et al., 2006a; Chi et al., 2013; Schöls et al., 1998; Abele et al., 2001; Dang & Cunnington, 2010). Our first research aim was to garner self-report data regarding sleep quality, mood, cognitive perceptions and quality of life from a large sample of patients with cerebellar plus syndrome, as well as those with pure cerebellar syndrome. This allowed us to not only shed light on the relationship between these functional domains in this patient sample, but also compare and contrast symptoms across the two cerebellar syndromes.

By means of an online battery including measures of sleep and neuropsychiatric function, we collected data from 176 patients with cerebellar ataxia (Chapter II). We reported strong evidence of poor subjective sleep quality, symptoms of movement-related sleep disorders, and excessive daytime sleepiness in this sample. In addition, poor subjective sleep was associated with diminished perceptions of cognitive abilities and depression symptomatology, thus demonstrating detriments to general well-being, mental health, self-sufficiency and self-perceptions of daytime functioning. Moreover, the relationship between disease severity -- specifically the degree of motor dysfunction -- and non-motor symptoms, such as symptoms of depression, appeared to be mediated by poor sleep quality. Finally, although severity of self-reported sleep disruptions and cognitive deficits were greater in patients with cerebellar plus syndromes, our data indicate diminished health-related quality of life in patients with pure cerebellar syndrome with evidence of dysfunction in a number of sleep-related domains. Taken together, these findings contribute evidence that inefficient sleep and the presence of sleep
disorders in patients with cerebellar ataxia might exacerbate, and even underlie, deficits in non-motor domains.

Our second aim was to elucidate the nature of sleep dysfunction in patients with cerebellar degeneration without extracerebellar pathology – in order to shed light on the role of the cerebellum in sleep physiology – and to explore whether the cognitive benefits of sleep are diminished as a result of poor sleep. Prior to this study, objective evidence of sleep disruptions by means of polysomnography (PSG) sleep-recordings was limited to one study in a small sample (n=5) of patients with SCA6 (Boesch et al., 2006). Using PSG, they reported periodic leg movements (PLMs) during sleep in all five patients in the study, thus representing an important step in the determination of cerebellar contribution to sleep behavior. Our study extends on these findings in a number of ways, and includes a larger sample of patients with pure cerebellar syndrome, as well as a comparison group consisting of age-, sex-, handedness-, and education-matched controls.

Our study is the first to provide robust evidence of disrupted sleep in patients with pure cerebellar syndrome relative to their healthy counterparts. Specifically, patients with pure cerebellar syndrome demonstrated significant fragmentation of sleep, resulting in inefficient sleep and reduced total sleep time. One mechanism underlying sleep fragmentation in this patient sample was the presence of PLMs at a frequency markedly greater than that observed in healthy matched-controls. Importantly, sleep fragmentation was linked to executive function deficits, as well as with diminished episodic learning. These data are in line with our previous study – in which patients self-reported poor sleep quality with daytime detriments in the cognitive domain – and has significant implications for disease management and patient care.
Sleep plays a crucial role in cognitive processes, such as attention, learning and memory (Walker & Stickgold, 2006). Information acquired over wake is further processed over sleep, and in many cases, even enhanced. We are the first to examine whether the disruptions in sleep observed in patients with pure cerebellar syndrome impact have a bearing on the cognitive benefits of sleep, namely consolidation of declarative memories. We found that the change in performance from pre- to post-sleep on a declarative word-pair association task was comparable across patients and controls despite significant learning impairments in patients. These findings suggest that sleep’s role in memory processing may not be reduced in patients with pure cerebellar syndrome.

Evidence of cognitive deficits in individuals with cerebellar degeneration has been mounting over the last few decades (Schmahmann and Sherman, 1998). These deficits may be a result of the direct involvement of the cerebellum and cerebro-cerebellar circuits during cognitive tasks, and indeed, functional neuroimaging studies have shown cerebellar activation during various cognitive tasks (Stoodley, 2011). However, here we provide evidence to show that these cognitive deficits may also be a result of an indirect pathway that is mediated by sleep. Disturbed sleep, therefore, has a serious and significant impact on health and quality of life in patients with pure cerebellar syndrome. Our findings contribute important knowledge on the spectrum of deficits associated with cerebellar degeneration, and consequently, inform clinical practice, patient care, and therapeutic strategies.
**Table 4.** Descriptive statistics for patients with pure cerebellar syndrome and matched-controls. *Subtype* = spinocerebellar ataxia (SCA) type 5, 6, 28 or autosomal recessive cerebellar ataxia type 1 (ARCA). *Severity* = total score on the Brief Ataxia Rating Scale (BARS) indicative of the severity of motor deficits in gait, kinetic function-arm, kinetic function-leg, speech and eye movements.

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Subtype</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Handedness</th>
<th>Education (years)</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
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<td>M</td>
<td>R</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>101</td>
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<td>L</td>
<td>16</td>
<td>4</td>
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<td>103</td>
<td>SCA6</td>
<td>66</td>
<td>M</td>
<td>R</td>
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<td>18.5</td>
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<td>R</td>
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</tr>
<tr>
<td>105</td>
<td>SCA8</td>
<td>66</td>
<td>M</td>
<td>R</td>
<td>12</td>
<td>21</td>
</tr>
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<td>107</td>
<td>SCA8</td>
<td>58</td>
<td>F</td>
<td>R</td>
<td>16</td>
<td>11</td>
</tr>
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<tr>
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<td>46</td>
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<td>L</td>
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<td>6</td>
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<tr>
<td>111</td>
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<td>F</td>
<td>R</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>112</td>
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<td>M</td>
<td>R</td>
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<td>9</td>
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<tr>
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<td>M</td>
<td>R</td>
<td>14</td>
<td>22.5</td>
</tr>
<tr>
<td>116</td>
<td>SCA8</td>
<td>55</td>
<td>M</td>
<td>R</td>
<td>14</td>
<td>5.5</td>
</tr>
<tr>
<td>117</td>
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<td>59</td>
<td>M</td>
<td>R</td>
<td>18</td>
<td>4.5</td>
</tr>
<tr>
<td>118</td>
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<td>68</td>
<td>F</td>
<td>R</td>
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<td>6.5</td>
</tr>
<tr>
<td>120</td>
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<td>M</td>
<td>R</td>
<td>16</td>
<td>11</td>
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<td>M</td>
<td>R</td>
<td>17</td>
<td>0</td>
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<tr>
<td>3</td>
<td>Control</td>
<td>66</td>
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<td>L</td>
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</tr>
<tr>
<td>4</td>
<td>Control</td>
<td>70</td>
<td>M</td>
<td>R</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Control</td>
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<td>F</td>
<td>R</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
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<td>Control</td>
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<td>F</td>
<td>R</td>
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<td>9</td>
<td>Control</td>
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<td>L</td>
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<td>10</td>
<td>Control</td>
<td>65</td>
<td>M</td>
<td>R</td>
<td>13</td>
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<tr>
<td>12</td>
<td>Control</td>
<td>68</td>
<td>F</td>
<td>R</td>
<td>17</td>
<td>0.5</td>
</tr>
<tr>
<td>14</td>
<td>Control</td>
<td>52</td>
<td>M</td>
<td>R</td>
<td>13</td>
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</tr>
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<td>15</td>
<td>Control</td>
<td>72</td>
<td>M</td>
<td>R</td>
<td>20</td>
<td>0.5</td>
</tr>
<tr>
<td>16</td>
<td>Control</td>
<td>74</td>
<td>M</td>
<td>R</td>
<td>18</td>
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</tr>
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<td>17</td>
<td>Control</td>
<td>61</td>
<td>M</td>
<td>R</td>
<td>16</td>
<td>0</td>
</tr>
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<td>18</td>
<td>Control</td>
<td>56</td>
<td>M</td>
<td>R</td>
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<td>19</td>
<td>Control</td>
<td>55</td>
<td>M</td>
<td>R</td>
<td>16</td>
<td>0</td>
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<td>Control</td>
<td>61</td>
<td>M</td>
<td>R</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>Control</td>
<td>64</td>
<td>M</td>
<td>R</td>
<td>16</td>
<td>0.5</td>
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</tbody>
</table>
Table 5. Means, standard deviations (SD), and \( p \)-values for comparisons between patients with pure cerebellar syndrome (Ataxia) and age-, sex-, handedness-, and education-matched controls for questionnaire measures. \* \( p \)-values that indicate significant differences between patients and controls.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Ataxia</th>
<th>Control</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>PSQI</td>
<td>6.87</td>
<td>4.10</td>
<td>5.06</td>
</tr>
<tr>
<td>ESS</td>
<td>8.00</td>
<td>4.86</td>
<td>6.13</td>
</tr>
<tr>
<td>MEQ</td>
<td>59.80</td>
<td>5.25</td>
<td>59.80</td>
</tr>
<tr>
<td>CH-RLSq</td>
<td>2.56</td>
<td>3.08</td>
<td>1.31</td>
</tr>
<tr>
<td>SSS1 (Evening)</td>
<td>2.85</td>
<td>1.07</td>
<td>1.69</td>
</tr>
<tr>
<td>SSS2 (Morning)</td>
<td>2.58</td>
<td>1.47</td>
<td>1.6</td>
</tr>
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</table>
Table 6. Means, standard deviations (SD), and \( p \)-values for comparisons between patients with pure cerebellar syndrome (Ataxia) and age-, sex-, handedness-, and education-matched controls for scores on the Cerebellar Cognitive Affective Syndrome Rating Scale (CCAS-RS), including total scores, number of failed tests, and scores in individual cognitive domains. *\( p \)-values that indicate significant differences between patients and controls.

<table>
<thead>
<tr>
<th>Measure of Executive Function</th>
<th>Ataxia</th>
<th>Control</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCAS-RS (Raw Score)</td>
<td>88.58</td>
<td>98.08</td>
<td>0.02*</td>
</tr>
<tr>
<td>CCAS-RS (# Failed Tests)</td>
<td>2.08</td>
<td>1.58</td>
<td>0.49</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>31.00</td>
<td>37.33</td>
<td>0.01*</td>
</tr>
<tr>
<td>Cognitive Flexibility</td>
<td>9.92</td>
<td>12.42</td>
<td>0.05</td>
</tr>
<tr>
<td>Abstract Reasoning</td>
<td>6.83</td>
<td>7.08</td>
<td>0.39</td>
</tr>
<tr>
<td>Inhibitory Control</td>
<td>1.33</td>
<td>1.67</td>
<td>0.27</td>
</tr>
<tr>
<td>Digit Span</td>
<td>10.92</td>
<td>10.50</td>
<td>0.51</td>
</tr>
<tr>
<td>Verbal Recall</td>
<td>10.17</td>
<td>9.92</td>
<td>0.87</td>
</tr>
<tr>
<td>Visuospatial Abilities</td>
<td>12.25</td>
<td>13.58</td>
<td>0.10</td>
</tr>
<tr>
<td>Affect</td>
<td>5.33</td>
<td>5.58</td>
<td>0.47</td>
</tr>
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</table>
Table 7. Means, standard deviations (SD), and p-values for comparisons between patients with pure cerebellar syndrome (Ataxia) and age-, sex-, handedness-, and education-matched controls for performance measures associated with the word-pair association task. *p-values that indicate significant differences between patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Ataxia Mean</th>
<th>Ataxia SD</th>
<th>Controls Mean</th>
<th>Controls SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Loops</td>
<td>4.23</td>
<td>1.17</td>
<td>4.00</td>
<td>1.22</td>
<td>0.63</td>
</tr>
<tr>
<td>Immediate Recall Accuracy</td>
<td>0.47</td>
<td>0.35</td>
<td>0.75</td>
<td>0.22</td>
<td>0.02*</td>
</tr>
<tr>
<td>Delayed Recall Accuracy</td>
<td>0.41</td>
<td>0.35</td>
<td>0.73</td>
<td>0.23</td>
<td>0.01*</td>
</tr>
<tr>
<td>Change in Accuracy (Delayed - Immediate)</td>
<td>-0.06</td>
<td>0.11</td>
<td>-0.02</td>
<td>0.06</td>
<td>0.32</td>
</tr>
</tbody>
</table>
Table 8. Means, standard deviations (SD), and $p$-values for comparisons between patients 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 patients and controls.

<table>
<thead>
<tr>
<th>Actigraphy Measure</th>
<th>Ataxia</th>
<th>Control</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Overnight Measures</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>484.01</td>
<td>39.95</td>
<td>475.44</td>
</tr>
<tr>
<td>OnsetLatency</td>
<td>3.03</td>
<td>2.67</td>
<td>2.04</td>
</tr>
<tr>
<td>Efficiency</td>
<td>90.13</td>
<td>4.71</td>
<td>92.71</td>
</tr>
<tr>
<td>WASO</td>
<td>42.25</td>
<td>21.51</td>
<td>30.48</td>
</tr>
<tr>
<td>MobileTime</td>
<td>8.72</td>
<td>3.70</td>
<td>6.30</td>
</tr>
<tr>
<td><strong>Nap Measures</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>33.45</td>
<td>33.18</td>
<td>34.43</td>
</tr>
<tr>
<td>OnsetLatency</td>
<td>0.46</td>
<td>0.75</td>
<td>0.35</td>
</tr>
<tr>
<td>Efficiency</td>
<td>52.21</td>
<td>47.05</td>
<td>52.50</td>
</tr>
<tr>
<td>WASO</td>
<td>2.59</td>
<td>3.93</td>
<td>2.99</td>
</tr>
<tr>
<td>MobileTime</td>
<td>4.70</td>
<td>5.61</td>
<td>4.37</td>
</tr>
</tbody>
</table>
Table 9. Means, standard deviations (SD), and $p$-values for comparisons between patients 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 patients and controls.

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>Ataxia</th>
<th>Control</th>
<th>$p$-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Sleep Architecture</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total Sleep Time (mins)</td>
<td>357.15</td>
<td>431.84</td>
<td>0.05*</td>
</tr>
<tr>
<td>Sleep Onset Latency (mins)</td>
<td>13.81</td>
<td>9.91</td>
<td>0.35</td>
</tr>
<tr>
<td>Wake After Sleep Onset (mins)</td>
<td>63.50</td>
<td>53.06</td>
<td>0.44</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>80.73</td>
<td>87.83</td>
<td>0.11</td>
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<tr>
<td>NREM Stage 1 (%)</td>
<td>28.49</td>
<td>23.24</td>
<td>0.24</td>
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<tr>
<td>NREM Stage 2 (%)</td>
<td>33.89</td>
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<td>0.91</td>
</tr>
<tr>
<td>Slow-Wave Sleep (%)</td>
<td>21.03</td>
<td>22.56</td>
<td>0.57</td>
</tr>
<tr>
<td>REM Sleep (%)</td>
<td>17.23</td>
<td>19.94</td>
<td>0.16</td>
</tr>
<tr>
<td>SFI (Transitions per Hour)</td>
<td>23.88</td>
<td>17.83</td>
<td>0.01*</td>
</tr>
<tr>
<td>AHI (# Events per Hour)</td>
<td>11.71</td>
<td>9.43</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Spectral Power Density</strong></td>
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<tr>
<td>Slow Oscillations (0.5-1 Hz)</td>
<td>113.22</td>
<td>106.64</td>
<td>0.81</td>
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<tr>
<td>Delta (1-4 Hz)</td>
<td>39.06</td>
<td>35.97</td>
<td>0.67</td>
</tr>
<tr>
<td>Theta (5-8 Hz)</td>
<td>5.21</td>
<td>4.16</td>
<td>0.23</td>
</tr>
<tr>
<td>Sigma (11-16 Hz)</td>
<td>2.27</td>
<td>1.86</td>
<td>0.24</td>
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<tr>
<td>Slow Sigma (11-13 Hz)</td>
<td>2.97</td>
<td>2.53</td>
<td>0.41</td>
</tr>
<tr>
<td>Fast Sigma (14-16 Hz)</td>
<td>1.55</td>
<td>1.17</td>
<td>0.05*</td>
</tr>
</tbody>
</table>
Figures

Figure 6. Experimental procedures

WORD PAIR TASK:
1. Encoding
2. Immediate Recall

POLYSOMNOGRAPHY

OVERNIGHT SLEEP

WORD PAIR TASK: Delayed Recall

Participants wear the actigraphy watch and maintain a sleep diary

Motor, Cognitive and Apnea Assessments

DAY 1 DAY 2 DAY 3 DAY 4 DAY 5 DAY 6 DAY 7

8PM 9PM 10PM 11PM 12AM 1AM 2AM 3AM 4AM 5AM 6AM 7AM
Figure 7. Compared to their age-, sex-, handedness-, and education-matched controls, patients with pure cerebellar syndrome (Ataxia) demonstrated impairments in a) verbal fluency and cognitive flexibility domains of the Cerebellar Cognitive Affective Syndrome Rating Scale (CCAS-RS), and b) accuracy at Immediate and Delayed Recall phases of the word-pair association task. * indicate significant differences between patients and controls.

(a) Scores on CCAS-RS Sub-Test

(b) Accuracy (Proportion Correct)
Figure 8. Compared to their age-, sex-, handedness-, and education-matched controls, patients 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. * indicate significant differences between patients and controls.

a) 

![Boxplot of Total Sleep Time (TST) for Ataxia and Control groups. Asterisk indicates significant difference.]

b) 

![Boxplot of Sleep Fragmentation Index (Transitions per Hour) for Ataxia and Control groups. Asterisk indicates significant difference.]

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**Figure 9.** Patients with pure cerebellar syndrome (Ataxia) had higher spectral power density in the fast sigma frequency range (14-16 Hz) during NREM over the frontal and central derivations compared to their age-, sex-, handedness-, and education-matched controls. * indicate significant differences between patients and controls.
Figure 10. Patients 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. * indicate significant differences between patients and controls.
**Figure 11.** Correlation between the severity of motor deficits and the Sleep Fragmentation Index, or the number of stage transitions and awakenings occurring per hour of sleep ($r_s = 0.447$, $p = 0.013$).
Figure 12. Correlations between the severity of motor deficits and raw scores on the Cerebellar Cognitive Affective Syndrome/Schmahmann Syndrome Rating Scale (CCAS/Schmahmann Syndrome-RS; $r_s = -0.556, p = 0.005$).
Figure 13. 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 executive function, as measured by the Cerebellar Cognitive Affective Syndrome Rating Scale (CCAS-RS; $r_s = -0.528, p = 0.008$), and b) the Sleep Fragmentation Index and baseline memory retrieval on the declarative word-pair association task ($r_s = -0.531, p = 0.001$).
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