The relationship between long-term sleep profiles and challenging behavior in individuals with low-functioning autism

Submitted by
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School of Psychological Sciences

To Marc Mer and my parents Arnold and Wendy for supporting me through this journey and offering unconditional love and patience.

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Table of Contents

Abstract

Autism spectrum disorder (or autism) is associated with a high prevalence of sleep problems and behavioral difficulties. Prior research indicates that between 40-80% of children with autism experience problems with sleep (Richdale & Schreck, 2009) and approximately 64-93% have at least one challenging behavior (Didden et al., 2012) (i.e., behaviors that are physically dangerous and impact learning; for example, aggression, self-injury or tantrums). Although the association between reduced sleep quality and increased frequency of challenging behaviors has been investigated in adults and children with high-functioning autism (Lambert et al., 2016; Hirata et al., 2016; Fadini et al., 2015), these relationships are not fully understood in individuals with low-functioning autism (i.e., individuals with severe social-communication difficulties and intellectual impairment, IQ ≤ 70). It is well known that individuals with low-functioning autism have a higher prevalence of sleep and behavioral problems compared to individuals with high-functioning autism due to the severity of their symptoms (Adams, Matson, Cervantes, & Goldin, 2014), however the nature of their sleep deficits and their relationship to behavior have not been extensively studied in this population. Furthermore, as previous research has focused only on broad global associations between sleep and behavior across individuals with autism, it remains unclear as to whether: i) these relationships translate in real-time for a given individual and ii) whether these relationships exist in a bidirectional manner (i.e., can we use also prior challenging behavior to predict future sleep problems in individuals with autism?).

Consequently, the overarching aim of this thesis was to systematically understand long-term patterns of sleep-wake behavior and their real-time relationship to daytime challenging behavior in an understudied population of individuals with low-functioning autism. To achieve this overall aim, this thesis capitalizes on an unprecedented dataset of nightly sleep-awake recordings and daily behavioral recordings across a 6 month to 6 year time range (over ~60,000 observations of sleep and behavior) recruited from a cohort of over 100 individuals with low-functioning autism living in two residential facilities in Boston, USA. Chapter two presents a comprehensive literature review on the nature of sleep difficulties in autism, and reviews studies that examine the association between sleep and behavior in this population. It highlights the limitations of the knowledge to date and areas for future research, including the focus on individuals with low-functioning autism. Chapter three provides an understanding of the dataset and the machine learning techniques used to analyse

patterns of sleep and behavior, using a large dataset of clinical observations from two residential schools.

Chapter four provides an investigation into the nature of sleep phenotypes and their relation to adaptive functioning in individuals with low-functioning autism using cluster-analysis. Findings from this study demonstrated the existences of two behaviorally determined sleep phenotypes in individuals with low-functioning autism, including a 'stable' and 'unstable' sleep phenotype. These phenotypes displayed significant differences in properties that were not used for clustering, such as intellectual functioning, communication and adaptive functioning. This study demonstrated the heterogeneous nature of sleep profiles and their link to symptom severity in individuals with low-functioning autism. Moreover, the findings provide a foundation for profiling sleep problems as a standard part of treatment in individuals with low-functioning autism.

Chapter five examines the real-time predictive relationship between prior sleep and daytime challenging behavior in individuals with low-functioning autism. For each of the 67 individuals examined, sleep feature summaries from the previous 1-14 nights across a 1.5-year recording period were calculated, and these features were used to train a support vector machine learning classifier to predict the presence or absence of a challenging behavior the next day. Taken across individuals, this study found a significant predictive relationship between prior sleep and challenging behavior, with accuracies that increased with the duration of prior sleep used to make the prediction (up to one week). This relationship was reproduced for all behaviors explored (including aggression, self-injury and tantrums), suggesting a robust cumulative effect of sleep history on daytime functioning in autism. Interestingly, individuals with greater overall prediction accuracy (of behavior from prior sleep) had greater impairments in adaptive functioning, highlighting a relationship between symptom severity, sleep and daytime challenging behavior in autism.

Finally, chapter six investigates the bidirectional relationship between nightly sleep duration and daily episodes of challenging behavior in children with low-functioning autism. To examine these associations, this study utilized linear mixed models with random effects to account for individual differences. Findings demonstrated a significant bidirectional relationship between nightly sleep duration and daily frequency of challenging behavior episodes averaged across individuals with low-functioning autism, with a large degree of inter-individual variability between these associations. Moreover, the relative strength of these relationships suggested that daily challenging behavior episodes more strongly predicted nightly sleep duration than the inverse relationship, highlighting the impact of daytime behavior on the subsequent night's sleep quality in autism. Furthermore, individuals with stronger predictive relationships between daily challenging behavior and nightly sleep duration had greater impairments in adaptive functioning. Together, the findings from chapters four and five pave the way for future work in developing real-time monitoring tool to pre-empt behavioral and sleep problems, which will help facilitate prophylactic treatment in individuals with autism.

In this thesis, we present the first examination into the relationship between long-term sleep-wake behavior patterns and daytime challenging behavior in individuals with low-functioning autism. Using an unprecedented dataset of nightly sleep-wake recordings and daily behavior observations, we found robust sleep phenotypes and a predictive relationship between prior sleep and challenging behavior in individuals with low-functioning autism. Importantly we were able to uncover these relationships despite coarse observational measurements of sleep-wake behavior and observations of daytime challenging behavior in individuals that varied in age, medications, sleep patterns, and behavioral profiles. Moreover, the comprehensive data processing and prediction algorithms introduced here constitute the first step in isolating robust sleep-wake relationships in large and complex temporal datasets (that will become easier to collect in the future with sensors and smartphone technology) and provide a foundation towards real-time clinical monitoring of sleep and behavior to inform patient care in individuals with autism.

Publications during enrolment

Cohen, S., Conduit, R., Lockley, S.W., Rajaratnam, S.W., & Cornish, K.M. (2014). The relationship between sleep and behavior in autism spectrum disorder (ASD): a review. *Journal of Neurodevelopmental Disorders, 6*(44), 1-10.

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Conference presentations

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2013 Australian Postgraduate Award – Australian Commonwealth Government.
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2015 Dissertation Travel Grant for the Gatlinburg Conference (Vanderbilt Kennedy Center, USA)

General Declaration

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Masters regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes one original papers published in a peer reviewed journal and three unpublished publications. The core theme of the thesis is to uncover the relationship between sleep and behavior in individuals with low-functioning autism. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Psychological Sciences under the supervision of Professor Kim Cornish.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 2, 4, 5, 6 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent (%) of students contribution
Two	The relationship between sleep and behavior in autism spectrum disorder (ASD): A review	Published	80% contribution by candidate: review of relevant literature and writing of literature review
Four	Behaviourally determined sleep phenotypes robustly associated with adaptive functioning in individuals with low-functioning autism	Submitted	70% contribution by candidate: project design, review of relevant literature, collection of data, analysis of data and writing up manuscript.
Five	Challenging behavioral events predicted from prior sleep patterns in individuals with low-functioning autism	Submitted	60% contribution by candidate: project design, review of relevant literature, collection of data, analysis of data and writing up manuscript.
Six	The bidirectional associations between daytime challenging behaviors and night-time sleep duration in children with low-functioning autism	Submitted	80% contribution by candidate: project design, review of relevant literature, collection of data, analysis of data and writing up manuscript.

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date:** 20/07/16

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work.

Main Supervisor signature: [redacted] **Date:** 20/07/16

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The completion of this PhD has been one of the most challenging yet rewarding goals of my life. While this journey has pushed me far out of my comfort zone, it has brought with it unmeasurable opportunities, invaluable experiences, collaborations, individuals and funding bodies to whom I owe my sincerest gratitude.

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Chapter 1: Introduction

1.1. Research Overview

Autism spectrum disorder (or autism) is a widely investigated neurodevelopmental disorder with characterized impairments in social-communication as well as repetitive and restricted interests and behaviors (American Psychiatric Association, 2013). Over the last few years, there has been a dramatic increase in the prevalence of autism from 1 in 88 children in 2008 to 1 in 68 children in 2014 (Baio, 2014). Moreover, the annual societal cost continues to escalate with recent predictions to be $126 billion in the US (Buescher, Cidav, Knapp, & Mandell, 2014). Autism is characterized by notable phenotypic heterogeneity, which increases the complexity in researching and understanding this disorder (Kim, Macari, Koller, & Chawarska, 2016). The degree of impairment in individuals with autism is variable, with approximately 20-50% of individuals affected by a co-morbid intellectual disability (otherwise known as individuals with low-functioning autism, IQ $\leq$ 70), while others have average to superior levels of intelligence (otherwise known as high-functioning autism (IQ > 70)). In addition to the diverse severity of autism symptoms, many individuals exhibit a range of challenging behaviors that includes tantrums, aggression and self-injurious behaviors (Jang, Dixon, Tarbox, & Granpeesheh, 2011). Not surprisingly, the considerable variation in symptom presentation within an individual, and across their life span, has significantly impacted the ability to understand the etiology, diagnosis, prognosis and treatment of autism (Georgiades et al., 2013). Due to the poor characterization of this disorder, there is a need to conduct studies beyond traditional cross-sectional designs in understudied and homogenous groups of individuals with autism.

One of the most common co-morbidities in autism is sleep difficulties with 40-60% of children experiencing sleep problems, compared to 25-50% in typically developing populations (Richdale & Schreck, 2009). Although sleep difficulties in individuals with high-functioning autism has been well characterized (including later sleep onset, shorter total sleep time and increased night awakenings) (Baker & Richdale, 2015; Cortesi, Giannotti, Ivanenko, & Johnson, 2010; Johnson, Giannotti, & Cortesi, 2009; Veatch, Maxwell-Horn, & Malow, 2015) there has been limited focus and attention on sleep problems that exist in children with low-functioning autism. While some studies have suggested that increased autism severity is associated with increased sleep deficits (Adams et al., 2014; Schreck, Mulick, & Smith, 2004), there is a lack of characterization of these sleep deficits. To date, it remains unknown whether individuals with low-functioning autism have difficulty with sleep initiation or sleep maintenance, and how these difficulties impact other pre-existing difficulties such as levels of adaptive functioning. Despite a large number of previous sleep studies in children with autism, there are limitations in the nature in which sleep disruptions are investigated including the use of broad heterogeneous autism samples, which include individuals with and/or without an intellectual disability, across broad age spans and the nature of cross-sectional designs which examine overall sleep disruption at one point in time. Moreover, there is a high reliance on parent report measures (such as the Child Sleep Habits Questionnaire), which although has been shown to be poorly validated against objective measures of sleep in autism (Hodge, Parnell, Hoffman, & Sweeney, 2012), a recent study has shown it to be as accurate as actigraphy when parents are provided with sleep education (Veatch et al., 2016). As such, the precise nature, impact and measurement of sleep difficulties affecting individuals with low-functioning autism remain unclear and understudied.

In a developing child, sleep serves multiple functions including energy conservation, brain growth, memory consolidation and cognition (Gregory & Sadeh, 2012). The importance of sleep across childhood is reflected throughout pediatric sleep literature, as inadequate sleep (both in terms of quality and quantity) has been shown to be associated with poor physical and behavioral outcomes (Vriend et al., 2013), reduced overall health (Smaldone, Honig, & Byrne, 2007) and increased risk of injuries (Hayes, 2010). Moreover, studies examining the effects of cumulative sleep loss have shown that sleep loss over 3-5 consecutive days produces temporary difficulties in cognition, behavior and physical health in typically developing children (see Jan et al., 2010 for review). Despite the highlighted links between sleep and behavior in typical children (Baum, Desai, Miller, Rausch, & Beebe, 2014; Chervin, Dillon, Archbold, & Ruzicka, 2003), few studies to date have examined the relationship between these domains in children with autism, and no study to date has examined these relationships at all in individuals with low-functioning autism. Given the importance of sleep in daily functioning, the consequence of disrupted sleep in individuals with autism is potentially serious and therefore requires further investigation.

The majority of past studies examining the relationship between sleep and behavior in autism have examined between-person differences in sleep and behavior in individuals with high-functioning autism or mixed autism diagnoses at one point in time in either experimental, cross-sectional or correlational studies. While cross-sectional studies have found an association between average sleep duration and average frequency of challenging behaviors (including tantrums, self-injury and aggression) across a 1-week period (Goldman et al., 2011; Sikora, Johnson, Clemons, & Katz, 2012, Hirata et al., 2016, Mazurek & Sohl, 2016), correlational studies have found no relationship between parent reported sleep duration and externalizing problems averaged across a 6-week time period (Fadini et al., 2015). Moreover, objective sleep studies using polysomnography (PSG) and actigraphy over a 2-week period have failed to find a relationship between sleep quality and behavior in autism (Goodlin-Jones, Tang, Liu, & Anders, 2009; Lambert et al., 2016). Thus the association between sleep and behavior in autism is inconclusive, and studies are currently limited by their use of cross-sectional designs, retrospective and subjective parent reports of sleep and behavior, short monitoring periods of sleep and primary focus on individuals with mixed autism diagnoses (both high and low functioning autism). As such, these inconsistent findings suggest that the relationship between sleep and behavior in autism requires further investigation.

Crucially, all previous research examining the relationship between sleep and behavior (both in autism and other populations) have focused on the association between an individuals' overall sleep and their overall behavior. These findings provide a *'static'* picture of the sleep-behavior relationship that tells us *which* individuals (on average) are more likely to exhibit poor behavior given their overall sleep. It therefore remains unclear whether these relationships apply only globally, or whether they have real-time predictive value for a given individual, i.e., whether fluctuations in sleep over time predict corresponding fluctuations in behavior over time. This *'temporal'* picture of the sleep-behavior relationship tells us *when* problem behaviors will occur, and thus can inform preventative interventions against future behaviors. Prior studies into the temporal sleep-behavior relationship are scarce and only one study to date has investigated the prediction of mood from prior sleep patterns (Sano et al., 2015). This thesis is the first to examine a temporal relationship between sleep and behavior and their bidirectional relationship in an understudied population of individuals with low-functioning autism, using an unprecedented dataset of nightly sleep-wake observations and daily behavior recordings.

This thesis builds on the research to date by expanding beyond traditional cross-sectional designs, using predictive modelling in order to uncover: i) unique long-term sleep-wake patterns in individuals with low-functioning autism and ii) the real-time predictive relationship between sleep and behavior in children with low-functioning autism and their bidirectional relationship. The investigation into the nature of sleep phenotypes in this population, and the ability to predict behavior and sleep disruptions in real-time, will lead to an enhanced understanding of treating symptoms of low-functioning autism, with the hope of reducing its global and economic burden. Gaining specific insight into the individual nature of sleep difficulties in autism opens up a novel avenue for designing interventions, as sleep and behavior is an area with a potential for remediation.

1.2. Research Aims

The overarching aim of this research was to identify systematically, the nature of long-term sleep difficulties and its relationship to challenging behavior in an understudied population of individuals with low-functioning autism. To achieve this overall aim this research examines an unprecedented dataset of nightly sleep-awake observations and daily behavioral observations across a 6 month to 6-year time range obtained from a cohort of 179 individuals with low-functioning autism living in two residential facilities in Boston, USA.

The primary aims of this thesis include:

1) To investigate the current literature into the understanding of the nature of sleep and behavioral difficulties in individuals with autism.
2) To identify clinically meaningful subgroups of individuals with low-functioning autism that is related to distinct patterns of sleep difficulties and clinical symptoms.
3) To develop a model, that prospectively predicts challenging behaviors from prior sleep in individuals with low-functioning autism.
4) To develop a model, that prospectively predicts both daytime challenging behaviors and night-time sleep duration from prior outcomes of sleep and behavior in children with low-functioning autism.

1.3. Research Outline

This thesis is structured as a series of published papers, chapters or manuscripts under review. There are additional sections of linking text were appropriate to ensure that this thesis is coherent. Chapter two reviews the existing evidence for the relationship between sleep and behavior in autism, and specifically highlights the need to profile sleep phenotypes and study these relationships in individuals with low-functioning autism. Chapter three provides an understanding of the dataset including the measurements of sleep and behavior and the statistical techniques used to study the relationships between sleep and behavior in this population. Chapter four examines behaviorally determined sleep phenotypes in individuals with low-functioning autism, and their relationship to clinical symptoms. Chapter five examines the real-time predictive relationship between prior sleep and future episodes of challenging behaviors, and investigates which sleep features are most predictive of future challenging behavioral events in this population. Finally, chapter six examines the bidirectional relationship between nightly sleep duration and daily episodes of challenging behavior in children with low-functioning autism. Given that this thesis is presented in formatted journal style, there will be unavoidable repetition in some sections. Finally, the general discussion evaluates the main findings in view of the overarching aims of this thesis.

Declaration for Thesis Chapter 2

Declaration by candidate

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Review of relevant literature and writing of literature review.	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Extent of contribution (%) student and co-authors only**
Dr Russell Conduit and Professor Kim Cornish	Contributed to discussion of theoretical issues, provided expertise on drafting and critically reviewed the manuscript	
Professor Steven W. Lockley and Professor Shantha M.W Rajaratnam	Critical review of the manuscript	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidates signature	[redacted]	Date: 20/07/16

Main supervisors signature	[redacted]	Date 20/07/16

Chapter 2: The relationship between sleep and behavior in children with autism spectrum disorder (ASD): A review

2.1 Preamble to review paper 1: The relationship between sleep and behavior in children with autism spectrum disorder (ASD): A review

This published review paper explores the existent literature on the relationship between sleep and behavior in children with autism spectrum disorder. This paper covers a range of pertinent topics in the field including an understanding of low-functioning autism, the etiology of sleep problems in individuals with autism, and the heterogeneity in sleep profiles in this population. It also provides an overview of the current research on the relationship between sleep and behavior in autism, and highlights areas for future research. This review highlights the gaps in the literature including profiling sleep phenotypes and the need to research the sleep-behavior relationships in children with low-functioning autism using unconventional longitudinal designs.

Cohen, S., Conduit, R., Lockley, S.W., Rajaratnam, S.W & Cornish, K. (2014). The relationship between sleep and behavior in children with autism spectrum disorder (ASD): A review. *Journal of Neurodevelopmental Disorders, 6*(44), 1-10.

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Cohen et al. Journal of Neurodevelopmental Disorders 2014, 6:44
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REVIEW — Open Access

The relationship between sleep and behavior in autism spectrum disorder (ASD): a review

Simonne Cohen[1*], Russell Conduit[2], Steven W Lockley[1,3,4], Shantha MW Rajaratnam[1,3,4] and Kim M Cornish[1*]

Abstract

Although there is evidence that significant sleep problems are common in children with autism spectrum disorder (ASD) and that poor sleep exacerbates problematic daytime behavior, such relationships have received very little attention in both research and clinical practice. Treatment guidelines to help manage challenging behaviors in ASD fail to mention sleep at all, or they present a very limited account. Moreover, limited attention is given to children with low-functioning autism, those individuals who often experience the most severe sleep disruption and behavioral problems. This paper describes the nature of sleep difficulties in ASD and highlights the complexities of sleep disruption in individuals with low-functioning autism. It is proposed that profiling ASD children based on the nature of their sleep disruption might help to understand symptom and behavioral profiles (or vice versa) and therefore lead to better-targeted interventions. This paper concludes with a discussion of the limitations of current knowledge and proposes areas that are important for future research. Treating disordered sleep in ASD has great potential to improve daytime behavior and family functioning in this vulnerable population.

Keywords: Autism spectrum disorder, Low-functioning autism, Sleep difficulties in ASD, Treating sleep in ASD

Review

Autism spectrum disorder (ASD) is a developmental disorder characterized by deficits in social communication and repetitive and stereotyped interests and behaviors [1]. Autism is among the most enigmatic disorders of child development, with a dramatic increase in prevalence from 1 in 88 children in 2008 to 1 in 68 children in 2010 [2]. While the global burden of ASD is currently unknown, in the United States, the annual societal cost of the condition was recently predicted to be $126 billion and $34 billion in the UK [3]. This escalation and economic burden identify individuals with ASD as one of the highest priority populations for clinical research and treatment development.

Currently, one of the most burdensome complaints among parents of children with autism is disrupted sleep, with more than 40–80% of children experiencing sleep problems, compared with 25–40% in typically developing children (TYP) [4,5]. In a developing child, sleep serves multiple functions, including energy conservation, brain growth, memory consolidation, and cognition [6]. Given the importance of sleep in daily functioning, the consequence of disrupted sleep in individuals with ASD is potentially serious. Recent research has shown that insufficient sleep exacerbates the severity of core ASD symptoms (e.g., repetitive behaviors, social and communication difficulties) [7,8], as well as other maladaptive behaviors (e.g., self–injury, tantrums, and aggression) [9,10]. To date, however, the relationship between sleep profiles and behavioral problems in individuals with ASD is limited. Current sleep treatments fail to target the specific nature of deficits in individuals with low-functioning autism. In this paper, we emphasize that the identification sleep profiles in children with low-functioning autism are necessary to identify targeted interventions, particularly for challenging behaviors in this disorder. This review concludes with methodological considerations and offers suggestions for future research designed to more clearly understand disrupted sleep so as to provide targeted treatments in this population.

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Low-functioning autism

ASD is characterized by notable phenotypic heterogeneity, which is often viewed as an obstacle to the study of etiology, diagnosis, treatment, and prognosis [11]. The degree of impairment among individuals with ASD is variable, thereby requiring the distinction between individuals with low-functioning autism and high-functioning autism, defined as those which have an intellectual quotient that is below average (<70) and above average (≥70), respectively [1]. What the current DSM-V fails to capture is that individuals with low-functioning autism experience significantly graver impairments than those experienced by their higher functioning counterparts [12]. In addition to displaying core symptoms of ASD, many children with low-functioning autism may exhibit serious behavioral disturbances such as tantrums, aggression, environmental destruction, socially inappropriate behavior, and self-injurious behavior [13]. Therefore, a child with low-functioning autism is likely to have a much more complex diagnostic picture, including a greater severity of ASD symptoms and associated co-morbidities and often require life-long extensive support. To date, these groups of individuals have not received comparable attention compared to individuals with high-functioning autism. This paper argues that these groups of individuals should be the focus of future research as they are most in need of treatment.

Sleep difficulties in autism spectrum disorder

ASD is frequently accompanied by co-morbid disorders and associated problems, one of which is sleep disruption [14,15]. One of the most burdensome and profound complaints among parents and caregivers of children with ASD is poor sleep. Research suggests that about 40–80% of individuals with an ASD experience a sleep problem, and the risk appears to be unrelated to the severity of cognitive impairment [16]. Other researchers have shown that individuals with low-functioning autism have a higher predisposition to chronic sleep-wake cycle disturbances when compared to higher-functioning individuals, given the degree and severity of their cognitive impairment [17]. This paper argues that understanding, identifying, and treating sleep disorders in low-functioning autism may impact favorably on associated conditions and daytime behavior and therefore improve the quality of life in this population.

Heterogeneity of sleep difficulties in ASD

Since ASD is considered to be a multifaceted disorder reflected in different symptom profiles across individuals, it is not surprising that a multitude of sleep problems are prevalent in this population. Moreover, the variability of sleep profiles in ASD is suggestive of the mixed phenotypic profiles of ASD samples. Among children with ASD, the most common sleep issues are prolonged sleep latency, decreased sleep efficiency, reduced total sleep time, increased waking after sleep-onset, bedtime resistance, and daytime sleepiness; see [18] for a review. Accordingly, there does not appear to be one particular sleep problem that characterizes children with ASD, but many. These sleep difficulties appear to persist throughout the lifespan [19] and individuals with ASD who experience one sleep problem will often experience co-existing sleep problems [20]. Several of these sleep difficulties can be classified according to the International Classification of Sleep Disorders (ICSD-3) as primary sleep disorders (e.g., insomnia, parasomnia, and circadian rhythm sleep-wake disorders) [21]. In Table 1, the most common sleep problems in ASD have been reported against the ICSD-3 broad criteria for classifying sleep disorders in order to give a sense of the range and scope of sleep difficulties that are present in ASD. To date, most of the studies exploring sleep in ASD have focused on individuals with high-functioning autism, those individuals who have an ability to communicate and cooperate during actigraphy and polysomnography sleep studies [22]. Currently, there is an inconsistent understanding of the nature and prevalence of sleep difficulties in low-functioning autism. One study has suggested that the severity of sleep problems (such as sleep-onset delay and sleep duration) increases with the severity of autism symptoms (such as communication deficits) [8]. Another study has suggested that increased autism severity predicts an increased likelihood of sleep problems [23]; however, these links are still speculative, and sleep profiles in low-functioning autism are yet to be elucidated. To date, it is still unclear what specific sleep problems and symptom relationships are unique to individuals with low-functioning autism.

The complex etiology of sleep disturbances in individuals with ASD

Although highly prevalent and persistent, the etiology of sleep problems in children with ASD remains uncertain [41]. Several theories have been put forward to suggest that sleep disruption may be a direct result of either i) the ASD condition or ii) other associated co-morbidities. Research has suggested that the underlying neurophysiology and neurochemistry may predispose individuals with ASD to have chronic sleep-wake disturbances. The development of circadian rhythms, which is established within 12–16 weeks of birth, requires the perception of the environmental time cues ("zeitgebers") to permit appropriate entrainment with the 24-h day (i.e., the synchronization of the internal biological clock to external time cues). The most powerful time cue is the 24-h light/dark cycle, but non-photic time cues such as timing of meals and social contacts can also have influence. Where brain damage or maldevelopment has occurred such as in ASD, these entrainment pathways may be impaired [19]. Children with low-functioning autism are subject to many variables that can potentially affect circadian entrainment, including decreased sensitivity to

Table 1 ICSD-3 Classification of sleep disorders in children with ASD including descriptions and evidence

ICSD-3 Classification	Sleep profile	Study	Sleep measures	Significant findings in ASD population
Insomnia	Persistent difficulty with sleep initiation, maintenance, duration, consolidation, or quality. Includes bedtime resistance, frequent night awakenings, and/or an inability to sleep independently	Wiggs *et al.* [24]	Actigraphy and SQ	Increased sleep latency, night awakenings, and poor sleep efficiency
		Malow *et al.* [25]	PSG and CSHQ	Poorer sleep efficiency, longer sleep latency, and frequent night awakenings (up to 2–3 h)
		Goodlin-Jones *et al.* [26]	Actigraphy and SD	Less total sleep time (TST) compared to TYP children or those with a DD
		Krakowiak *et al.* [27]	SQ	Higher sleep-onset factor scores and night awakenings compared to typical children
		Souders *et al.* [28]	CSHQ, SD, and actigraphy	Behavioral insomnia evident in 66% of children with ASD compared to 45.9% in controls
		Anders *et al.* [29]	Actigraphy and SD	ASD children aged 2–5 years slept less per 24-h period on average compared to controls
		Giannotti *et al.* [30]	PSG and CSHQ	Children with regressive ASD ($n = 18$) had greater bedtime resistance, sleep-onset latency, and less TST than controls
		Sivertsen *et al.* [31]	Parent report	Prevalence of chronic insomnia was ten times higher in children with ASD symptoms compared to controls
		Baker *et al.* [32]	Actigraphy and SD	Adolescents with ASD were three times more likely to have symptoms of insomnia than their TYP peers
Parasomnias	Undesirable physical experiences which occur within sleep or during arousal from sleep. Includes nightmares, wake screaming, complex movements, dreams, and automatic nervous system activity	Hering *et al.* [33]	Actigraphy and SQ	54% of children with ASD had multiple and early night arousals
		Doo *et al.* [34] Schreck *et al.* [35] Liu *et al.* [20]	SQ, CSHQ, and actigraphy	All reported evidence of higher rates of parasomnias in children with ASD compared to comparison groups
		Goldman *et al.* [36]	CSHQ	Younger children with ASD had more parasomnias than older children
Circadian rhythm sleep-wake disorders	Alterations of the circadian time-keeping system, its entrainment mechanisms, or misalignment of the endogenous circadian rhythm and the external environment. Manifests in difficulty initiating and maintaining sleep	Giannotti *et al.* [37]	PSG and CSHQ	More than 10% of children with ASD were found to have sleep problems that varied by season due to fluctuations in light/dark cycles
		Tordjman *et al.* [38]	Measures of melatonin	Elevated daytime and lower nocturnal melatonin in individuals with ASD compared with controls
		Hayashi [39] Segawa [40]	SD, CSHQ, and PEQ	"Free-running" sleep (not entrained to 24-h), sleep-onset delay, and early morning awakening in children with ASD

CSHQ Child Sleep Habit Questionnaire, *DD* developmental disability, *TYP* typical development, *PEQ* Parenting Events Questionnaire, *PSG* polysomnography, *SD* sleep diary, *SQ* Sleep Questionnaire.

social cues, and possible misalignment between circadian phase and imposed light/dark cycles due to variations in light sensitivity [42]. There is also evidence of biological abnormalities in the timing of melatonin secretion (a neurohormone which regulates the sleep-wake cycle). Studies have shown elevated daytime melatonin and significantly less nocturnal melatonin in individuals with ASD compared to controls [43]. Other studies have found variability in melatonin production with some individuals having normal melatonin profiles, suggesting that there is a subgroup of individuals with ASD that may have a dysregulation in their circadian rhythms [43,44]. It is also important to note that melatonin abnormalities have been found in several other disorders with intellectual disability [45,46], raising the issue of non-specificity of the melatonin findings in ASD [38]. Nevertheless, early speculations suggest that the influence on melatonin and altered rhythms in a subset of children with ASD may lead to differences in sleep schedules and result in perceived problematic behavior around bedtime and morning routines.

Other theories have been put forward to suggest that sleep disruption may be a secondary condition influenced by other co-occurring medical and psychiatric conditions that are present in ASD. Gastrointestinal disorders (GI) are common in ASD children with more than 50% of children experiencing constipation or diarrhea, often resulting in induced toilet awakenings throughout the night [47]. Seizures and epilepsy are also common in children with low-functioning autism (6–60%), and research has shown that sleep deprivation can often facilitate seizures, and conversely, seizures adversely affect sleep architecture [48]. Children with ASD are also 25–70% more likely to have co-morbid psychiatric conditions such as anxiety and attention-deficit/hyperactivity disorder (ADHD), displaying symptoms of inattention and high levels of arousal such as hyperactivity [49]. These conditions influence pre-sleep arousal, significantly delayed sleep onset, and over time may be linked to the development of insomnia [50]. Medications known to treat medical and behavioral conditions, such as antipsychotics and serotonin reuptake inhibitors (SSRIs) may also disrupt the sleep-wake cycle in ASD [18]. Understanding the nature of sleep disturbances in ASD is a complex dynamic process whereby there is a multi-directional relationship between sleep and certain factors. Further exploration of such relationships may elucidate mechanisms, which may in turn suggest effective treatment strategies to reduce sleep symptoms in individuals with low-functioning autism.

Treating sleep disruptions in children with ASD

There is increasing evidence of severe sleep problems in children with autism, although little research exists for evidence-based sleep treatments within this population [51]. Sleep disorders in ASD often remain untreated and ignored as other behavioral difficulties tend to take precedence [52]. Some research supports the efficacy of melatonin in decreasing sleep-onset latency and increasing total sleep time when administered close to bedtime [53,54]. In contrast, studies have suggested that melatonin is only effective for children with ASD who have difficulties with sleep latency, as it is known to increase night awakenings and disrupt sleep maintenance [55]. Additionally, the effectiveness of melatonin is influenced by the type of sleep disturbance, environmental factors, and other associated medical conditions [56]. After excluding biological factors, parent-based education and behavioral interventions are the first line of treatment for sleep disruption in ASD [57]. Behavioral interventions such as sleep hygiene approaches which focus on changing the environment in order to promote regular sleep-wake cycle have been shown to be effective interventions in improving sleep onset and maintenance in ASD [58]. The basic principles of sleep hygiene include selecting an appropriate bedtime and set routine, minimizing television watching, and reducing emotional and behavioral stimulation at night [16]. This behavioral treatment approach is optimal for individuals with low-functioning autism who on average have minimal or no verbal skills. Currently, however, the efficacy of behavioral treatment approaches is based on small studies and lack objective sleep measures and has been performed with the inclusion of children having a variety of diagnoses not limited to ASD [59]. Light therapy is effective in advancing or delaying the sleep phase in patients with circadian sleep disorders and can be considered for children with an ASD who present with circadian dysfunction [16]; however, there is limited research available with light therapy with individuals with low-functioning autism. Given the associations between inadequate sleep, intensified daytime problem behaviors, and parental stress in ASD, there is a strong need to develop effective sleep interventions adapted to a child's cognitive and developmental level.

The relationship between poor sleep and challenging behaviors in ASD

In typical development, sleep disruption is associated with emotional and behavioral problems such as internalizing and externalizing symptoms [60]. Moreover, a growing body of evidence shows that childhood sleep disturbances may widely impact children's health, behavior, attention, cognition, and school performance [61]. Given the nature of autism and its associated challenging behaviors, the effects of sleep disruption in this disorder are potentially serious. Sleep problems have been found to exacerbate ASD symptoms. Fewer hours of sleep have been shown to correlate with and predict greater ASD severity such as social skill deficits [41], communication impairments, higher rates of stereotypic behaviors, and stricter adherence to non-functional routines [62]. In addition to exacerbating ASD symptoms, sleep difficulties have been shown to be associated with increased rates of overactivity, disruption, non-compliance, aggression, irritability, and affective problems, which are all problems that could significantly interfere with daytime functioning in ASD [19,25,62,63]. Table 2 summarizes studies conducted to date exploring the relationship between sleep and challenging behaviors, ordered by date of publication, and summarized by their method, significant findings, and effect sizes. Despite the research exploring the relationship between sleep difficulties and challenging behavior in ASD, the influence of sleep problems in children with low-functioning autism has been neglected. Moreover, limited research has been conducted on the bi-directional relationship between sleep and behavior in these individuals.

Table 2 Studies exploring the relationship between sleep and challenging behaviors in ASD

Study	Type of study	Participants	Measurements	Significant findings	Effect sizes (*r*)[1]
Schreck *et al.* [62]	Cross sectional	55 parents of children with mixed ASD functioning aged 5–12 years	GARS, BEDS, and PSQ	Fewer hours of sleep per night predicted ASD severity score, social skill deficit, and stereotypic behavior	0.33–0.34[b]
Liu *et al.* [20]	Cross sectional	27 children with ASD symptoms, and 32 with other DD ($M = 8.8$)	ADOS, CHSQ, and PSQ	Hypersensitivity to stimuli, younger age, co-sleeping, medication, epilepsy, history of sleep problems, and ADHD was associated with sleep problems in individuals with ASD	0.09[a]–0.31[b]
DeVincent *et al.* [64]	Cross sectional	Parents of children with PDD ($n = 112$) and TYP ($n = 497$) aged 3–5	Early childhood inventory-4 and PSQ	PDD children with sleep problems had higher rates of ADHD, oppositional behavior, and psychiatric symptoms compared to children without sleep problems	0.22–0.26[a]
Goodlin-Jones *et al.* [65]	Cross sectional	68 HFASD children, matched to 57 with DD, 69 TYP, aged 24–69 months	Actigraphy, MELC, VABC, ADOS, ADIR, MSEL, SD, CSHQ, ESS, and CBCL	Controlling for diagnosis and age, night-time sleep problems determined by parent report were significantly associated with decrements in daytime behavior	0.30–0.43[b]
Mayes *et al.* [66]	Cross sectional	Parents of 477 children with a range of ASD diagnoses (aged 1–15)	CARS, PBS, PSQ, WISC, WPPSI, and GDS	Sleep problems increased with severity of ASD symptoms. Oppositional behavior, aggression, ADHD, and mood variability predicted sleep disturbance in ASD	0.59[c]
Goldman *et al.* [67]	Cross sectional	42 mixed ASD samples and 16 TYP children aged 4–10 years	PCQ, CSHQ, RBS-R, CBCL, PSG, and Actigraphy	Poor sleepers with ASD had more ADHD symptoms and more restricted and repetitive behaviors (RRBs) than good sleepers. Sleep fragmentation was correlated with more RRBs	0.48[b]–0.69[c]
Moon *et al.* [68]	Case study	3 children (aged 8–9 years) diagnosed with an ASD	Actigraphy, SD, CSHQ, CBCL, and PSQ	Daytime behavior improved for 2/3 ASD patients following an intensive sleep treatment	*x*
Rzepecka *et al.* [69]	Cross sectional	187 parents with child aged 5–18 years with an ID and/or ASD from Scotland	ADOS, CSHQ, SCAS-P, and ABC	Sleep problems were the highest predictor of challenging behaviors in ASD	0.62[c]
Henderson *et al.* [9]	Cross sectional	Parents of children aged 6–12 years with ASD, Asperger's ($n = 58$), and non-ASD ($n = 57$)	CSBQ, CRQ, BRQ, CSHS, CSWS, and CBCL	In the ASD group, poor sleep quality and hygiene were related to higher levels of externalizing behaviors	0.60[c]
Goldman *et al.* [10]	Cross sectional	Parents of 1,784 children, ages 2–18 with high-functioning autism (USA)	ADOS, CHSQ, and PCQ	Poor sleepers had a higher percentage of behavioral problems on all PCQ scales (e.g., aggression, RRBs, stereotypy, and hyperactivity) than good sleepers	0.11[a]–0.34[b]
Sikora *et al.* [70]	Cross sectional	Parents of 1,193 children with mixed ASD diagnosis aged 4–10 years (USA)	CSHQ, VABS, and MSEL	Moderate-severe sleep problems in ASD resulted in higher daytime externalizing behavior and poorer adaptive skills than those with ASD with no sleep problems	*x*
Anders *et al.* [71]	Cross sectional	Parents of children with an ID ($n = 57$), ASD ($n = 68$), and TYP ($n = 69$), aged 24–66 months	ADOS, ADIR, MSEL, CBCL, actigraphy, CSHQ, and WISC	Parent-reported sleep problem but not actigraphy recordings were associated with more core behavior problems in ASD	0.12[a]–0.39[b]
Tudor *et al.* [8]	Cross sectional	Parents of 109 children with a diagnosis of ASD (aged 3–18 years)	CSHQ, GARS, and PECS board	Sleep-onset delay and duration was positively correlated with ASD severity and symptoms and was the strongest predictor of communication deficits and stereotypic behavior	0.34[b]–0.51[c]
Park *et al.* [7]	Cross sectional	Parents of 166 ASD children and 111 unaffected siblings aged 4–15 years from Korea	ADIR, ADOS, CSHQ, WISC, and K-CBCL	Communication abnormalities and RRBs were associated with increased risk of sleep problems in ASD. ASD individuals had higher, internalizing, and externalizing problems compared to their unaffected siblings	0.31–0.43[b]

Table 2 Studies exploring the relationship between sleep and challenging behaviors in ASD *(Continued)*

Taylor *et al.* [72]	Cross sectional	Parents of children with an ASD ($n = 335$) aged 1–10 years ($M = 5.5$)	BEDS, WISC, WPPSI, MSEL, SIB-R, and VABS	Children who slept fewer hours per night had lower IQ, verbal skills, adaptive functioning, socialization, and communication skills	0.40–0.44[b]
Holloway *et al.* [73]	Cross sectional	1,583 ASD children from Autism Treatment Network aged 2–17 years	CSHQ, VABS, MSEL, Stanford Binet, CBCL, ADOS, and SSP	Anxiety, ASD severity, sensory sensitivity, and GI issues all predicted sleep disturbance. IQ positively predicted sleep disturbance	0.17[a]–0.44[b]
Schwichtenberg *et al.* [74]	Cross sectional	ASD siblings ($n = 104$) and families with no history of ASD ($n = 76$)	MSEL, ADOS, CBCL, and PCQ	For both groups, sleep problems were associated with elevated behavior problems (e.g., reactivity, anxiety, somatic complaints, withdrawal, inattention, and aggression)	0.16–0.21[a]
Mannion *et al.* [47]	Cross sectional	Parents of 89 children and adolescents (aged 3–16) with mixed ASD subtypes in Ireland	ASD-CC, GSI, and CSHQ	Avoidant behavior, under-eating, and GI symptoms predicted sleep problems in individuals with an ASD	0.46[b]–0.50[c]
May *et al.* [75]	Longitudinal	Gender-matched children with high-functioning autism ($n = 46$) and TYP ($n = 38$) aged 7–12 years from Melbourne (Australia)	Conner's third edition, SCAS, and CSHQ	The ASD group had more sleep disturbance than the TYP group. Sleep disturbance decreased over the year in children with ASD, and this was associated with improved social ability	0.41[b]–0.69[c]
Richdale *et al.* [50]	Cross sectional	27 adolescents with high-functioning autism (aged 15–16) and 27 matched TYP controls	SD, actigraphy, CSRQ, CED-S, DASS-21, and SAAQ	Sleep variables significantly accounted for 57% of the variance of daytime functioning symptoms of insufficient sleep in the high-functioning ASD group	0.75[c]
Adams *et al.* [23]	Cross sectional	548 children and adolescents (2–18 years), with ASD symptoms	ASD-CC	Individuals with severe sleep problems had higher levels of total challenging behaviors than those with mild sleep problems	−0.47[b]

ABC Aberrant Behavior Checklist, *ADIR* Autism Diagnostic Interview (revised), *ADOS* Autism Diagnostic Observation Schedule, *ASD-CC* autism spectrum disorder co-morbid for children, *ASD* autism spectrum disorders, *BEDS* bedtime evaluation of disorders of sleep, *BRQ* Bedtime Routines Questionnaire, *CARS* Checklist for Autism Spectrum Disorders, *CBCL* Child Behavior Checklist, *CES-D* Centre for Epidemiological Studies Depression Scale, *CRQ* Child Routine Questionnaire, *CSBQ* Children's Social Behavior Questionnaire, *CSHQ* Child Sleep Habit Questionnaire, *CSHS* Children's Sleep Hygiene Scale, *CSRQ* Chronic Sleep Reduction Questionnaire, *CSWS* Children's Sleep-Wake Scale, *DASS-21* Depression, Anxiety, and Stress Scale, *DD* Developmental disability, *ESS* Epworth Sleepiness Scale, *GARS* Gilliam Autism Rating Scale, *GDS* Gordon Diagnostic System, *GI* Gastrointestinal disorder, *GSI* Gastrointestinal Symptoms Inventory, *HFASD* High-functioning autism spectrum disorder, *ID* Intellectual disability, *IQ* Intellectual quotient, *K-CBCL* Korean Version of Child Behavior Checklist, *MELC* Mullen Early Learning Composite, *MSEL* Mullen Scales of Early learning, *PEQ* Parenting Events Questionnaire, *PBS* Pediatric Behavior Scale, *PCQ* Parental Concerns Questionnaire, *PDD* Pervasive developmental disorder, *PPVT* Peabody Picture Vocabulary Test-III, *PSG* Polysomnography, *PSQ* Parental Sleep Questionnaire, *RBS-R* Repetitive Behavior Scales-revised, *RRB* Repetitive and restricted behaviours, *SAAQ* Sleep Anticipatory Anxiety Questionnaire, *SCAS-P* Spence Anxiety Scale Parent Version, *SD* Sleep diary, *SIB-R* Scales of Independent Behavior-Revised, *SIB* self-injurious behavior, *SQ* Sleep Questionnaire, *SSP* Short Sensory Profile, *TYP* typical development, *VABC* Vineland Adaptive Behavior Checklist, *WISC* Wechsler Intelligence Scale for Children, *WPPSI* Wechsler Preschool and Primary School Scale of Intelligence, *x* insufficient information provided to calculate effect sizes.

[a]small ($r \geq 0.1$), classification of effect size.

[b]medium ($r > 0.30$), classification of effect size.

[c]large ($r > 0.5$), classification of effect size.

Future directions: the relationship of sleep and behavior in ASD

Researched areas

The current research highlights clear uni-directional relationships between sleep and behavior in individuals with an ASD. It is well researched that sleep problems worsen ASD symptomatology across most core domains, as well as exacerbate pre-existing behavioral problems. These relationships have been fairly well investigated in cross-sectional studies using objective measures with individuals with mixed groups of ASD samples and individuals with high-functioning autism. Objective tools such as polysomnography (a tool that monitors physiological parameters during sleep such as electroencephalogram) and wrist actigraphy (a tool that uses an accelerometer to detect and record muscle activity) have been used successfully to validate relationships between poor sleep and daytime behaviors in a mixed sample of ASD children [51,65,71]. There is also modest evidence to suggest that holistic parent report measures such as the CSHQ is a superior single-item response measure which helps gage overall quality of ASD children's sleep [76]. In light of knowledge about the severity of sleep disorders in ASD, there is evidence to suggest that sleep is amendable to treatment in certain populations with ASD. Studies have shown that parent-based education (behavioral therapy) improves sleep-onset delay in children with high-functioning autism [59] and that pharmacological treatments such as melatonin is an effective sleep treatment for children with autism [77]. Moreover, treating sleep in a subgroup of individuals with ASD has been shown to improve core ASD symptoms (e.g., communication and socialization impairments) as well as reduce the severity of challenging behaviors in ASD [38,68]. Applied behavior analysis (ABA) treatment approach is known to be efficacious for the treatment of challenging behavior in a minority of children with ASD [62]; however, its outcomes are influenced by learning rate and cognitive performance. Given that sleep is implicated in behaviors that affect learning, such as compliance, irritability, hyperactivity, and aggression, there is now more evidence to suggest that sleep is a possible obstacle to ABA treatment success in ASD [62]. Given the bi-directional relationship between challenging behaviors and sleep disturbance in ASD, preliminary evidence suggests that treating sleep disturbances and challenging behavior in isolation may not lead to successful outcomes [50]. The foregoing relationship between sleep problems for children with ASD and daytime inappropriate behavior suggests additional research is required to delineate direct connections among specific sleep problems and the specific daytime behavior patterns that may affect individuals with ASD.

Areas for further research

Although previous studies have identified clear relationships between poor sleep and challenging behaviors in ASD, as reviewed above, it is still unclear what specific sleep problems and symptom relationships are unique to individuals with low-functioning autism. As mentioned, current research has primarily focused on individuals on the higher functioning end of the autism spectrum, and individuals with low-functioning autism who potentially have the most severe sleep and behavioral deficits have been relatively ignored in the literature. Studying sleep in children with low-functioning autism presents with unique methodological challenges, namely subjective parent reports confer reporting bias and negative halo effects [78] and individuals have difficulty tolerating objective measures such as PSG and actigraphy tools due to sensory sensitivities and lack of cooperation [76]. Given that the National Sleep Foundation [79] identifies children with ASD as one of the highest priority populations for sleep research, there is a need for more accurate, objective, non-invasive measures of sleep, as well as data from children with low-functioning autism in order to better characterize the quality and quantity of sleep in this population.

Another key limitation of the research to date is that very few studies examine behavioral problems and sleep disturbances in ASD longitudinally, with most studies being cross-sectional. Cross-sectional studies only capture an ASD profile at one specific age presentation, and most studies have combined both children and adolescents in their samples. Little is known about how sleep changes over time in ASD and what factors might be associated with this change, for example, age and stages of development. In ASD, one study found no relation between sleep difficulties and developmental stage (i.e., childhood, adolescents, or adulthood) [66], whereas other studies, albeit cross sectional, have found a decline in sleep difficulties with age similar to typical development [36,37]. The severity of ASD symptoms and behavioral disturbance have been known to wax and wane across development, with some behaviors improving with age [80]. Given that different behavioral profiles occur at particular age ranges and developmental age often does not match chronological age in ASD, there is a need to study relationships through longitudinal designs. Only one study to date has compared the relationship between sleep disturbances and behavior longitudinally, in high-functioning autism and in typically developing controls [75]. Thus, to uncover core ASD phenotypes and link these to sleep profiles, more longitudinal studies are required to trace sleep trajectories in this population to understand what unique variables might influence change. For example, sleep difficulties in ASD may vary according to medication use, environment factors such as seasonal changes, or co-morbidities such as epilepsy or GI issues. It is difficult to determine whether co-occurring conditions cause the behavior problems, maintain existing problems, or exacerbate problems already present in ASD. Studies need to be done to address this poignant question.

Lastly, treatment guidelines to help manage challenging behaviors in individuals with low-functioning autism often fail to mention sleep at all, or they present a very limited account. Identifying and providing treatment for sleep problems in ASD is imperative for improving sleep, as well as for encouraging more positive prognoses by improving daytime behavior and family functioning in this population. One specific proposal is for researchers to identify factors that result in an ASD phenotype and then design targeted therapeutic interventions to reverse or ameliorate specific deficits. For example, exposure to highly arousing stimuli before bed may increase pre-sleep arousal and sleep-onset latency and result in an increase in self regulatory behaviors (such as self-injurious behaviors) the following day in children with low-functioning autism. Heightened light sensitivity from exposure to blue-enriched light from computer and/or tablet screens might also be linked to circadian timing and melatonin issues, increasing sleep-wake circadian rhythm abnormalities in this population. Sound sensitivity inherent within ASD may be linked to lower waking thresholds, sleep fragmentation, and so on. In this paper, it is proposed that profiling ASD children based on the nature of their sleep disruption might help understand symptom and behavioral profiles (or vice versa) and therefore lead to better-targeted interventions.

Conclusions

Although there is reason to believe that serious sleep problems are common in children with ASD and that poor sleep exacerbates problematic daytime behavior, these conclusions are still premature and require further investigation. Gaining more specific insight into the individual nature of sleep difficulties in ASD opens up a novel avenue for designing interventions, as sleep is an area with a potential for remediation. Since sleep is a central mechanism for adaptive functioning (e.g., learning, memory, neuroplasticity), it is highly plausible that sleep deficits play a leading role in the symptoms seen in ASD including the exacerbation of challenging behaviors. To date, however, studies have failed to provide conclusive evidence about the relationship between sleep and behaviors seen in low-functioning individuals (of all ages) with autism. This review highlights the value of defining sleep profiles for children with ASD and integrating different aspects of their symptom profile to their sleep deficits (and vice versa). In turn, this knowledge will result in novel therapeutic targets and interventions that will hopefully improve long-term outcomes of nearly 1 in 68 individuals affected by this pervasive, developmental disorder.

Abbreviations

ABC: Aberrant Behavior Checklist; ADHD: Attention deficit hyperactivity disorder; ADIR: Autism Diagnostic Interview (revised); ADOS: Autism Diagnostic Observation Schedule; ASD-CC: Autism spectrum disorder co-morbid for children; ASD: Autism spectrum disorders; BEDS: Bedtime evaluation of disorders of sleep; BRQ: Bedtime Routines Questionnaire; CARS: Checklist for Autism Spectrum Disorders; CBCL: Child Behavior Checklist; CRQ: Child Routine Questionnaire; CSBQ: Children's Social Behavior Questionnaire; CSHQ: Child Sleep Habit Questionnaire; CSHS: Children's Sleep Hygiene Scale; CSWS: Children's Sleep-Wake Scale; DD: Developmental disability; ESS: Epworth Sleepiness Scale; GARS: Gilliam Autism Rating Scale; GDS: Gordon Diagnostic System; GSI: Gastrointestinal symptoms inventory; HFASD: High-functioning autism spectrum disorder; ID: Intellectual disability; IQ: Intellectual quotient; K-CBCL: Korean Version of Child Behavior Checklist; LFASD: Low-functioning autism; MELC: Mullen Early Learning Composite; MSEL: Mullen Scales of Early Learning; PEQ: Parenting Events Questionnaire; PBS: Pediatric Behavior Scale; PCQ: Parental Concerns Questionnaire; PDD: Pervasive developmental disorder; PPVT: Peabody Picture Vocabulary Test-III; PSG: Polysomnography; PSQ: Parental Sleep Questionnaire; RBS-R: Repetitive Behavior Scales-Revised; RRB: Repetitive and restricted behaviours; SCAS-P: Spence Anxiety Scale Parent Version; SD: Sleep diary; SIB-R: Scales of Independent Behavior-Revised; SIB: Self-injurious behavior; SQ: Sleep questionnaire; SSP: Short Sensory Profile; TYP: Typical development; VABC: Vineland Aberrant Behavior Checklist; WISC: Wechsler Intelligence Scale for Children; WPPSI: Wechsler Preschool and Primary School Scale of Intelligence.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SC wrote the paper with contributions from RC, SWL, SWR, and KMC. All authors read and approved the final manuscript.

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Chapter 3: Dataset and methodology overview

One of the main outcomes from chapter two was that there is a need to study the relationship between sleep and behavior in individuals with low-functioning autism, using comprehensive longitudinal designs, which expand beyond traditional cross-sectional designs. To address the gaps in the literature, this thesis capitalizes on a large dataset of 179 individuals with low-functioning autism with sleep-wake and behavior observations spanning 6 months to 6 years, collected in a real-world setting from two-residential facilities near Boston, USA. The aim of this chapter is to provide a detailed understanding of the nature of the dataset, as the well as methods used to analyze this large, temporally rich and longitudinal dataset. The first section of this chapter explains the structure of the dataset, including the clinical and demographic characteristics of individuals available for this study and the nature of the observational measures of behavior and sleep. The second section of this chapter will explain the statistical techniques used to uncover the robust relationships between sleep and behavior in individuals with autism that varied in age, medications, sleep patterns, and behavioral profiles. This chapter helps to inform the methodology used in chapters four, five and six.

3.1. The Dataset

3.1.1. Research consortium

Melmark New England (MNE) and the New England Center for Children (NECC) are two residential schools near Boston, Massachusetts (USA) that provide a 24-hour structured educational and residential environment for individuals with autism, developmental disabilities, neurological disorders across a wide age span from 5- 28 years. MNE and NECC both have an inpatient (where students reside at the facility) and outpatient (where students return to their parents) school program. The outpatient day school programs run from 8:30am-3:00pm, 237 days a year; and the residential school programs run from 3:00pm until 8:30am, 365 days a year. Approximately, 100 and 500 students attend the day program at MNE and NECC, respectively. There are 49 and 132 children attending the residential program at MNE and NECC, respectively.

Each individual enrolled at MNE and NECC is provided with an individual education plan (IEP), which specifies the individuals learning goals and targets for intervention. All goals within the IEP are delivered via Applied Behavior Analysis (ABA) principles, which is the best evidence based intensive therapy designed for children with autism (Odom, Boyd, Hall, & Hume, 2010). ABA relies on the principles of operant conditioning, whereby positive reinforcement and punishments are used to shape behavior. ABA therapy is used at both facilities to improve all areas of development including communication (verbal and non-verbal), self-help skills, fine-motor skills, gross-motor skills and broader problematic behaviors such as self-injury, tantrums, aggression, and property destruction. The ABA program at NECC and MNE are run by Board Certified Behavior Analysts (BCBA's) who have over 10 years of experience in working with individuals with autism. At the day school programs at both facilities, there is a 1:1 clinician to student ratio, which allows for ongoing monitoring of students throughout the day.

For students who had IEP objectives that required a 24-hour therapeutic and structured learning environment, MNE and NECC offers inpatient residential placements within six homes at MNE and eighteen homes at NECC. Students of similar ages are placed in the same residential home. There are between 5-10 individuals in each home at MNE and 4-9 individuals in each home at NECC. MNE offers students their own bedrooms, whereas NECC offers shared rooms with 2-4 students in a bedroom. At both facilities, the bedrooms have no distractions such as toys or electronics. All bedrooms at MNE have curtains to block outside light in the mornings and some bedrooms at NECC have curtains, others have shutters due to strangulation risk. Each school has set bedtime routines, which includes no consumption of food 2-hours before bed, and calm down activities (such as reading) 1-hour before bed. Figure 1 shows an example of a bedroom at MNE, illustrating minimal distractions, curtains and adequate lighting to facilitate sleep. All non-verbal students at NECC and MNE have communication devices (iPads), which are primarily used during the day and are restricted during sleep hours. Each home at MNE and NECC are staffed with a 1:2 ratio of ABA therapists who collect data based on IEP goals.

Figure 1: Two examples of bedrooms at MNE illustrating the sleep environment, with no distractions, adequate lighting and curtains.

3.1.2. Clinical and medical assessments

Upon enrollment at MNE and NECC each individual is required to have diagnostic, cognitive, and behavioral assessment which is conducted by a Psychiatrist and Pediatrician. Diagnostic assessments were made based on the DSM-IV criteria for Autism Spectrum Disorder and other associated co-morbid disorders (e.g., anxiety or mood disorders). Cognitive assessments of intellectual functioning (IQ) were assessed using either the Leiter-R International Performance Scale - Third Edition (n = 22) or the Stanford-Binet Intelligence Scale-Fifth Edition (SB-5) (n = 21). Missing IQ recordings (n = 137) were due to students being unable to participate in standardized testing as a result of their severity of deficits (including lack of verbal language and severe behaviors) or due to lack of availability of electronic IQ data. Adaptive functioning was measured using the Vineland Adaptive Behavior Scales (VABS) (n = 82), which measures five domains of functioning: communication, daily living, socialization, motor skills and maladaptive behavior. The total score across these domains yields an overall composite score of adaptive functioning. Missing VABS scores (n = 97) were either due to missing electronic data or to unavailability of parents to engage in formal assessments. Both residential facilities also collected demographic information (such as age, gender, ethnicity) and daily medication administration (including dose, time and frequency of medications taken) via electronic records. Medications were taken to manage associated co-morbidities such as challenging behaviors or medical symptoms such as gastro-intestinal issues (see Table 1 for number of students on medications).

3.1.3. Student characteristics

There was a large degree of variability in student characteristics, including age range, associated psychological and medical co-morbidities as well as medication usage. For inclusion in this study all individuals were required to meet diagnostic criteria for Autism Spectrum Disorder, and a significant proportion of individuals met criteria for low-functioning autism (n = 149) as confirmed by IQ scores, VABS scores and formal assessments conducted by Psychiatrists or Pediatricians. The table below shows the participant characteristics of those enrolled in MNE and NECC.

Table 1: Full student characteristics at MNE and NECC

	Melmark New England	**New England Center for Children**
Number of students in residential programs	47	132
Number of males	37	101
Number of students with an autism diagnosis	44	120
Age range	6.2-26.5	6.6-21.6
(M±SD)	(15.40±4.24)	(15.50±2.99)
Intellectual quotient (IQ) range	30-120	30- 58
(M±SD)	(43.90±18.52)	(41.75±12.28)
Adaptive behavior score range	20-86	21-74.25
(M±SD)	(43.69±15.70)	(44.60±15.19)
Number of subjects with:		
Gastro-intestinal disorder(GI)	7	15
Epilepsy	7	29
Reflux	4	1
Anxiety / Mood disorders	5	8
Attention deficit hyperactivity disorder (ADHD)	2	6
Race:		
Caucasian	42	115
Asian	4	3
Native American	1	4
Hispanic	0	10
Number of subjects on medications:		
Anti-depressant	13	24
Melatonin	10	13
Anti-histamine	14	70
Anti-convulsant	18	18
Anti-psychotic	31	45
Benzodiazepines	4	4
Range of days with challenging behaviors:		
Aggression	130-1888	123-1236
Self-injury	130-1888	46-1236
Property destruction	146-1888	111-1224
Tantrums	160-1888	111-1236

3.1.4. Behavior observations

At the outpatient day program, each student at both NECC and MNE was assigned a 1:1 clinician throughout the day, and clinicians rotated hourly between students. Hourly counts of 40 different types of behavior including appropriate behaviors (*n* = 22) and inappropriate challenging behavior (*n* = 18) episodes were manually recorded by clinicians throughout the day from 8:00am-21:00pm, which was then summed to give a total frequency score of the behavior across the day. Appropriate behavior episodes included listening, paying attention, compliance, making requests and spontaneous communication etc. Challenging behavior episodes included aggression, self-injury, tantrums, property destruction etc. Of the eighteen challenging behaviors, here we analyze four of the most abundant behaviors in the sample (as shown in Figure 2) with the total number of subjects exhibiting: i) aggression (*n* = 83), defined as any incident of hitting, kicking, scratching, pinching, or biting towards a student or staff member; ii) self-injury (n = 87), defined as harm to one's body, including head banging, hair pulling and skin-picking; iii) tantrums (n = 67), defined as screaming, shouting, whining or slamming doors; and iv) property destruction (n = 65), defined as damage to items including hitting desks, walls or throwing items (see Table 1 for data-range of challenging behavior data available across individuals).

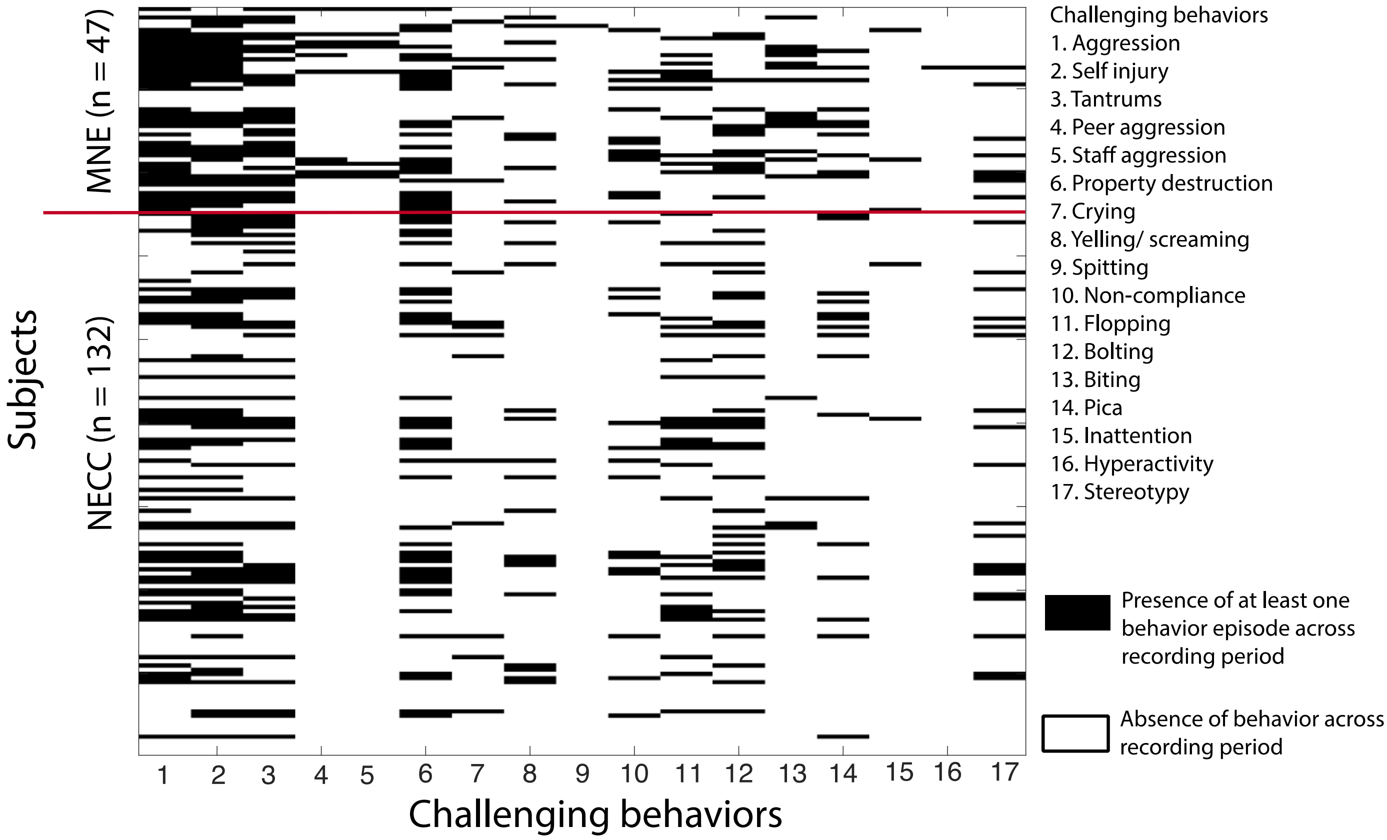

Figure 2: Challenging behavior profiles of all 179 individuals with autism spectrum disorder, separated by school (red line). Each row represents an individual subject, and each column represents a challenging behavior (as shown by the key on the right). Here, we analyze the most prevalent challenging behaviors in the sample (as shown in black), which included aggression, self-injury, tantrums and property destruction.

3.1.5. Sleep-wake observations

As a part of routine clinical care, sleep-wake behavior was assessed by continuous clinical observations by ABA clinicians at both residential facilities. Sleep-wake behavior was measured every 30 minutes at MNE and every 15 minutes at NECC from 19:00pm-7:00am, whereby clinicians conducted frequent bed checks and made an observation as to whether the student was awake (out of bed) or asleep (in bed with eyes closed). Sleep was not permitted outside of this time window at either facility. The doors of all bedrooms were kept shut during sleep-wake observations and each door had an observation window to ensure that sleep was not disrupted during night-time observations. Moreover, noise levels were kept to a minimum and individuals with significant sleep difficulties had blue lights and white noise to facilitate sleep. Students at NECC had a standard fixed lights-off time of 21:00pm, with no prompted night awakenings. In contrast, students residing at MNE had variable bed times which changed throughout their stay in the residential facility. At the time of data collection, 4/47 had a bedtime of 19:00pm, 8/47 had a bedtime of 20:00pm, 6/47 had bedtime at 20:30pm, and 18/47 children had a bedtime before 21:00pm. Set bedtimes were determined based on the age of the student. Many individuals at MNE had prompted or unprompted toilet awakenings throughout the night due to night-time incontinence. Both schools had fixed wake times at 7:00am, where carers would wake the student in preparation for school. At both facilities, sleep schedules and routines were maintained on weekends and holiday periods, although sleep-wake observations were only conducted from Monday to Friday.

Students at both residential facilities had variable sleep profiles, including different patterns of sleep across time, which varied in recording length. This wide inter-individual variability in sleep patterns is not surprising given that similar inter-individual variations in sleep have been shown to exist in healthy populations. For example, individual’s chronotoypes have been shown to vary depending on the season, gender, and day-length (Lehnkering & Siegmund, 2007). The raster plots below (a double plot of an individuals sleep-wake behavior across their recording period) is shown in Figure 3 demonstrating the variable sleep patterns across a sample of students from MNE and NECC.

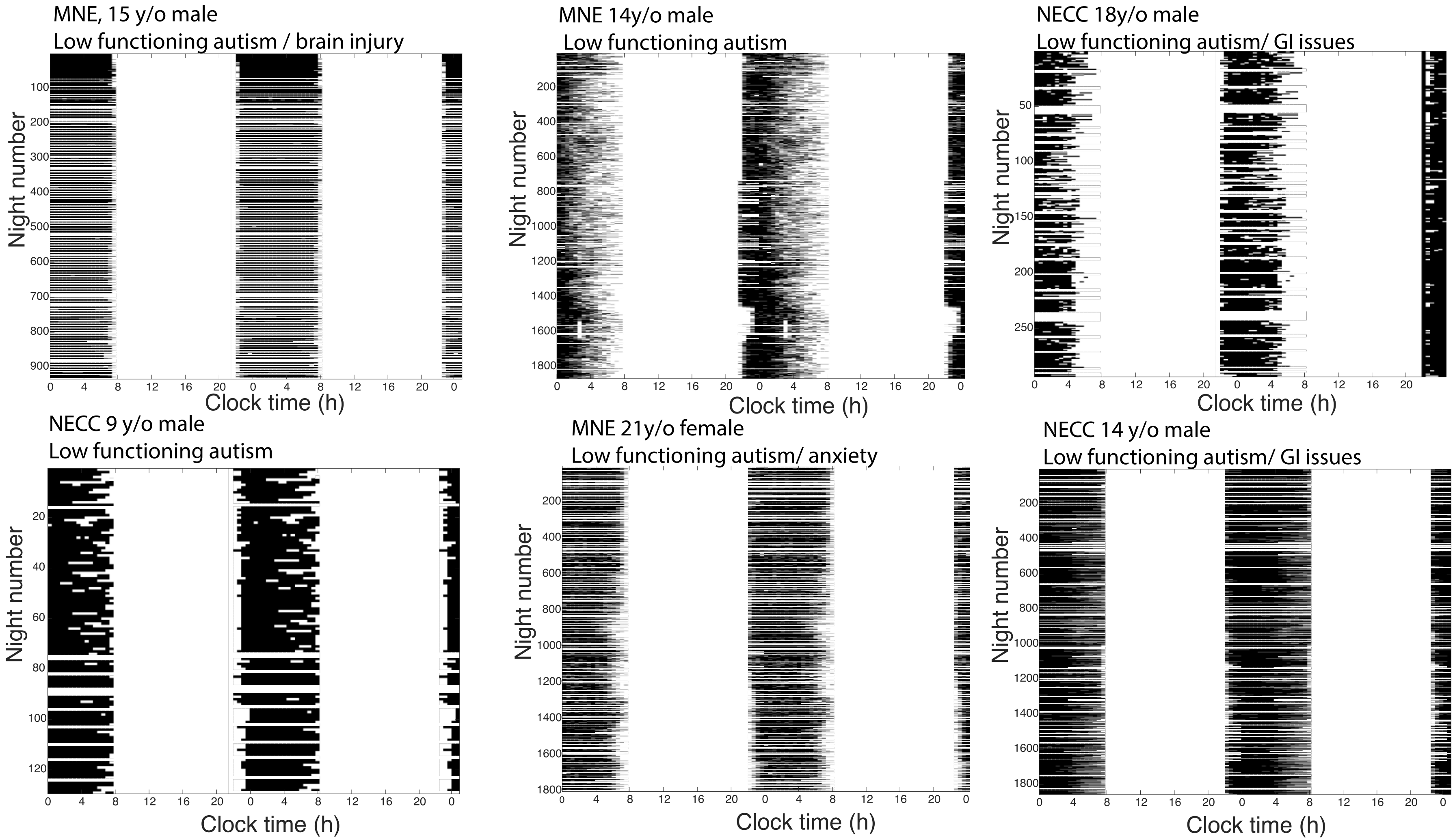

Figure 3: Raster plots demonstrate a significant degree of variability of sleep-wake behavior over time and across individuals living in two residential facilities. Raster plots for a random subset of individuals (n = 6) show a double plot of sleep-wake behavior across a 24 hour day (x-axis) for an individuals available recording period (y-axis). Black illustrates periods of sleep, and white illustrates period of awake. Each student demonstrates a unique pattern of sleep-wake behavior with variable changes in sleep patterns across time.

3.1.6. Calculating sleep parameters from sleep-wake observations

The goal of this thesis was to understand patterns of sleep-wake behavior in individuals with low-functioning autism. In order to learn these patterns, the coarse temporal sleep-wake observations needed to be summarized into meaningful sleep parameters. Each night of recorded sleep was quantified as a set of regular observational measurements of ‘sleep’ or ‘awake’ measured by clinicians throughout the night (at either 15 minute or 30 minute intervals, depending on the facility). We summarized each night of sleep using six sleep parameters: i) sleep interval (the time between sleep onset and sleep offset); ii) total sleep time (total time spent asleep); iii) sleep onset (time at the start of the first episode of sleep); iv) sleep offset (time at the end of the last episode of sleep); v) sleep efficiency (total sleep time, divided by the sleep interval, reported as a percentage) and vi) number of night awakenings (total number of awakenings recorded, with each awakening followed by an episode of sleep). These six sleep parameters captured information about a single night of sleep. In chapters four and five we were interested in obtaining a measurement of sleep-wake patterns across multiple nights of sleep. Thus in order to encapsulate sleep properties across multiple nights (*n*), we calculated sleep feature summaries from the six sleep parameters (x_i) which included the:

1) Mean: $\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$

2) Standard deviation: $\sigma = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(x_i - \bar{x})^2}$

3) Auto-correlation (night-to-night correlation): $AC_{t=1} = \frac{\sum_{i=1}^{n-t}(x_i-\bar{x})((x_{i+t}-\bar{x})}{\sum_{i=1}^{n}(x_i-\bar{x})^2}$ (where t was the time between nights examined).

We also computed ‘sleep regularity’ index (or sleep stability index), which has shown to be useful in predicting exam scores in college students beyond total sleep time (Clerx et al., 2014). Mathematically, this was computed as $\langle s(t+24).s(t)\rangle_t$, where *s* is a sleep indicator (1 for awake, -1 for sleep) and *t* represents time (hours), and the mean, $\langle\ \rangle_t$, is taken across all sleep observations with a matching observation 24 hours later. A sleep regularity value of 1 indicated a perfectly regular sleep/wake pattern that repeats itself every 24 hours. This measure accounts for variable bedtimes as it was calculated from the start of the sleep episode. These sleep features (as shown in Figure 4) were chosen as they provide information about cumulative sleep, and an index of sleep continuity/timing. Moreover, these sleep features were chosen as they were the most exhaustive and accurate measures that could be calculated from this coarse temporal dataset.

3.1.7. Sleep feature selection

In order to avoid redundancies in sleep features, which is known to reduce accuracy when learning patterns in large datasets (Hastie, Tibshirani, & Friedman, 2009), we examined relationships between sleep features to ensure that they were independent from each other. For each individual, we selected 1-year of sleep-data, and then calculated the mean, standard deviation and auto-correlation of all six nightly sleep parameters as well as a sleep stability index across two nights. A two-night period was selected for the sleep stability index as we were interested in the stability of sleep across a small time window as opposed to a week or two weeks. Thus each individual had a set of nineteen sleep features, which summarized sleep properties averaged across two nights for year of their recording period. We then agglomerated sleep features across individuals and calculated the absolute correlation coefficient (pairwise correlation, which takes a positive value between 0-1, where 0 = no association, 1= strong association) between pairs of nightly sleep features with each other. The magnitudes of the sleep feature correlations were compared using Euclidean distances and then re-ordered using Wards linkage clustering to place similar sleep features close to one another.

Figure 4 shows a color matrix demonstrating the magnitude of the absolute correlation coefficients between all pairs of sleep features as well as their relative distance to one another as shown in the dendrogram above. The sleep features clustered into three distinct groups; with features that measured the autocorrelation, standard deviation and mean/ sleep stability of features. Within each group, each feature had small to medium pairwise night-to-night correlations ranging from $R = 0.2$ to $R = 0.6$. This suggests that individual sleep features within each group were relatively independent ($R < 1$) from one another capturing unique nightly sleep properties for individuals with autism. Interestingly, mean sleep efficiency and sleep stability was highly correlated ($R = 0.8$) with one another, which is not surprising given that high sleep efficiency across two nights may be associated with high sleep stability across two nights. Surprisingly, mean total sleep time was independent from mean night awakenings ($R = 0.1$), suggesting that high or low total sleep time was not associated with the number of awakenings averaged across two nights. Another point to note is that sleep interval measures was highly correlated with total sleep time ($R > 0.9$), suggesting that on most nights individuals fell asleep between sleep onset and sleep offset. Due to this redundancy, sleep interval based measures were removed. In this way, a more manageable and representative set of 16 features was identified that effectively captures important sleep characteristics in this population. All 16 sleep features were used in the chapter four to understand unique sleep phenotypes in individuals with low-functioning autism. Only a subset of the sleep features (mean, standard deviation and sleep stability) were used in chapter five to develop a predictive model of challenging behavior from prior sleep in individuals with low-functioning autism and for simplicity only the sleep duration parameter was used in chapter six. It is important to note that the results did not drastically differ with the addition of redundant features and therefore subsequent analyses did not take into consideration weighting features based on their dependence with one another.

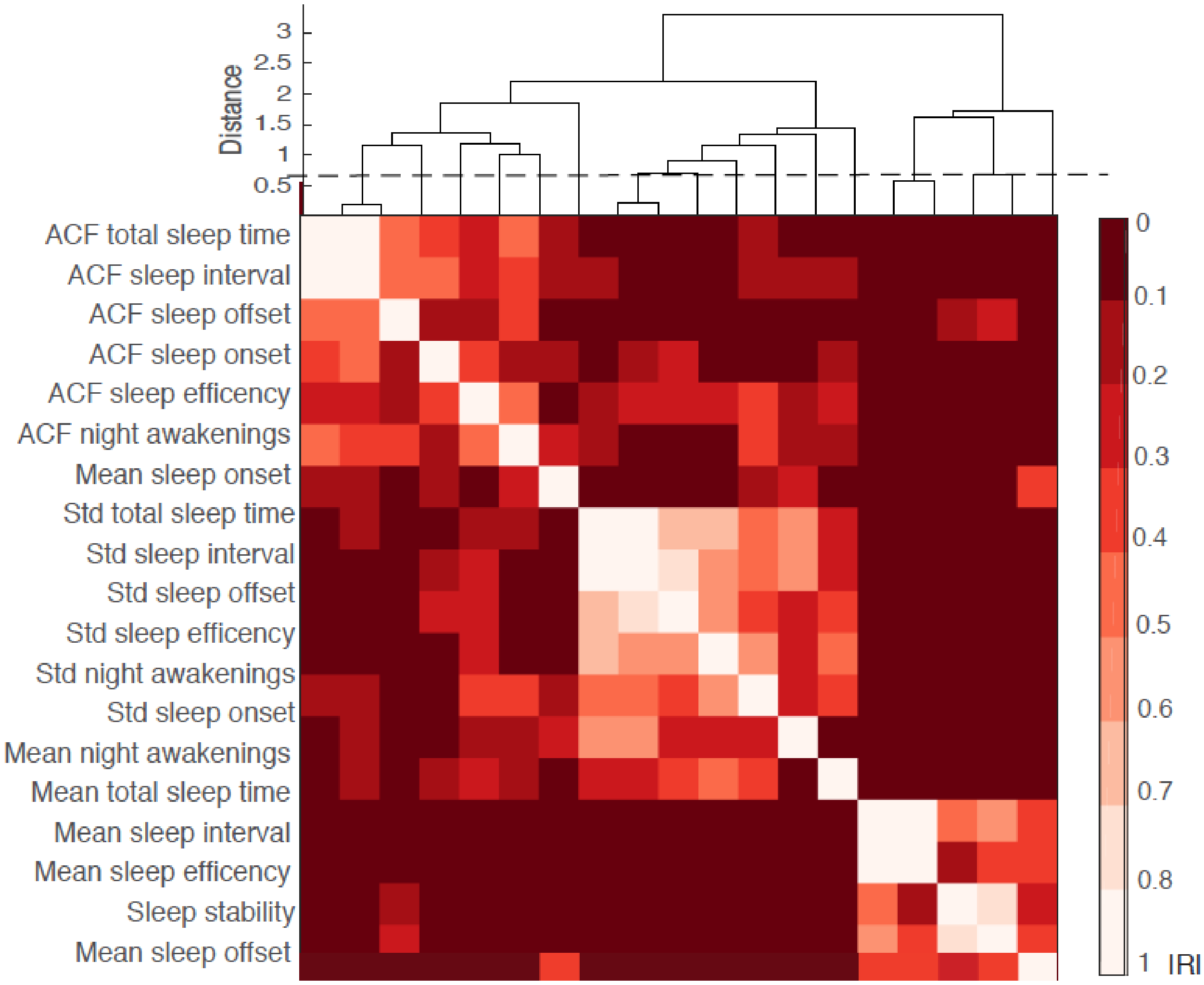

Figure 4: Absolute pair-wise linear correlation coefficients between sleep feature pairs demonstrated relative independence of the mean, standard deviation, autocorrelation and sleep stability of all sleep features. The colored matrix shows the magnitude of the absolute correlation coefficients between pairs of sleep features (which measures properties of sleep across two-nights) with darker colors showing high independence between sleep features and cooler colors showing low independence between sleep features. Sleep features are re-ordered based on their relative magnitude with one another, and the dendrogram above shows the distance between the magnitudes of sleep feature correlations with each other. As illustrated, sleep features fell into three distinct clusters of measurements: mean, standard deviation, and autocorrelations. Within these groups, the majority of sleep feature pairs were independent with each other ($R < 0.6$) and therefore were justified to be unique sleep features to learn patterns of sleep-wake behavior in individuals with autism.

3.1.8. The overall dataset

This dataset presented with an unprecedented volume of high quality data, spanning across over 100 individuals. Figure 5 shows the age range of the recording period for each individual (in order of increasing age according to school), for individuals who had *both* sleep data and behavior data available (*n* = 132). As illustrated, individuals varied in age and recording length of sleep and behavior data, with data spanning between 6 months to 6 years across individuals. In this thesis, we applied an age-based restriction to the dataset, as only individuals or nights from an individual less than 20 years of age were studied. Thus, although this dataset facilitated an analysis of sleep-behavior to be studied across a broad age-span we restricted our analysis to a specific age range to limit our findings to children and adolescents with autism.

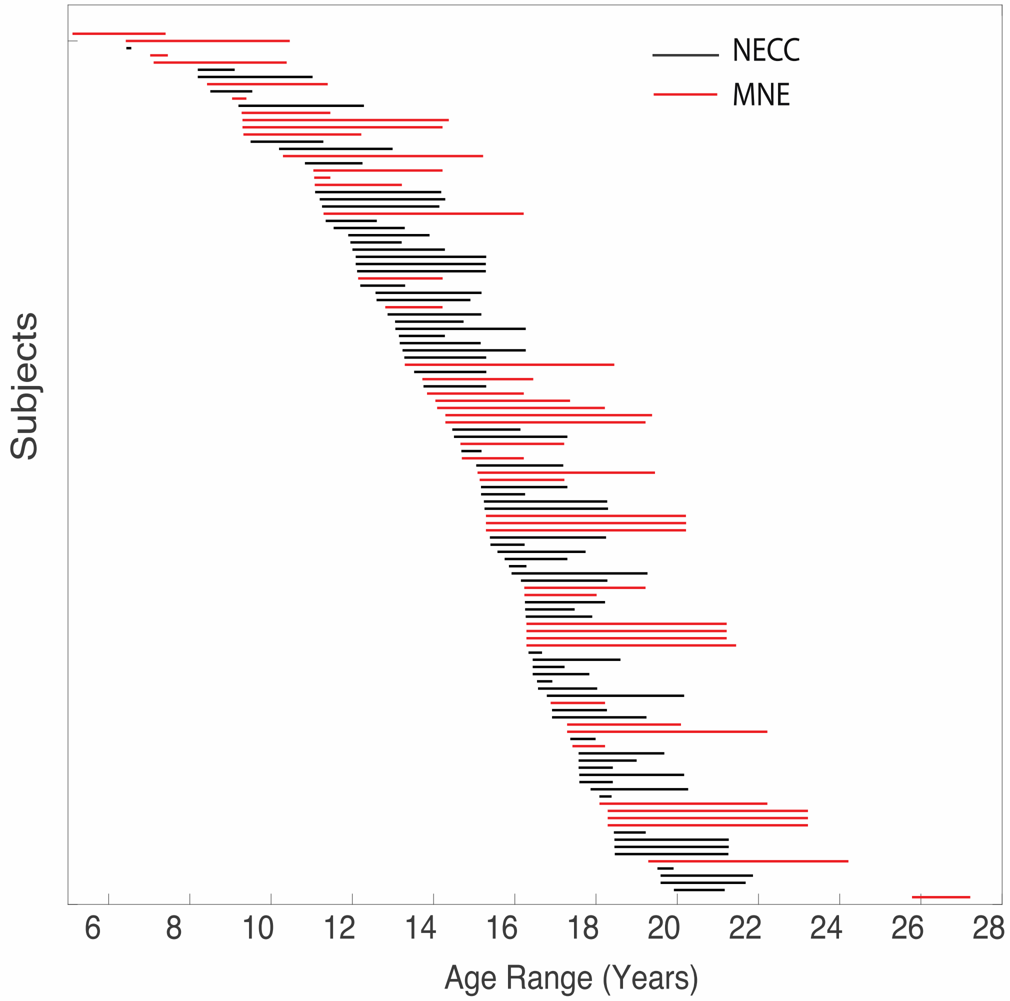

Figure 5: This dataset presented with a large volume of data across individuals of varied ages and recording lengths Each row represents an individual subject (for those that had both sleep and behavior data available), with red lines representing students from Melmark New England (MNE) and black lines representing students from the New England Center for Children (NECC). The age range of individuals across their available recording period of sleep and behavior (x-axis) is shown in order of increasing age.

A notable feature of this dataset was the wide range of individual heterogeneity in terms of changing distribution of behaviors, distinctive sleep patterns, medication profiles, individuals of diverse ages and recording periods of varied lengths. Figure 6 demonstrates the significant heterogeneity in terms of individual sleep, behavior and medication profiles for a random subset of individuals, with subject numbers corresponding to the row number in Figure 5. As illustrated, each individual had a unique profile and distribution of total sleep time and challenging behavior episodes. For example, subject 1 shows a consistent pattern in total sleep time, while subjects 2, 7 and 8 show distinct fluctuations in total sleep time. Furthermore, this dataset presented with two main challenges with regards to the distribution of behavior observations, which had the potential to bias results when predicting behavior from prior sleep-wake behavior. Firstly, several individuals had extended strings of the same behavior every day (as shown by subject 2), which had the ability to bias predictions due to constant episodes of behavior days. Secondly, the number of days with a given behavior was often different to the number of days without a behavior (as shown by subject 1 and 2), suggesting that there was an imbalance in behavior and non-behavior days that could add bias to the data when learning the predictive relationship between sleep and behavior. Hence both of these factors needed to be taken into account in the analysis, therefore a number of subjects and nights were excluded to avoid this bias. It is also important to note that changes in sleep and behavior across time may have been due to changing medications across time (as shown by subject 1 and subject 2, with increasing behavior associated with changing medications). Moreover, the changing distributions of both sleep and behavior over time may have been due to maturation, seasonal changes or the effects of ongoing therapy and interventions. This dataset also presented with the challenge of missing data, which were due to absences, weekends, holiday breaks or changing goals for behavior recordings (as shown by subject 8).

The size, complexity and heterogeneity of this dataset meant that traditional data processing applications (such as simple univariate statistics) were inadequate. Thus the dataset required a set of statistical techniques that was able to learn patterns from changing distributions of nightly sleep features and daily behaviors across a wide time range in a large sample of individuals with low-functioning autism. The next section will outline the statistical techniques used to uncover patterns in this large temporal dataset.

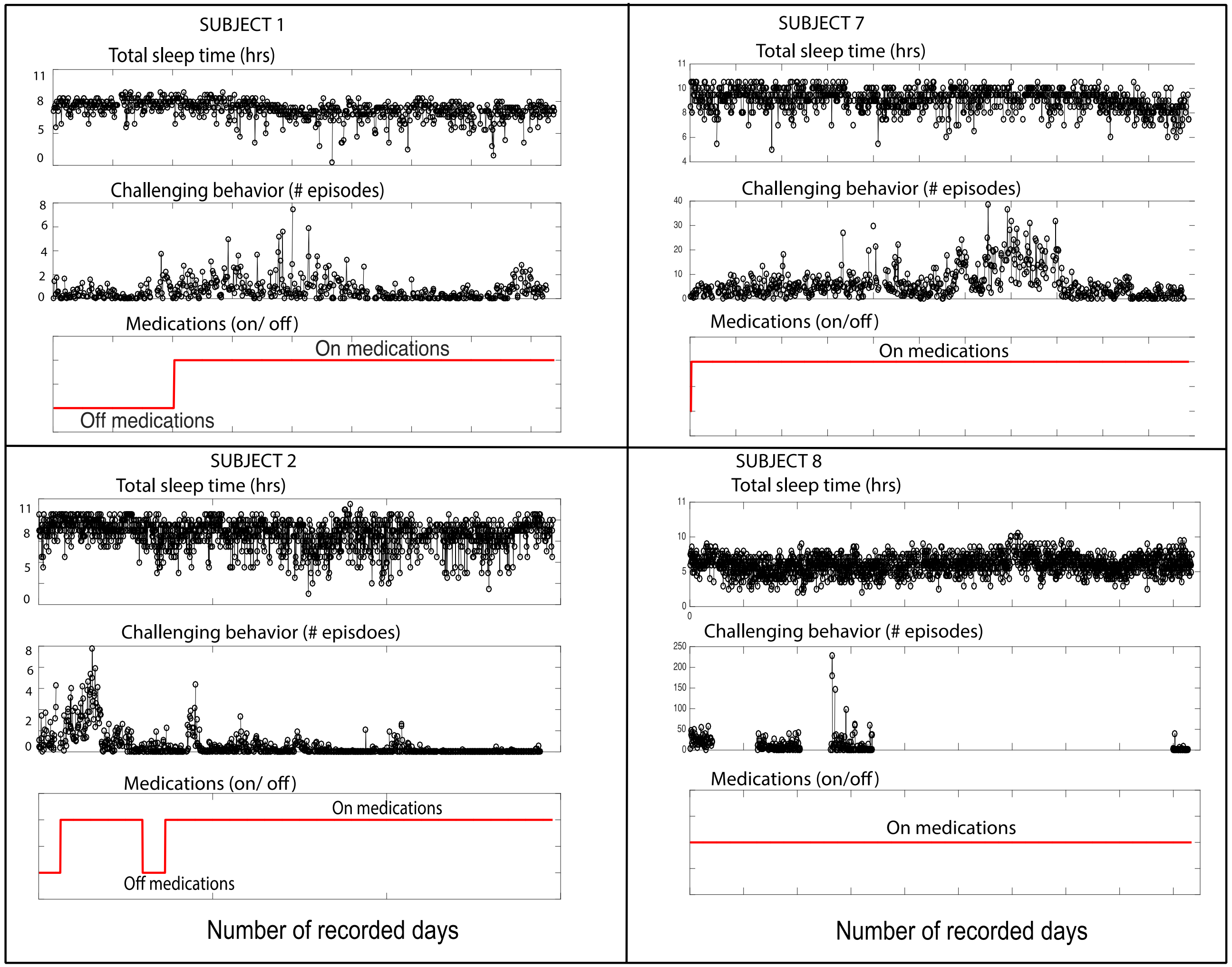

Figure 6: The size and complexity of this dataset meant that each individual had a unique distribution of sleep, behavior and medication profiles across varied lengths of time. Each plot shows a different subject (corresponding to the row number in Figure 5). The distribution of total sleep time (hours), challenging behavior episodes (frequency) and medication administration (including days on/off medications) is shown for each subject.

3.2. Machine learning techniques to learn patterns in large datasets

In recent years, there has been growing interest in the use of machine learning techniques to learn complex patterns in large medical datasets. Machine learning algorithms learn patterns in a set of measured features in order to either: i) derive structure from the data by 'clustering' similar features (unsupervised learning), ii) predict a target outcome variable from a set of measured features (supervised learning). In contrast to simple univariate statistical methods (which examine the static relationship between features), machine learning techniques can identify complex and changing patterns in large datasets through the use of statistical algorithms.

In recent years, unsupervised machine learning techniques (or cluster analysis) has been used to identify homogenous subgroups within heterogeneous medical datasets, including profiling sleep apnoea subtypes (Ye et al., 2014), dietary profiles among healthy individuals (Walthouwer, Oenema, Soetens, Lechner, & de Vries, 2014) and asthma phenotypes among children (Serrano-Pariente, Rodrigo, Fiz, Crespo, & Plaza, 2015). In the field of autism, cluster analysis has been used to identify subgroups of individuals with autism on the basis of their core symptoms (Brennan, Barton, Chen, Green, & Fein, 2015; Palmer, Paton, Enticott, & Hohwy, 2015), and their genetic phenotypes (Veatch et al., 2014), however no study has used these methods to understand sleep profiles in this population. Addressing this shortcoming, we used cluster analysis in chapter 4 to identify clinically meaningful subgroups of individuals with low-functioning autism that are related to distinct patterns of sleep difficulties. This methodology is advantageous as it provides a framework for identifying homogenous subgroups (or clusters), which will assist in the diagnostic assessment of sleep difficulties in this population.

Other machine learning approaches (such as supervised machine learning) have been used in the medical field to learn patterns from large medical datasets to predict future outcomes in patient care. For example, machine learning approaches have been used to predict Parkinson's disease from speech recordings (Tsanas, Little, McSharry, Spielman, & Ramig, 2012), congestive heart failure from heart beat signals (Isler & Kuntalp, 2007), and seizure detection from electroencephalography data (Moghim & Corne, 2013). Predictive models have also been used in the field of sleep medicine, for example sleep loss has been used to predict cognitive impairment in typical subjects (St Hilaire et al., 2013), and sleep history has been used to predict happy-sad mood in college students (Sano et al., 2015). No study to date has used these techniques to predict challenging behavior from prior sleep in any population. Addressing this shortcoming, we used supervised machine learning techniques (such as classification and regression) to make predictions of i) challenging behavior based on prior sleep (chapter five) and ii) nightly sleep duration based on daily challenging behaviors (and vice versa) (chapter six) in individuals with low-functioning autism. The advantage of these statistical approaches is that they provide a methodological framework for predicting daily outcomes in real-time from coarse observational measurements of nightly sleep-wake behaviors, a method with clear translational opportunities for improving patient care in an age of increasing technological monitoring capabilities. The next section will provide a brief outline of the methodological framework of both supervised and unsupervised machine learning approaches used in this thesis.

3.2.1. Unsupervised machine learning

The first goal of this thesis (chapter four) was to identify clinically meaningful subgroups of individuals with low-functioning autism that are related to distinct patterns of sleep difficulties. That is, we were interested in whether the sleep features for an individual clustered into a number of meaningful and distinctive groups, and if so whether individuals in these groups were similar to each other. The unprecedented volume of data available in this study (including 16 indiscriminate sleep features measured across ~100 individuals) motivated the use of cluster analysis to find natural groupings of sleep phenotypes among individuals with low-functioning autism. Figure 7 provides a schematic of how cluster analysis was performed when using a two-dimensional feature space. Hierarchical cluster analysis was the primary method used in chapter four, which identifies groups (or clusters) of data objects (here, nights) based on their similarity across a range of observations (here, the sleep features), by measuring the distance between pairs of observations (or sleep features). This method requires both a distance criteria (i.e., Euclidean distance metric) and a linkage criteria (i.e., Wards method) (Hastie et al., 2009). In chapter four, we tested a range of distance criteria (including squared Euclidean distance, Manhattan distance, maximum distance etc.) and linkage criteria (mean, minimum, maximum, centroid), all of which produced similar cluster solutions (Kaufman & Rousseeuw, 1990). We also evaluated cluster solutions by comparing them against other methods including k-means clustering (Hastie et al., 2009), the Gap Statistic (Tibshirani et al., 2001), Silhouette method (Rousseeuw, 1987) and Calinski-Harabrasz criterion (Calinski and Harabasz, 1974). All methods confirmed a two-cluster solution when identifying meaningful sleep phenotypes in individuals with low-functioning autism.

3.2.2. Supervised machine learning

The second goal of this thesis was to develop a model to predict sleep and behavior outcomes in individuals with low-functioning autism. That is, we were interested in whether a prior night of sleep or multiple nights of sleep could be used to predict real-time outcomes of daily challenging behavior events (chapter five), and whether these relationships existed in a bidirectional manner (chapter six). The size and volume of this dataset motivated the application of supervised machine learning techniques to learn patterns in sleep features to predict daily outcomes. Figure 7 provides a schematic to aid in the understanding of how supervised machine learning can be used to make predictions based on features from a two-dimensional space. This thesis utilized two types of supervised machine learning techniques; i) classification: which involved using a classifier to learn patterns in sleep features that are predictive of a response that has two outcomes (e.g., presence or absence of a behavior), ii) regression: which involved using linear mixed regression to model the relationship between sleep and behavior across individuals to produce an outcome that has a real number (e.g., frequency of behaviors or hours of total sleep time). In chapter five, a range of classification techniques were tested including Naïve Bayes classification, classification trees, k-Nearest neighbours, and discriminant analysis (Hastie et al., 2009), however we reported results using the most common method in the field of medicine: support vector machine classifier (SVM). That is, an SVM classifier with linear kernel was used to learn patterns in features (here, sleep features) that are predictive of a binary outcome (presence or absence of behavior) by separating the feature space in the form of a linear boundary (as shown in Figure 7). This method also addresses the difficulty of class imbalance (i.e., balancing out days of challenging behavior with days of no challenging behavior), by ensuring an equal total cost to misclassifying both classes, regardless of their distribution (Mirza, Lin, & Toh, 2013).

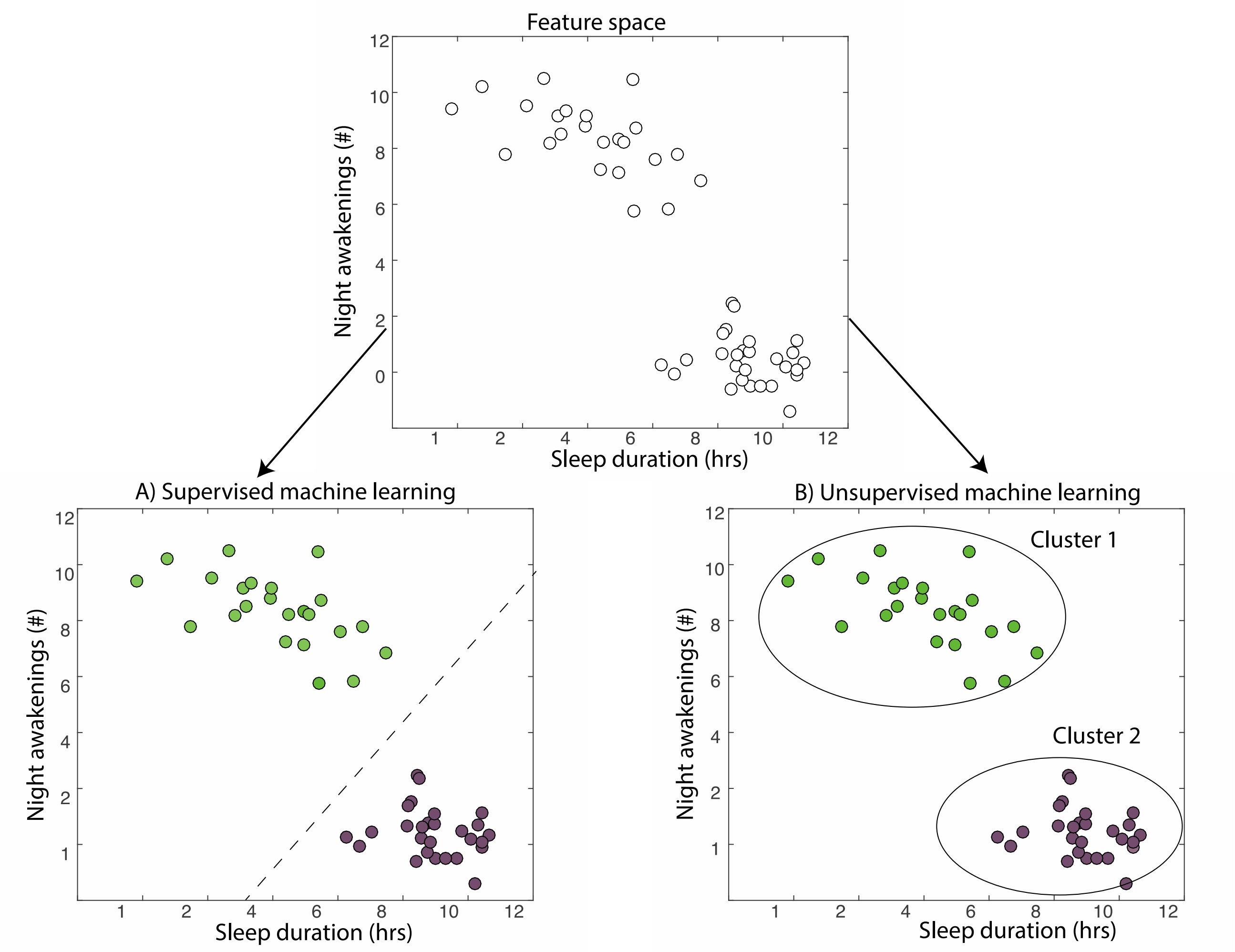

Figure 7: Schematic of the machine learning methodology used to uncover robust patterns and relationships of sleep and behavior in autism. The top illustration shows an example of a two-dimensional feature space, showing sleep duration (x-axis) as a function of the number of night awakenings (y-axis). For simplicity a restricted range of data is shown with each data point representing a single night of sleep duration and single night of night awakening for one individual. **A**) Supervised machine learning uses a support vector machine classifier (dotted line) to learn patterns in sleep features that are predictive of an outcome (either presence (green markers) or absence (purple markers) of behavior), by separating the feature space in the form of a linear boundary. In a linear regression, a regression line is fitted to the two-dimensional feature space to model the relationship between sleep features. This regression function was then used to make predictions about future behavior outcomes (i.e., frequency of behavior episodes). **B)** Unsupervised machine learning such as hierarchical cluster analysis, examines the similarity between data objects (here, nights of sleep duration), based on their similarity across observations (here, number of night awakenings). Pairs of clusters merge based on their similarity (i.e., Euclidean distance between pairs of observations), as shown by the two clusters 1 (green markers) and cluster 2 (purple markers).

3.2.3. Summary

To date, the nature of sleep phenotypes as well as the real-time predictive relationship between sleep and behavior in individuals with low-functioning autism remains understudied. The dataset presented here offers the opportunity to explore these relationships across a large population of individuals with low-functioning autism, with ecologically valid sleep and behavior data that is collected across several years. Moreover, the statistical techniques explored in this section including machine learning methodology, facilitated the discovery of robust sleep-behavior relationships in autism, which could not be accurately captured using simple univariate statistical methods. The following thesis chapters will be utilizing the statistical methods as outlined in this section.

Declaration for Thesis Chapter 4

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Project design, review of relevant literature, collection of data, analysis of data and writing of manuscript	70%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Extent of contribution (%) student and co-authors only**
Dr Ben D. Fulcher	Contributed to review of relevant literature, analysis of data and writing of manuscript.	
Dr Russell Conduit, Professor Kim Cornish, Professor Steven W. Lockley and Professor Shantha Rajaratnam	Contributed to discussion of theoretical issues, provided expertise on drafting and critical review of the manuscript.	
Jason Sullivan, Dr Melissa St Hilaire, Dr Tobias Loddenkemper, Dr Sanjeev Kothare, Dr Kelly McConnell, Dr Paula Braga-Kenyon, Andrew Shelsinger, Dr Jacqueline Potter, Frank Bird, Dr William Ahearn	Critical review of manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidates signature	[redacted]	Date 20/07/16

Main supervisors signature	[redacted]	Date 20/07/16

Chapter 4: Behaviorally determined sleep phenotypes are robustly associated with adaptive functioning in individuals with low-functioning autism

<u>4.1. Preamble to empirical paper 2</u>: Behaviorally determined sleep phenotypes are robustly associated with adaptive functioning in individuals with low-functioning autism.

Although chapter two raised the possibility that children with low-functioning autism have a high prevalence of sleep difficulties due to the severity of their impairments, the nature of sleep-wake difficulties in this population remains unknown. For example, it remains unknown as to whether individuals with low-functioning autism have difficulties with sleep initiation or sleep maintenance, and whether these difficulties are associated with clinical impairments in autism. Moreover, the stability of sleep (i.e., sleep continuity and night-to-night variability) and its link to the severity of functioning in autism have been unexplored in the literature. The following empirical paper presents the first investigation into the nature of sleep profiles using cluster analysis performed on sixteen indiscriminate sleep features measured for over 100 individuals with low-functioning autism. This study also examined whether behaviorally determined sleep phenotypes predict other impairments in autism such as intellectual impairment and adaptive functioning.

Cohen, S., Fulcher, B.D., Rajaratnam, S.M.W., Conduit, R., Sullivan, J., St Hilaire, M., Loddenkepmer, T., Kothare, S., McConnell, K., Braga-Kenyon, P., Shlesinger, A., McConnell, K., Bird, F., Ahearn, W., Cornish, K.M., & Lockley, S.W. (submitted). Behaviorally determined sleep phenotypes are robustly associated with adaptive functioning in individuals with low-functioning autism.

Note: This paper has been submitted to the journal of *Research in Autism Spectrum Disorders*

ABSTRACT

Despite sleep disturbance being a common complaint in individuals with Autism Spectrum Disorder (autism), specific sleep phenotypes and their relationship to adaptive functioning have yet to be identified.In this study, we used cluster analysis to find distinct sleep patterns and relate them to independent measures of adaptive functioning in individuals with low functioning autism. Approximately 50,000 nights of care-giver sleep/wake logs were collected on school-days for 106 individuals with low functioning autism (87 boys, 14.77 ± 3.11 years) for 0.5-6 years (2.2 ± 1.5 years) from two residential schools.Using hierarchical cluster analysis, performed on summary statistics of each individual across their recording duration, two clusters of individuals with clearly distinguishable sleep phenotypes were found. The groups were summarized as 'unstable' sleepers (cluster 1, n = 41) and 'stable' sleepers (cluster 2, n = 65), with the former exhibiting reduced sleep duration, earlier sleep offset, and less stability in sleep timing. The 'stable' and 'unstable' sleep clusters displayed significant differences in properties that were not used for clustering, such as intellectual functioning, communication, and socialization, demonstrating that sleep phenotypes are associated with symptom severity in individuals with autism.This study provides foundational evidence for profiling sleep problems as a standard part of the diagnostic assessment and for targeting sleep problems for therapeutic interventions in individuals with low functioning autism.

Keywords: autism, low-functioning, hierarchical cluster analysis, sleep stability

INTRODUCTION

Autism Spectrum Disorder (or autism) is a complex developmental disorder characterized by deficits in social-communication and repetitive and stereotyped interests and behaviors (American Psychiatric Association, 2013). One of the most common complaints among caregivers of children with autism is disrupted sleep, with 40-80% of children experiencing sleep problems, compared with 25-40% in typically developing children (Meltzer and Mindell, 2008; Reynolds and Malow, 2011). Previous research has demonstrated a range of sleep difficulties among children with autism, including reduced total sleep time, delayed sleep onset, early sleep offset, and increased night awakenings (Malow and McGrew, 2008; Herrmann, 2015). To date, there is a lack of understanding about the relationship between sleep difficulties and clinical symptoms in individuals with low functioning autism (i.e., individuals with a severe intellectual, communication, and socialization impairment).

It is likely that the development and persistence of sleep difficulties in children with autism is multi-factorial. Pre-disposing factors – including abnormalities in co-morbid medical (Malow, 2004) and psychiatric (Mannion, Leader, & Healy, 2013; Stein, Weiss, & Hlavaty, 2012) conditions, and an imbalance in melatonin levels (Rossingnol & Frye, 2014) – have been known to cause sleep disturbances in children with autism. Precipitating events, such as family sleeping practices (Richdale & Schreck, 2009) and emotional and behavioral difficulties (Gregory, Eley, O'Connor, & Plomin, 2004), are also known to disrupt the sleep-wake cycle in autism. Further, medications administered to decrease challenging behavior in autism have been shown to affect sleep, increase existing sleep problems, and induce fatigue, insomnia and/or sedation (Stigler, 2014). Further exploration of factors that play a role in the etiology of sleep problems in autism may be beneficial for the development of treatment strategies to remediate sleep disturbance in individuals with autism.

Prior research has showed consistently that sleep problems are associated with core autism symptoms (Kotagal and Broomall, 2012; May et al., 2015), including social deficits, communication impairments, and repetitive and stereotyped behaviors (Schreck et al., 2004; Gabriels et al., 2005). Studies in the field to date, however, are primarily cross sectional and have focused on individuals with high functioning autism, who have the ability to communicate vocally and can tolerate actigraphic and polysomnographic (PSG) measurements of sleep (Baker and Richdale, 2015; Elrod and Hood, 2015; Lambert et al., 2016). While other studies have focused on the entire range of autism severity using subjective parent report measures (Johnson et al., 2012; Sikora et al., 2012), the nature and prevalence of sleep difficulties specifically in individuals with low functioning autism remains relatively unexplored. Studies have suggested that the severity of sleep disruption increases with the severity of autism symptoms, but the extent of the sleep disruption remains unexplored. A cross-sectional study by Tudor et al. (2012) found that the severity of sleep problems (such as sleep onset delay and sleep duration) as defined by the Children's Sleep Habits Questionnaire increased with the severity of autism symptoms (such as communication deficits) as defined by the Gilliam Autism Rating Scale. Moreover, a recent cross-sectional study by Adams et al. (2014) using autism and sleep assessment batteries similarly found that autism severity was associated with an increased likelihood of sleep problems. Previous studies, however, have primarily focused on disruptive sleep phenotypes in autism such as sleep duration and night awakenings in autism (Cortesi et al., 2010). Consequently, the stability of sleep (i.e., sleep continuity and night-to-night variability) and its link to the severity of functioning in autism have been unexplored in the literature. It remains unknown, therefore, what types of sleep problems predict what types of impairments in individuals with low functioning autism.

Cluster analysis is a method for identifying homogeneous subgroups (or clusters) within a dataset. In the autism literature, previous studies have used cluster analysis to clarify diagnostic heterogeneity in the disorder, but have been limited to identifying subgroups of autism on the basis of core symptoms rather than sleep (Palmer et al., 2015; Brennan et al., 2015, Kitzoe et al., 2016). Overall there is limited evidence on sleep problems in children with low functioning autism. Addressing this shortcoming, we used cluster analysis to identify clinically meaningful subgroups of individuals with low functioning autism that are related to distinct patterns of sleep difficulties. We then examined whether differences in sleep phenotypes were associated with differences in clinical symptoms (e.g., intellectual functioning and adaptive functioning). We tested the hypothesis that differences in sleep characteristics can predict differences in the severity of adaptive functioning and core clinical symptoms in low functioning autism.

METHODS

Data

This study was approved by the Partners Healthcare Institution Review Board (USA) and the Monash University Human Research Ethics Committee (Australia). A waiver of consent was obtained to access de-identified clinical data from both residential facilities.

Participants

The data were collected from Melmark New England (MNE) and the New England Center for Children (NECC), two residential schools in Massachusetts, USA that offer intense applied behavior analysis therapy for individuals with autism and other developmental disabilities. All participants with a diagnosis of autism were assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000) by a Pediatrician or Psychiatrist. The study inclusion criteria were residential pupils under the age of 18 years with low functioning autism, confirmed by having an Intellectual Quotient (IQ) $\leq$ 70, as measured by either the Leiter-R International Performance Scale-Third Edition (Roid and Miller, 1997) (n = 18) or the Stanford-Binet Intelligence Scale-Fifth edition (Terman and Merill, 1960) (n = 40); or impairments in communication, socialization, and adaptive functioning, as measured by the Vineland Adaptive Behavior Scales (VABS) (n = 60). Missing IQ and VABS scores were due to individuals being unable to participate in standardized testing due to the extent of their impairments (i.e., severe deficits that could not be quantified by formal assessments), therefore these individuals were still included in the analysis.

Data were collected on 41 children (35 boys, 6 girls) with a mean age (± SD) of 14.56 ± 3.63 years from a total of 47 children who were resident at MNE from 2008 to 2013. Data were also collected on 65 children (52 boys, 13 girls, M = 14.91 ± 2.74 years) from a total of 132 children who were resident at NECC from 2010-2013. The 6 MNE residents and 67 NECC residents who were excluded from the study cohort were either considered to have an alternative diagnosis or were above 18 years of age. Eighteen years of age was considered a reasonable inclusion criterion for participants to be labeled as adolescents. The total sample consisted of 106 individuals with clinically diagnosed low functioning autism who were between 5 and 18 years old (87 boys, 14.77 ± 3.11 years). The data collection duration for each participant ranged from 0.5 to 5.9 years (2.2 ± 1.5 years, between February 2008 and November 2013) and each individual contributed between 42 to 1858 nights of data (734 ± 424 nights). Eighty percent of the participants were White (n = 94), and the remaining demographic sample included African American (n = 4), Hispanic (n = 2), Asian (n = 2) and individuals of unknown ethnicity (n = 4).

Sleep-wake recordings

As a part of routine clinical care, trained care-givers on duty at both residential facilities were responsible for recording sleep-wake state from 19:00 to 7:00 h during frequent bed checks and making a judgment as to whether the participant was awake (defined as eyes open with bedroom activity) or asleep (defined as eyes closed with no bedroom activity). Sleep-wake behavior was measured every 30 minutes at MNE and every 15 minutes at NECC, and recordings were taken every night from initial entry into the residential facility. Participants residing at MNE had variable ‘lights-off’ times, which could change throughout their stay in the residential facility. Seven participants residing at MNE had prompted or unprompted toilet awakenings throughout the night due to incontinence, which was considered as time awake in this analysis. Participants at NECC had a standard fixed lights-off time of 21:00 h with no prompted night awakenings. Both schools had fixed lights on/wake times at 7:00 h. Bed-time routines were maintained on weekends at both residential facilities. A total of 77,838 nights of sleep-wake recordings were available from this dataset.

Clinical information

Clinical information was obtained from the school databases, which included demographic information (such as age, gender), and clinical information as screened by a Psychiatrist of Pediatrician. The clinical information available from this dataset included, medical information (such as seizures, gastrointestinal disorders), psychological information (such as anxiety, attention deficit hyperactivity disorder), and medication information (including nights with and without medications). These variables (with the exception of age) were transformed into binary variables and were coded as a 0 (absence of characteristic) or 1 (presence of characteristic). Medications were grouped into drug classes that affect sleep (including SSRI’s, anti-histamines, anti-psychotics, melatonin, beta-blockers and benzodiazepines) and the proportion of nights on each medication class was calculated for each individual. Adaptive functioning scores were also available using VABS, which measures five domains: communication, daily living, socialization, motor skills, and maladaptive behavior. These domains make up an overall composite score of adaptive behavior (Sparrow et al., 1984). The VABS has demonstrated adequate internal consistency reliability and good test-retest reliability with coefficients ranging between 0.80 and 0.90 (Sparrow et al., 1984). Both IQ and adaptive functioning were only assessed upon entry into the residential facility, but are considered to be a stable measure of developmental functioning across an individual’s lifespan (Freeman et al., 1999).

Calculating sleep statistics and sleep features

Sleep parameters were computed from nightly observations of sleep and wake including: i) total sleep time, ii) sleep onset, iii) sleep offset, iv) sleep efficiency, and v) number of night awakenings (see Table 1 below for definition of parameters). The five sleep parameters were chosen, as they were the exhaustive and accurate sleep measurements that could be calculated from this coarse temporal dataset. It is important to note that although the quality of measurement in our sample may be less accurate than lab-based, controlled studies (such as sleep-lab or actigraphy studies), the dataset is unique in comprising an unprecedented volume of real world data, thus providing an ecologically valid analysis of sleep in this population. To ensure good data quality, nights containing any missing data points (missing 15-30 minute recordings, for example), or nights with no data (due to weekends or holiday breaks, for example) were excluded from our analysis. In total, 26% of nights (n = 20,484) were excluded due to missing data prior to performing sleep calculations. The remaining dataset consisted of 29,756 nights of data from individuals at MNE and 27,598 nights of data from individuals at NECC, yielding a total dataset containing 57,354 nights of sleep-wake data. This data included all the sleep-wake recordings for every individual across their available recording period. However, we also examined a restricted range of data across a 1-year recording period to assess the stability of the cluster analysis results across time.

Table 1: Five sleep statistics used to summarize each individual night of sleep-wake data.

Sleep statistic	**Definition**
Total sleep time (h)	Total time spent asleep.
Sleep onset time (hh:mm)	Time at the start of the first episode of sleep.
Sleep offset time (hh:mm)	Time at the end of the last episode of sleep.
Sleep efficiency (%)	Total sleep time divided by the sleep interval (sleep offset – sleep onset).
Night awakenings (#)	The total number of awakenings recorded. Each awakening had to be followed by an episode of sleep.

Next, we computed summary statistics including the mean and standard deviation of each of the five sleep parameters. These 10 sleep features (as shown in the key for Figure 1) encapsulated participant-level summaries of sleep-wake behavior. In addition to these 10 sleep features, a sleep stability measure was also included, which was introduced in recent work by Clerx et al (2014). The 'sleep stability' feature was calculated by comparing similarity of each individual's nightly sleep/wake patterns at a time-lag of 24 h. Mathematically, sleep stability was computed as the sum $\frac{1}{T}\sum_t S_t \times S_{t+24}$ where s is a sleep indicator (1 for wake, -1 for sleep) and the sum over time t (hours) was taken over all T sleep observations with matching observation 24 h later. Sleep stability takes a maximum value of 1 for a perfectly regular sleep/wake pattern that repeats itself every 24 h, and a minimum value of -1 when the sleep/wake pattern never matches itself at a lag of 24 h. This measure also accounts for variable bedtimes, as it was calculated from the start of the sleep episode. Thus a total of 11 sleep features were used to summarize the sleep of each participant across their available recording period and across a one-year recording period. No pairs of sleep variables showed a strong linear dependence, as all pairwise Pearson Correlation coefficients between sleep variables were small ($R^2 < 0.30$).

Cluster analysis

Prior to performing a cluster analysis, an outlier-robust sigmoidal normalizing transformation was applied to each sleep feature (as this transformation normalizes scores according to the median and interquartile range (iqr)). Mathematically, this was computed as $\tilde{x} = \left(x - \mathrm{median}(x)\right)/\left(1.35\mathrm{iqr}(x)\right)$. This calculation adjusted for outliers in the data and allowed sleep features with different ranges to be compared meaningfully (Fulcher et al., 2014). Hierarchical clustering was performed using Ward's method with a Euclidean distance metric. To evaluate the optimal number of clusters in our data, we used several evaluation methods, including the Gap Statistic (Tibshirani et al., 2001), Silhouette method (Rousseeuw, 1987), and Calinski-Harabrasz criterion (Calinski and Harabasz, 1974). The number of clusters was determined as the value of *k* that was the most consistent across these evaluation methods.

Differences in sleep features (including total sleep time and sleep onset), clinical characteristics (including IQ and adaptive functioning), drug classes that impact sleep, and medical and psychological co-morbidities (including anxiety, attention deficit hyperactivity disorder, gastro-intestional disorders and epilepsy) between clusters were quantified using a Welch's t-test, correcting for multiple comparisons using the method of Bonferroni. Univariate linear regression was used to evaluate the correlation of each participant's 11 sleep features to each of the clinical variables (e.g., IQ, communication scores, socialization scores, daily living scores) separately to investigate whether any single sleep feature predicted any single clinical variable. These comparisons were only performed using individuals in sleep clusters that had clinical data such as IQ scores and adaptive functioning scores available.

RESULTS

Sleep phenotypes in children and adolescents with low-functioning autism

Using a set of 11 sleep features, we performed hierarchical cluster analysis on all 106 individuals, as shown in Figure 1. The results of the hierarchical cluster analysis show two robust clusters of individuals within the sample: cluster 1 (n = 41) and cluster 2 (n = 65). A two-cluster solution was consistent across a range of parameters controlling the hierarchical clustering, including distance metrics, linkage methods, and evaluation criterion. Moreover, this two-cluster solution was evident when examining an individual's sleep-wake recording over a 1-year period suggesting stability of cluster membership for an individual across time. Examples of individual raster plots for each cluster are shown in Figure 2.

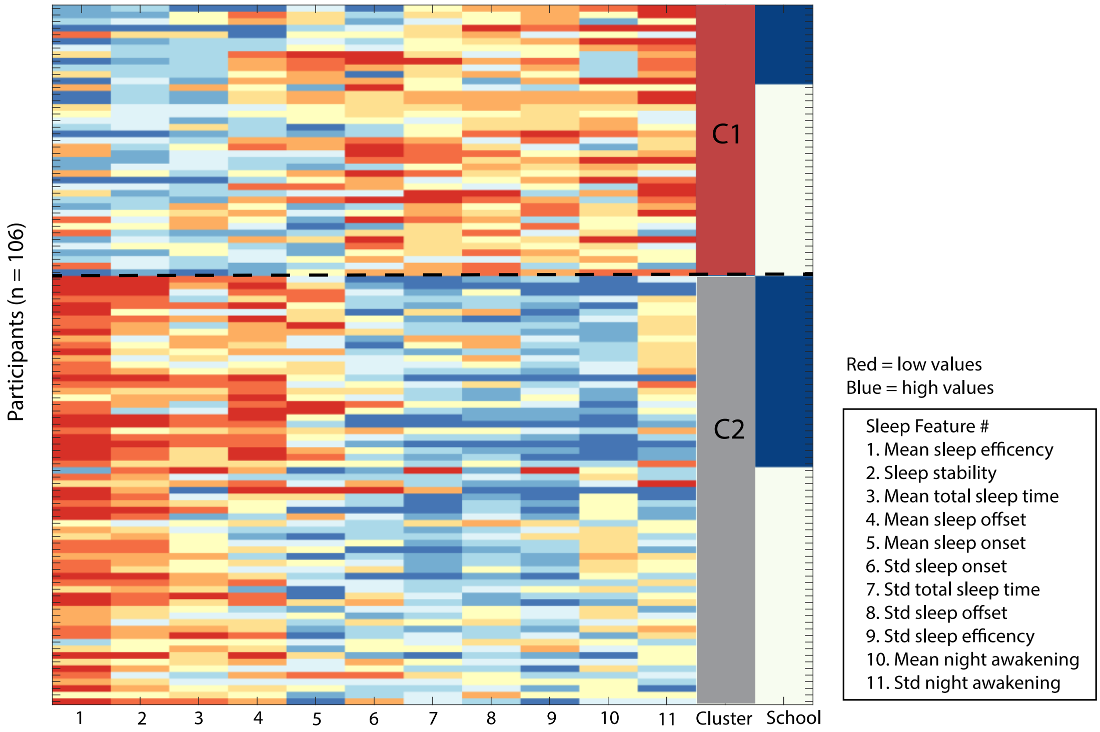

Figure. 1: A visual representation of the sleep profiles for each individual across the 11 sleep features, including the cluster solutions. Elements in the sleep features matrix were normalized and visualized using color from blue (high values) to red (low values). Participants (rows) and sleep features (columns) were compared using squared Euclidean distances and were then reordered using Wards linkage clustering to place similar sleep features and similar participants close to one another. The results produced two distinct clusters; C1 (stable sleepers, *n* =41) and C2 (unstable sleepers, *n* =65), which is represented by the far right bar. The school number is indicated in the right bar with the white representing MNE and blue representing NECC. The sleep features are labeled 1-11 on the horizontal axis. Std = standard deviation.

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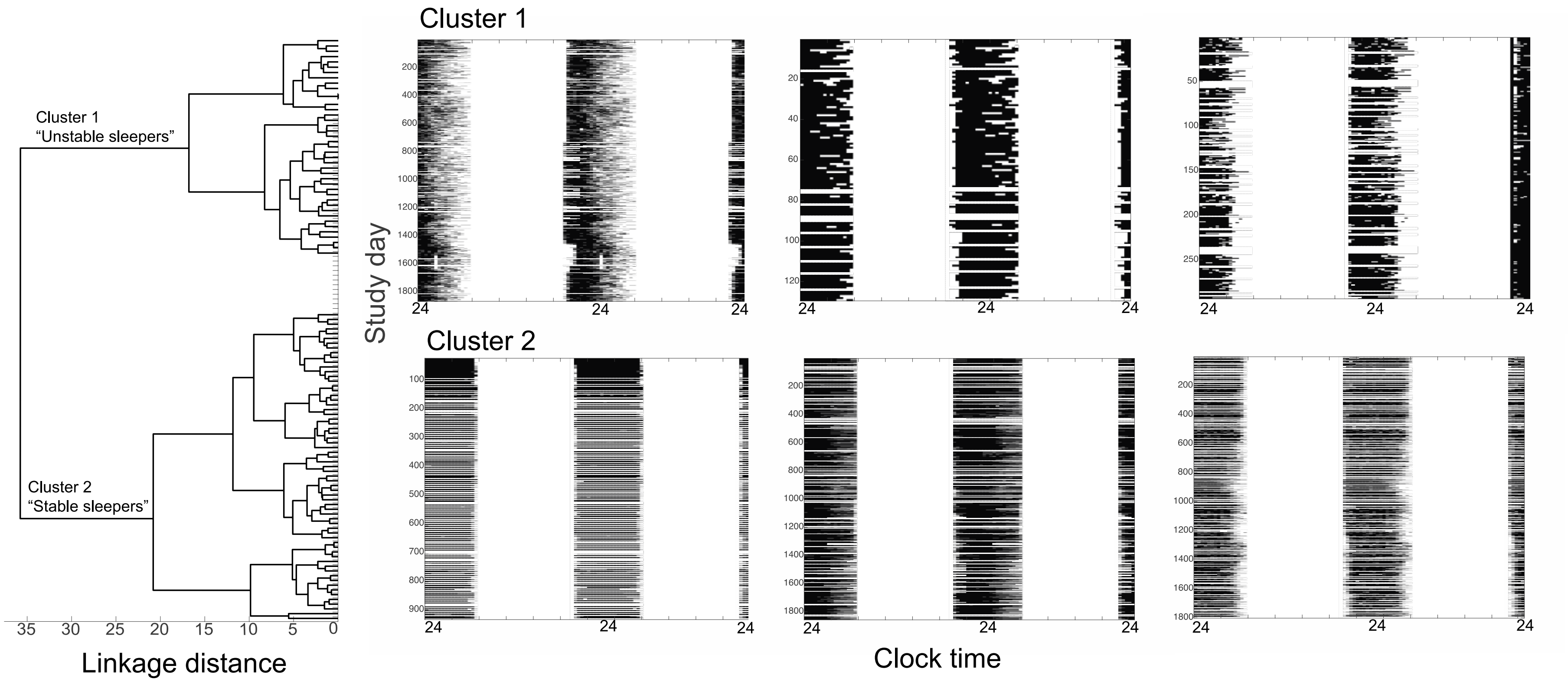

Figure 2: A dendrogram is an interpretable visualization of the hierarchical cluster analysis and useful summary of the data. Each observation (or individual) is represented by a node placed on the vertical axis, and the horizontal axis (linkage distance) indicates the distance between observations in a cluster. A random selection of individual participant sleep raster within each sleep cluster is plotted to the right of the dendrogram. The raster plot shows a double plot of individuals sleep-wake behavior across their recording period. These plots suggest a two-cluster solution (cluster 1 and 2), distinguished by their severity of sleep disruption.

Cluster 1 and cluster 2 differed significantly in 10 of the 11 sleep features ($p < 0.004$) (see Figure 3 for 10 of the 11 sleep features that were significant). Participants in cluster 2 had significantly longer and less variable total sleep time (TST) (M = 8.86, SD = 0.72), reduced variability in sleep onset (M = 0.67, SD = 0.20), later and less variable sleep offset (M = 06:16, SD = 0.54), increased sleep stability (M = 0.78, SD = 0.07), higher and less variable sleep efficiency (M = 99.21, SD = 0.74), and fewer night awakenings (M = 0.67, SD = 0.37) when compared to participants in cluster 1. Cluster 1 was characterized by sleep features that indicate highly variable and unstable sleep and therefore this group was given the label 'unstable' sleepers relative to cluster 2, who were labeled 'stable' sleepers.

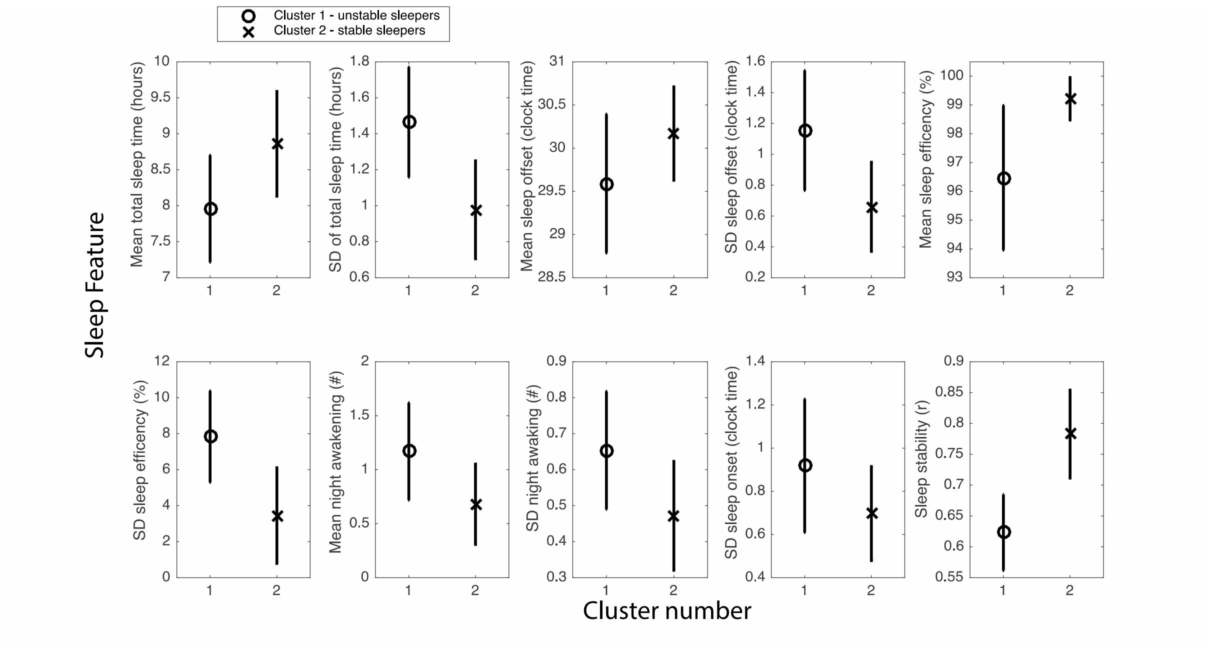

Figure 3: Sleep features that significantly distinguish the stable (*n* = 41) and unstable (*n* = 65*)* sleep clusters using Welsch's t-tests. The means ± standard deviations are plotted for each cluster. * $p < 0.05/11$.

To investigate the robustness of the clusters, we repeated the cluster analysis for participants in each school separately. Again, hierarchical clustering and evaluation procedures consistently indicated a two-cluster solution within each school. The two clusters obtained in each school individually matched the same characteristics found in the full clustering as described above, allowing us again to use the 'stable' and 'unstable' labels to describe the two clusters. Eleven participants at MNE (26.3%) and 29 participants at NECC (44.6%) matched an 'unstable' sleep profile when compared to 30 participants at MNE (73.1%) and 36 participants at NECC (55.36%) who matched a 'stable' sleep profile. We also examined the reproducibility of cluster solutions by deriving a cluster solution from MNE and applying it to individuals at NECC (and vice versa). The predicted cluster accuracy for MNE (based on cluster solution from NECC) was 73%, and the predicted cluster accuracy from NECC (based on cluster solution from MNE) was 68%. This suggests that in approximately 70% of cases we can predict cluster assignments from one school and apply it another school, highlighting the stability of cluster solutions.

Characterizing and evaluating sleep phenotypes

Next we investigated whether the individuals in the two sleep clusters were distinguished by their clinical, medical, and metadata scores. Welch's t-tests, adjusted for multiple comparisons, were used to investigate differences in sleep clusters on all clinical information provided. The 'unstable' sleep group had significantly reduced full-scale IQ scores, communication scores, and daily living and overall adaptive behavior composite scores when compared to participants in the 'stable' sleep group (see Figure 4). No significant differences between clusters were found when examining age (p = 0.34), gender (p = 0.17), presence of an anxiety disorder (p = 0.19), ADHD (p = 0.16), gastro-intestinal disorders (p = 0.39), seizures (p = 0.57), and number of medications that impact sleep (p = 0.83). Welch's t-tests also found no significant differences in the portion of children from each cluster using drug classes (including SSRI's, anti-convulsant, anti-psychotics) that are known to affect sleep (p > 0.06).

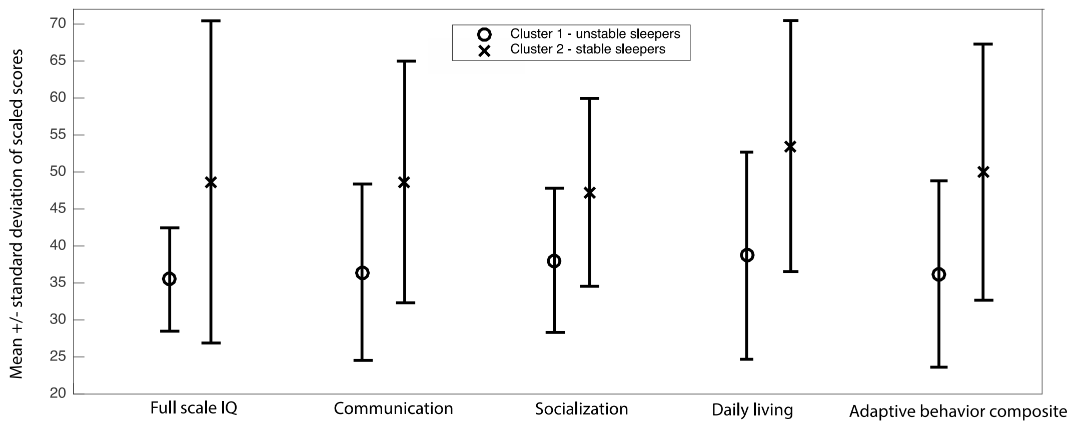

Figure. 4: The two sleep groups were distinguished by scores that determine adaptive functioning in autism. Profile of scaled scores for intellectual quotient (IQ) and Vineland Adaptive Behavior Scales parent ratings of communication, socialization, daily living and adaptive behavior composite across the distinct two-sleep phenotypes * p < 0.05/5.

Finally, univariate linear regression was used to evaluate the correlation of each participant's sleep features and their clinical features such as IQ and adaptive functioning scores. Each individual had a small correlation ($R^2 \leq 0.04$) between their 11 sleep features and IQ, socialization, communication and daily living scores, suggesting that a combination of sleep features (rather than one key feature) contributes to a small change in the clinical symptoms of autism. These results demonstrate that cluster analysis uses a wide range of sleep features to determine sleep phenotypes rather than a single sleep feature (such as total sleep time).

DISCUSSION AND IMPLICATIONS

This study is the first to report robust clusters of sleep behavior in children with low functioning autism using an unprecedented dataset of over 50,000 nights of sleep. We report two distinct sleep phenotypes, labeled 'stable' and 'unstable' sleepers each with characteristic differences in the severity of key sleep features. Notably, the unstable sleepers displayed greater impairments in functioning, including lower IQ scores as well as adaptive functioning scores, when compared to the stable sleep group. The same qualitative findings were obtained when considering individual schools separately, and these findings were independent of age, gender, and medication administration. The findings from this study coincide with previous research suggesting that sleep deficits increase with autism symptom severity (e.g., Tudor et al., 2012; Adams et al., 2014), and alongside recent work by Palmer et al., (2015) and Kitazoe et al., (2016) highlights the utility of cluster analysis in the clinical sub-typing of autism. The implications of this study are significant, as it identifies stable and unstable sleep profiles in autism, and links robust changes in sleep behavior to adaptive functioning in individuals with low functioning autism. Moreover, this study draws attention to sleep patterns over time, and demonstrates how sleep continuity (not just hours of sleep or night time awakenings) is associated with adaptive functioning in autism.

Clinical subtyping has been defined as one of the major short-term challenges in autism research, given the challenge of clinical heterogeneity in autism (Arango, 2010). Previous studies have been unable to capture distinct sleep profiles in autism, as they have primarily used cross-sectional data from individuals with high functioning autism, and have limited their measurements to parent reports, or small PSG and actigraphy studies (Goldman et al., 2009; Anders et al., 2012). Current objective sleep measures pose methodological challenges, as individuals with autism often have difficulty tolerating these tools due to sensory sensitivities (Hodge et al., 2012). Moreover, a recent study has shown that infrequent random parental observations of sleep are correlated with actigraphy measured sleep duration (Veatch et al., 2016), which challenges the notion that sleep recordings need to be objectively measured in order to be validated. The nature of our dataset (longitudinal observations over a period of 5 years and the ability to extract a large number of sleep characteristics from each individual) allowed us to identify distinct patterns of sleep-wake behavior in individuals with low functioning autism with ecological validity. We also incorporated new measures of variability such as sleep stability, which allowed us to measure more subtle properties of sleep-wake behavior including sleep timing. Further investigation using these representative features could provide new insights into the sleep profiles of individuals with sleep disorders, or high functioning autism. Although the present findings will require more complete assessments and independent replications, they suggest that cluster analysis may be able to partition individuals with low functioning autism into clinically meaningful subgroups on the basis of their sleep-wake behavior.

Limitations and future directions

This study should be viewed as an initial step towards the identification of sleep phenotypes using cluster analysis in low functioning autism, and as such, our results need to be interpreted in the context of the data acquisition. Sleep-wake recordings were based on discrete 15-30 minute observations – an approach that differs from the continuous recordings obtained from actigraphy or PSG. Hence, the reliability and validity of the observations poses a limitation, in addition to the accuracy of sleep measurements, which are based on a coarse time-sampling approach. We acknowledge that although the quality of sleep measurement in our study is less accurate than traditional lab-based studies using objective measures such as actigraphy, this limitation was counterbalanced by the uniqueness of this dataset in that it comprises an unprecedented volume of real world data. This study focused on a relatively small and understudied population of individuals with low functioning autism, which may not be generalizable to outpatient autism samples, who are not living in residential care, nor children with high functioning autism. Further validation of independent cohorts, including a wider variety of demographics, greater sample sizes, outpatient samples, and levels of autism severity is needed to allow for generalizability of findings. While night awakenings from MNE were not taken into account in this analysis, the same consistent sleep clusters were evident in both schools, suggesting that sleep clusters were not systematically biased by artificial night awakenings. Furthermore, adaptive functioning test results (i.e., VABS scores) were only determined at one point in time when participants were initially enrolled at the residential facilities, when their autism symptoms were potentially most severe. While it is possible that later intervention may have moderated these scores, and therefore the association between sleep phenotypes and adaptive functioning, this is unlikely given the same sleep phenotypes were evident when performing cluster analysis of individual sleep recordings across a one-year recording period. Future studies examining sleep patterns could examine sleep profiles and adaptive behavior data at concurrent time points, in order to validate this finding and assess effects of any clinical interventions. Thus, the timing and type of clinical assessments used in this study present a potential limitation. Lastly, we acknowledge that the clusters identified using this method are based on a group effect, and while individual variability between participants exists, this method does not characterize individual sleep phenotypes. While this dataset contained a wide range of ages, demographic characteristics, medications, and recording periods, the robustness of our results validate our assumption that this large volume of detailed data is sufficient to overcome its limitations.

Implications of findings

Overall, the findings of this study suggest a deeper relationship between sleep and autism than has previously been acknowledged. We used over 50,000 nights of data to uncover two distinct sleep phenotypes with associated differences in symptomatic profiles. Our study demonstrates that screening for sleep difficulties in routine assessments can be a cost-effective means of reducing the severity of the disability in individuals with low functioning autism, and has important public policy implications for the allocation of treatment resources in autism. The identification of distinctive sleep profiles in individuals with low functioning autism creates a foundation for the development of enhanced diagnostic algorithms and the potential to offer more personalized therapies in the future that will hopefully improve long-term outcomes for the nearly 1 in 68 individuals affected by this pervasive developmental disorder (Dawson, 2013).

Conflict of interest

The authors declare no conflict of interests nor any competing financial interests in relation to this work described.

Acknowledgements

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Declaration for Thesis Chapter 5

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Project design, review of relevant literature, collection of data, analysis of data and writing of manuscript	60%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Extent of contribution (%) student and co-authors only**
Dr Ben D. Fulcher	Contributed to discussion of theoretical issues, provided expertise on analysis and drafting and critically reviewed the manuscript.	40%
Dr Russell Conduit, Professor Kim Cornish, Professor Steven W Lockley and Professor Shantha MW Rajaratnam	Contributed to discussion of theoretical issues and critical review of the manuscript.	
Jason Sullivan, Dr Melissa St Hilaire, Dr Tobias Loddenkemper, Dr Sanjeev Kothare, Dr Kelly McConnell, Dr Paula Braga-Kenyon, Andrew Shelsinger, Dr Jaqueline Potter, Frank Bird, Dr William Ahearn	Critical review of the manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidates signature	[redacted]	Date 20/07/16

Main supervisors signature	[redacted]	Date 20/07/16

Chapter 5: Challenging behavioral events predicted from prior sleep patterns in individuals with low-functioning autism

<u>5.1. Preamble to empirical paper 3:</u> Challenging behavioral events predicted from prior sleep patterns in individuals with low-functioning autism

The findings from the chapter four demonstrate the heterogeneous nature of sleep phenotypes in individuals with low-functioning autism. Chapter five, considers the implications of sleep difficulties in autism and whether prior sleep can be used to predict challenging behavior in real-time in individuals with low-functioning autism. Previous studies in the field have examined overall relationships between sleep and behavior using cross-sectional designs, and while they report mixed findings, it remains unknown whether these results translate to real-world application. That is, can a prior night sleep or multiple nights of sleep be used to predict future likelihood of problematic behavior in autism? Thus the focus of this paper is to determine whether there is a real-time predictive relationship between sleep and behavior in autism, and if so, on what time-scale is this relationship the most predictive and for whom is this relationship most predictive. This is an area that has received very little attention in the literature and can be seen as the first step towards implementing a clinical tool to predict challenging behavior in the future in individuals with low-functioning autism.

Cohen, S., Fulcher, B.D., Rajaratnam, S.M.W., Conduit, R., Sullivan, J., St Hilaire, M., Loddenkepmer, T., Kothare, S., McConnell, K., Braga-Kenyon, P., Shlesinger, A., McConnell, K., Bird, F., Ahearn, W., Cornish, K., & Lockley, S.W. (submitted). Challenging behavioral events predicted from prior sleep patterns in children with low functioning autism.

Note: This paper has been submitted to the journal *Translational Psychiatry*

ABSTRACT

Increased severity of problematic daytime behavior has been associated with poorer overall sleep quality in individuals with autism. However, it is not known whether this relationship holds in a real-time setting, such that an individual's sleep (measured on a timescale of days) is predictive of their subsequent daytime behavior. In this work, we show that challenging daytime behaviors (aggression, self-injury, tantrums, property destruction, and a combined challenging behavior index) can be robustly predicted from prior sleep in individuals with low-functioning autism. We analyzed an extensive real-world dataset containing over 20,000 observations of nightly sleep matched to subsequent daytime behavior across 67 individuals living in two U.S. residential facilities. Using support vector machine classifiers to learn individual-specific relationships between sleep and challenging behavior, we found a statistically significant predictive relationship in 75% of our sample ($P < 0.05$). For all five behaviors examined, prediction accuracy increased with the number of nights of prior sleep used to make the prediction, from 1 prior night (mean classification rate: 51-54%) up to approximately 7 prior nights (mean classification rate: 56-60%), indicating that the behavioral effects of sleep may manifest over this longer timescale. The strongest individual predictors of challenging behavior were measures of sleep variability, highlighting the importance of regular sleep patterns for daytime functioning. On an individual level, greater impairments in adaptive functioning were associated with more predictable sleep-behavior relationships. This study is the first to demonstrate a robust temporal relationship between sleep and behavior that varies with autism symptom severity, and to characterize the timescale and sleep properties that drive the prediction. Our results pave the way for the development a real-time monitoring tool to pre-empt behavioral episodes and facilitate prophylactic treatment for individuals with autism.

INTRODUCTION

Autism spectrum disorder (or autism) is associated with a high prevalence of sleep and behavioral difficulties. Prior research indicates that between 40-80% of individuals with autism experience problems with sleep (Allik, Larsson, & Smedje, 2008; Anders, Iosif, Schwichtenberg, Tang, & Goodlin-Jones, 2011; Rzepecka, McKenzie, McClure, & Murphy, 2011) and approximately 64-93% exhibit at least one challenging behavior (i.e., behaviors that are physically dangerous and impact learning; for example, aggression, self injury or tantrums) (Hattier, Matson, Belva, & Horovitz, 2011; Matson, Mahan, Hess, Fodstad, & Neal, 2010). Although the association between sleep and behavior has been investigated in adults and individuals with high-functioning autism (Fadini et al., 2015; Goldman et al., 2011; Hirata et al., 2016; Hollaway, Aman, & Butter, 2013; Mayes & Calhoun, 2009; Mazurek & Sohl, 2016), these relationships are understudied in individuals with low-functioning autism (i.e., individuals with severe intellectual and social-communication impairment) (Cohen, Conduit, Lockley, Rajaratnam, & Cornish, 2014). Crucially, all previous research on the relationship between sleep and behavior (both in autism and other populations) has focused on the association between an individual's overall sleep and their overall behavior. It therefore remains unclear whether these relationships apply only globally, or whether they have real-time predictive value for a given individual, i.e., whether fluctuations in sleep over time predict corresponding fluctuations in behavior over time.

Sleep disturbance in typically developing individuals has been associated with higher rates of behavioral problems, and impairments in attention and cognition (Baum et al., 2014; Chervin et al.; Gregory & Sadeh, 2012). In individuals with high-functioning autism, however, studies investigating the relationship between overall sleep quality and behavior have reported mixed results. In some studies, decreased quality of sleep (such as reduced sleep duration and increased night awakenings) was associated with increased rates of challenging daytime behaviors (such as tantrums, aggression and self-injurious behaviors) using retrospective parent reports of average sleep over a few days or weeks (Fadini et al., 2015; Goldman et al., 2011; Mazurek & Sohl, 2016; Sikora et al., 2012). Other studies that used more objective measures of sleep such as polysomnography (PSG) and actigraphy over a longer two-week time window, failed to find any relationship between sleep quality and behavior (Goodlin-Jones et al., 2009; Lambert et al., 2016). A further study examining longitudinal associations between sleep and behavior found that improvements in sleep quality across a year were not associated with improvements in parent reported ratings of aggression (May, Cornish, Conduit, Rajaratnam, & Rinehart, 2015). Individuals with autism (including low-functioning autism) present with a high degree of heterogeneity, in terms of their severity of sleep (Fadini et al., 2015), behavioral functioning (Maskey, Warnell, Parr, Le Couteur, & McConachie, 2013), and medication profiles (Siegel & Beaulieu, 2012), which may contribute to these inconsistent findings. The ability to capture the sleep-behavior relationship in prior studies is further complicated by small sample sizes, short monitoring periods, and subjectivity of retrospective parent-reported sleep measurements. The inconsistency of previous results suggests that the relationship between sleep and behavior in autism requires further investigation.

Existing studies have investigated the overall relationship between an individual's sleep and rates/severity of daytime challenging behaviors, providing a 'static' picture of the sleep-behavior relationship that tells us *which* individuals (on average) are more likely to exhibit poor behavior given their overall sleep. No study to date has examined whether this relationship is predictive through time of the day-to-day behavior of a given individual (e.g., whether there is a greater probability of problem behaviors immediately following a period of particularly poor sleep). This 'temporal' picture of the sleep-behavior relationship tells us *when* problem behaviors occur, and can thus inform preventative interventions against future behaviors. Investigating a temporal sleep-behavior relationship requires large volumes of data over time, the expense of which typically prohibits controlled, lab-based studies. Large ecological datasets collected over years, as per the dataset available in this study, have increased real-world validity, but present methodological challenges in dealing with coarser measurements of sleep and behavior in individuals of different (and time varying) ages, medications, sleep patterns, behavioral profiles, and behavioral triggers. Prior studies into the temporal sleep-behavior relationship are scarce and only one study to date has investigated the prediction of mood from prior sleep patterns (Sano et al., 2015). This study is the first to examine a temporal relationship between sleep and daytime behavior in individuals with autism.

The timescale on which sleep affects daytime behavior is another key question that a temporal examination of the sleep-behavior relationship can address. For example, is the previous night of sleep sufficient to predict today's behavior, or are multiple prior nights of sleep more informative? Cumulative sleep loss over several days has been associated with disruptions in cognitive performance in adults (Belenky et al., 2003; Dinges, Pack, WIlliams, & et al., 1997; Haavisto et al., 2010; Sallinen et al., 2013; Van Dongen, Rogers, & Dinges, 2003). For example, a study by Van Dongen et al. (2003) found that sleep restriction (4-6 hours sleep per night) resulted in cumulative deficits in cognitive performance and sustained attention across a 2-14 day time period (Van Dongen, Maislin, Mullington, & Dinges, 2003). Other studies have examined the effects of cumulative sleep loss over 3-5 days, reporting that sleep loss over consecutive days produced temporary difficulties in cognition, behavior and physical health in typically developing individuals (Fallone, Acebo, Arnedt, Seifer, & Carskadon, 2001; Jan et al., 2010; Randazzo, Muehlibach, Schweitzer, & Walsh, 1998). The longitudinal dataset analyzed in this work is sufficiently comprehensive to allow us to investigate whether a similar cumulative relationship between multiple nights of sleep and subsequent daytime functioning are generalizable to a real-world sample of individuals with low-functioning autism.

In this work we analyze an extensive longitudinal dataset of 67 individuals with low-functioning autism in a residential setting across approximately 20,000 nights of sleep measurements matched to subsequent daily behavioral recordings, with the broad aim of uncovering real-time predictive relationships between sleep and challenging behavior. In particular, we investigate the following: (i) whether challenging behavior can be predicted from prior sleep, (ii) the timescale on which this temporal sleep-behavior relationship is most predictive, (iii) the types of sleep characteristics that drive successful classification performance, and (iv) whether the strength of the sleep-behavior relationship varies as a function of autism symptom severity. This work represents the first step towards developing a system that could warn caregivers of impending problem behaviors, and motivate treatment responses for individuals with autism.

MATERIALS AND METHODS

Data Collection

This study was approved by the Partners Research Committee (USA) and the Monash University Human Research Ethics Committee (Australia). A waiver of consent was obtained to access de-identified clinical data. The data were collected from Melmark New England (MNE) and the New England Center for Children (NECC), two residential schools in Massachusetts (USA) that provide a 24-hour structured educational and residential environment for individuals with autism. As part of their clinical care, NECC and MNE conduct frequent assessments of sleep and behavior. Nightly sleep-wake behavior was measured every 30 minutes at MNE and every 15 minutes at NECC from 19:00-7:00h, whereby caretakers conducted frequent bed checks to observe whether the individual was awake (out of bed or eyes open and awake in bed) or asleep (in bed with eyes closed). Individuals residing at MNE had variable 'lights-off' times, between the hours of 19:00-21:00h which could change throughout their stay in the residential facility. Individuals at NECC had a standard fixed lights-off time of 21:00h with no prompted night awakenings. Sleep-wake recordings were taken at lights-off. Sleep was not permitted outside of this time window at either facility. Each individual was assigned a one-on-one clinician throughout the day, and clinicians rotated hourly between students. Hourly counts of 40 different types of behaviors were manually recorded by trained behavior clinicians throughout the day from 8:00-21:00h, which were then summed to give a total frequency score of each behavior on each day. Of these 40 behaviors, here we analyze the four of the most abundant behaviors in the sample: i) aggression, defined as any incident of hitting, kicking, scratching, pinching, biting towards a student or staff member; ii) self-injury, defined as harm to one's body, including head banging, hair pulling and skin-picking; iii) tantrums, defined as screaming, shouting, whining or slamming doors; and iv) property destruction, defined as damage to items including hitting desks, walls or throwing items (see Table 1 for characteristics of patients with the behaviors investigated). We analyze the presence or absence of four behaviors, as well as a 'challenging behavior' index, which indicates the presence, or absence of at least one of these four behaviors for a given individual.

Individuals at both residential facilities underwent diagnostic, behavioral, and physical assessments upon entry. Adaptive functioning was measured using the Vineland Adaptive Behavior Scales (VABS) (Sparrow, Balla, & Cicchetti, 1984), which measures five domains: communication, daily living, socialization, motor skills, and maladaptive behavior, to give an overall composite score of adaptive behavior (Sparrow et al., 1984). Missing Vineland Adaptive Scale scores were due to care-givers being unavailable to participate in standardized testing (see Cohen et al, 2016 for additional details about dataset). For inclusion in this analysis, only individuals <19 years of age (Tarbox, Dixon, Sturmey, & Matson, 2014) with an autism diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-IV) criteria and of the low-functioning subtype (limited communication and adaptive skills) according to the VABS were included. Each individual was required to have at least 20 days of recorded behaviors or non-behaviors from at least one of the types: aggression, tantrum, self-injury, and property destruction. Further inclusion criteria were then applied based on data quality for each individual (taking into account missing data, uneven and changing distributions of behaviors and non/behaviors over time, and ensuring a sufficient number of temporally matched sleep-behavior data-points to perform classification, as detailed in later sections). A total of 67 individuals met all inclusion criteria for this study (33 from MNE, 34 from NECC, aged 6.6 – 19.4 years, mean ± s.d.: 13.3 ± 3.1) and for each individual we took a maximum of 18 months of sleep (48 - 534 nights, mean ± s.d.: 306 ± 138) and behavior (68 – 537 days, mean ± s.d.: 346 ± 140) data, yielding a total of 21,518 observations of nightly sleep/awake behavior and 23,223 observations of behavior days available for analysis (Table 1). Fifty-nine individuals were Caucasian (88%), three were Hispanic (4.5%), three were Asian (4.5%), and two were Native American (2.9%).

Table 1: Demographic information for the 67 participants included in this study, organized by the five behavior types investigated here (including the overall challenging behavior index).

	Aggression	Self injury	Tantrums	Property destruction	Challenging behavior index
Number of individuals	37	40	29	38	67
Number of males	29	30	24	31	54
Number of individuals from MNE	22	18	11	24	33
Age range (all) (mean± s.d.)	6.60-19.21 (12.91±3.32)	6.60-19.25 (13.72±3.22)	8.85-18.99 (13.35±3.11)	6.42-19.19 (13.86±3.10)	6.61-19.44 (13.29±3.06)
Adaptive scores, (mean± s.d.) (*n*)	43.12 (9.53) (*n* = 26)	42.32 (14.73) (*n* = 23)	40.39 (13.11) (*n* = 17)	43.57 (12.68) (*n* = 26)	42.36 (14.31) (*n* = 40)
Proportion of nights on medications (mean± s.d.) (*n*)	0.80 (0.50) (*n* = 35)	0.65 (0.32) (*n* = 36)	0.65 (0.38) (*n* = 25)	0.81 (0.24) (*n* = 35)	0.60 (0.28) (*n* = 60)

Sleep and behavior summaries

This complex dataset, unprecedented in its size for sleep and autism studies, spans 67 individuals of varying ages, recording lengths, and exhibiting different and fluctuating patterns of sleep and behavioral profiles over time. Each night of recorded sleep was quantified as set of regular observational measurements of ‘sleep’ or ‘awake’ taken by carers throughout the night (at either 15 min or 30 min intervals, depending on the facility). We summarized each night of sleep using five statistics: i) total sleep time (total time spent asleep), ii) sleep onset (time at the start of the first episode of sleep), iii) sleep offset (time at the end of the last episode of sleep), iv) sleep efficiency (total sleep time, divided by the sleep interval, reported as a percentage) and v) number of night awakenings (total number of awakenings recorded, with each awakening followed by an episode of sleep), as illustrated in Figure 1A. For each of the five behaviors analyzed here, each day was summarized as either the presence (1) or absence (0) of that behavior, as depicted in Figure 1B. The high inter-individual variability of sleep and behavioral profiles (and their changes across time) can be seen visually in Figures 1A and 1B. The presence of missing sleep and behavior data (e.g., due to absence, weekends, or holiday breaks, shown black in Figures 1A and 1B) add additional challenges to our aim of uncovering a temporal relationship between sleep and behavior.

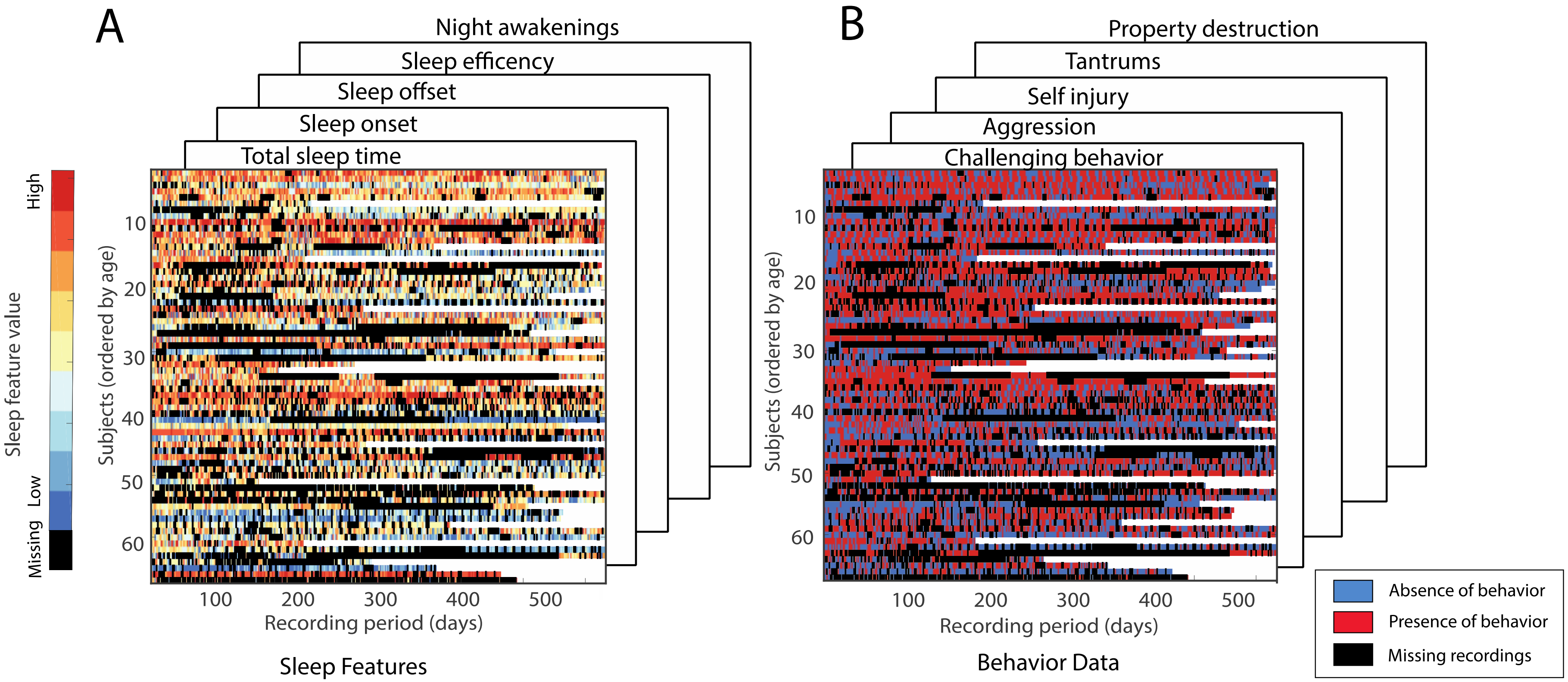

Figure 1: Patterns of sleep and behavior vary widely across individuals and fluctuate through time. A) For each individual (vertical axis, ordered by increasing age), five summary statistics (shown in panels) were computed for every night of their recorded sleep (horizontal axis). Sleep recordings for total sleep time are shown in color, and similar plots were made for each sleep feature (indicated by panels behind). Nights containing missing sleep data (or nights of prior sleep that did not contain a matching day of subsequent behavior) are shown in black, and unrecorded nights shown in white. **B)** The presence (red) or absence (blue) for challenging behaviors across time for each individual (ordered by age as in A) is shown, with similar plots made for each of the four behaviors (indicated by panels behind). Missing and filtered days (days of behavior filtered due to repeated patterns of behavior/ no behavior) are shown in black and unrecorded days shown in white.

The size of our dataset allowed us to investigate not only whether a single night of sleep was predictive of the presence of a problem behavior on the following day, but also whether multiple prior nights of sleep (2-14 nights) yield better or worse prediction of the following day's behavior. To summarize multiple nights of sleep, we used both the mean and the standard deviation of each of the five nightly statistics (resulting in a set of ten statistics) as well as the 'sleep regularity' statistic (Clerx et al., 2014), yielding a total of eleven features (illustrated in Figure 2A). Sleep regularity takes a value between 0-1 (where 1 indicates a perfectly regular nightly pattern of sleep and wake), by calculating the cross-correlation between sleep-wake episodes (Clerx et al., 2014).

Given the absence of recorded sleep data (e.g., due to weekends spent outside of the facility, or incomplete measurement, shown black in Figure 1A), summarizing sleep across multiple nights sometimes included missing nights of data. Computing a fair estimate of the mean and standard deviation of nightly sleep features across multiple nights requires a minimum proportion of prior nights of sleep to have been measured. We tested a range of such proportions (from 0.5 to 1) and found 0.6 to represent a fair trade-off between retaining sufficient data and maintaining data quality. The main qualitative results of this paper were reproduced with other choices in this range, however there was a significant reduction in sample size when using more stringent criteria.

Data processing

To ensure that our results represent a true predictive relationship between sleep and behavior, we addressed two main sources of bias. Firstly, some individuals had extended periods of the same behavior (e.g., a tantrum every day for months), which can be predicted with a high accuracy that does not reflect a temporal relationship between sleep and behavior (rather, it simply tells us that repeating patterns of behavior or non-behavior are easy to predict in general). To avoid producing optimistic classification results due to this effect, we excluded days of behavior (or non-behavior) that did not have an associated opposite behavior within 14 days. This approach ensured that our analysis is focused on quantifying the role of prior sleep in distinguishing alternating behavioral and non-behavioral events, rather than constant strings of the same repeated behavior, which may occur independent of sleep. Secondly, recorded data for some individuals spanned many years and developmental periods, over which both sleep and behavior change markedly. Although successful training of multivariate classification models is aided by large amounts of data, training across a long period of time is undermined by a changing relationship between sleep and behavior. To address this trade-off, here we analyzed a maximum of 18 months for each subject (taken from the earliest section of their recording period.

Classification model

Supervised machine learning algorithms, such as the support vector machine (SVM) classifier, learn patterns in a set of measured ‘features’ that help predict a target outcome variable. We used an SVM classifier with a linear kernel (Hastie et al., 2009) to learn the relationship between the properties of sleep across a given timescale and the presence or absence of a challenging behavior on the following day (after processing the data according to the criteria described above). We repeated this analysis for each of five behaviors, for each individual exhibiting at least 20 days of that behavior, and each timescale of prior nights (1-14), as shown schematically in Figure 2 for a selected individual and behavior. In total, 2,954 sleep-behavior models were fitted in this study.

The number of days with a given behavior was often different to the number of days without a behavior. We addressed this class imbalance using an inverse class probability cost in the SVM classifier (Mirza et al., 2013), which ensured an equal total cost to misclassifying both behaviors and non-behaviors, regardless of their distribution. Alternative procedures, including balanced resampling (i.e., including an equal number of days with behavior and non-behavior, distributed ~evenly through time across the recording period of an individual) produced qualitatively similar results to those reported here. Classification performance was estimated using 10-fold cross validation, measuring classification accuracy (overall proportion of correct predictions), sensitivity (proportion of behavior days that were correctly identified), and specificity (proportion of non-behavior days that were correctly identified).

To determine which sleep features were driving successful classification, we analyzed the components of the unit beta vector for each SVM classifier, which defines the linear decision boundary, providing an interpretable measure of feature importance for each trained classifier (Johnson, 2000). Statistical significance was assessed using permutation-testing (Ojala & Garringa, 2010), whereby an empirical null distribution was obtained by repeating the full cross-validation classification procedure for every model (i.e., for every individual, timescale, and duration of prior sleep) 200 times using randomly permuted behavior labels. We chose to permute the sample 200 times as this was the average number of behavior days per individual.

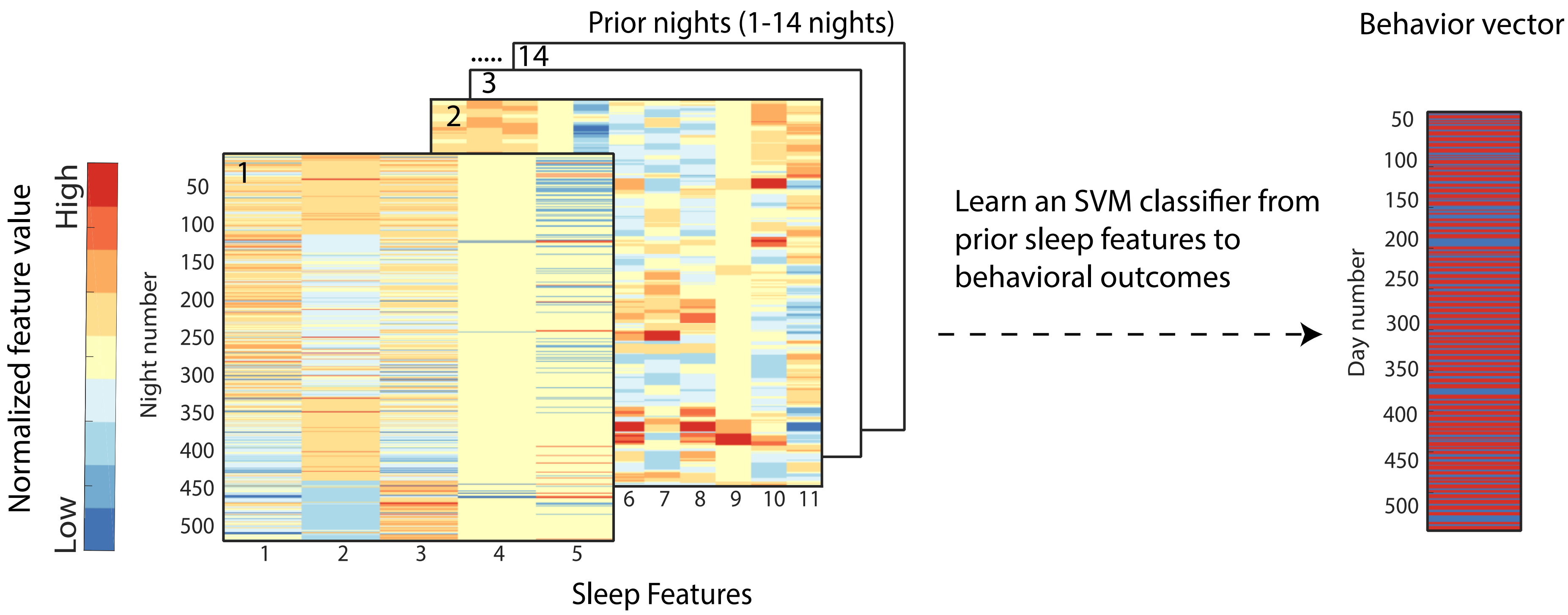

Figure 2: Classification of behavior from features of prior sleep across a range of timescales, illustrated here for a selected individual (youngest subject; top row of Fig1A and 1B) and behavior (challenging behavior index). For a single night of prior sleep, five sleep features were measured; total sleep time, sleep onset, sleep offset, night awakenings, sleep efficiency (labeled horizontally 1-5 in sleep features). For multiple nights of sleep, 11 sleep features were measured as the mean and standard deviation of each nightly measure plus a sleep regularity index (see text for details). As shown on the left, values of all sleep features (columns) across time (rows) are represented as color, from low (red) to high (blue) values following a z-score transformation. Each row in the feature matrix for a given duration of prior sleep is matched to the presence (red) or absence (blue) of a problem behavior the following day, shown on the right. For each duration of prior sleep (1-14 nights), we used an SVM classifier to learn the patterns in the prior sleep features that were predictive of subsequent behavior, evaluating performance as classification accuracy, sensitivity, and specificity using 10-fold cross validation. This procedure was repeated for all individuals and all problem behaviors.

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Correlations with clinical characteristics

To investigate whether individuals with a stronger sleep-behavior relationship showed differences in clinical characteristics, we computed Pearson correlations between mean overall prediction accuracy for an individual (averaged across 1-14 nights of prior sleep) and their adaptive behavior scaled scores (including communication scores, socialization scores, and overall adaptive behavior) (n = 40). To investigate whether our results were biased by differences in the characteristics of the dataset including age, data availability and medications, we also computed Pearson correlations between overall prediction accuracy of any individual and their i) age, ii) number of days available to perform classification, iii) proportion of days in the recording period that an individual was on medication); including days on serotonin reuptake inhibitors, melatonin, anti-psychotics, beta-blockers, or anti-convulsants. Statistical significance of correlations were estimated using an F-test, and multiple comparisons correction was performed using the method of Bonferroni (Bonferroni, 1936).

RESULTS

Classification of daily behavior using temporal sleep patterns

We first investigated: (i) whether prior sleep can predict the occurrence of a given problem behavior the following day, and (ii) the dependence of the prediction accuracy on the timescale over which prior sleep is measured. The 10-fold cross-validated classification accuracy of the overall challenging behavior index (i.e., the presence or absence of any challenging behavior) for all 67 individuals and across each duration of prior sleep (1-14 prior nights) is plotted in Figure 3A. As an initial analysis, we averaged the classification accuracy obtained from all durations of prior sleep to get a single overall accuracy score for each individual (with 50% reflecting chance-level prediction). Across individuals, the classification accuracies ranged from 27-82%, with 50 out of the 67 individuals displaying a statistically significant predictive relationship between prior sleep and the presence of challenging behavior (permutation test, $P < 0.05$). Note that the minimum threshold for a statistically significant classification accuracy ($P < 0.05$) varied across individuals from 51-59%, depending on their recording duration and distribution of behaviors. We thus report a predictive real-time relationship between prior sleep and behavior in the majority of individuals (75%) in our low-functioning autism sample, despite marked inter-individual variability in behavioral profiles and sleep quality (see Figure 1), as well as differences in age, data quantity, and medications.

For most individuals, the accuracy of predicting behavior from prior sleep increased with the number of nights used to make the prediction (i.e., colors changing from cooler to warmer across rows in Figure 3A). This dependence is shown explicitly in Figure 3B, where the mean and standard deviation of prediction accuracy (taken across individuals) is plotted as a function of the number of prior nights of sleep used to predict behavior. Mean classification accuracy was statistically significant at all durations of prior sleep history (permutation test, $P < 0.05$), being lowest for a single prior night of sleep (mean accuracy = 54%, s.d. = 8%), and increasing with the number of prior nights measured, saturating after approximately 7 days of prior sleep (mean accuracy = 58%, s.d. = 7%).

We repeated the same analysis for each behavior making up the challenging behavior index: aggression (shown in Figure 3C), self-injury (Figure 3D), tantrums (Figure 3E), and property destruction (Figure 3F). The mean classification accuracy across individuals was statistically significant for all behaviors and timescales (permutation test, $P < 0.05$), with the exception of the models for aggression and tantrum that used only one prior night of sleep (shown gray in Figures 3C, E). Furthermore, for all behaviors, classification accuracy was consistently minimal when learning from only the past night's sleep, and increased with prior nights of sleep, again saturating after approximately 7 days of prior sleep, where the mean classification accuracy across individuals was 56% (s.d. = 8%) for tantrums, 59% (s.d. = 7%) for property destruction, 58% (s.d. = 7%) for aggression, and 59% (s.d. = 7%) for self-injury.

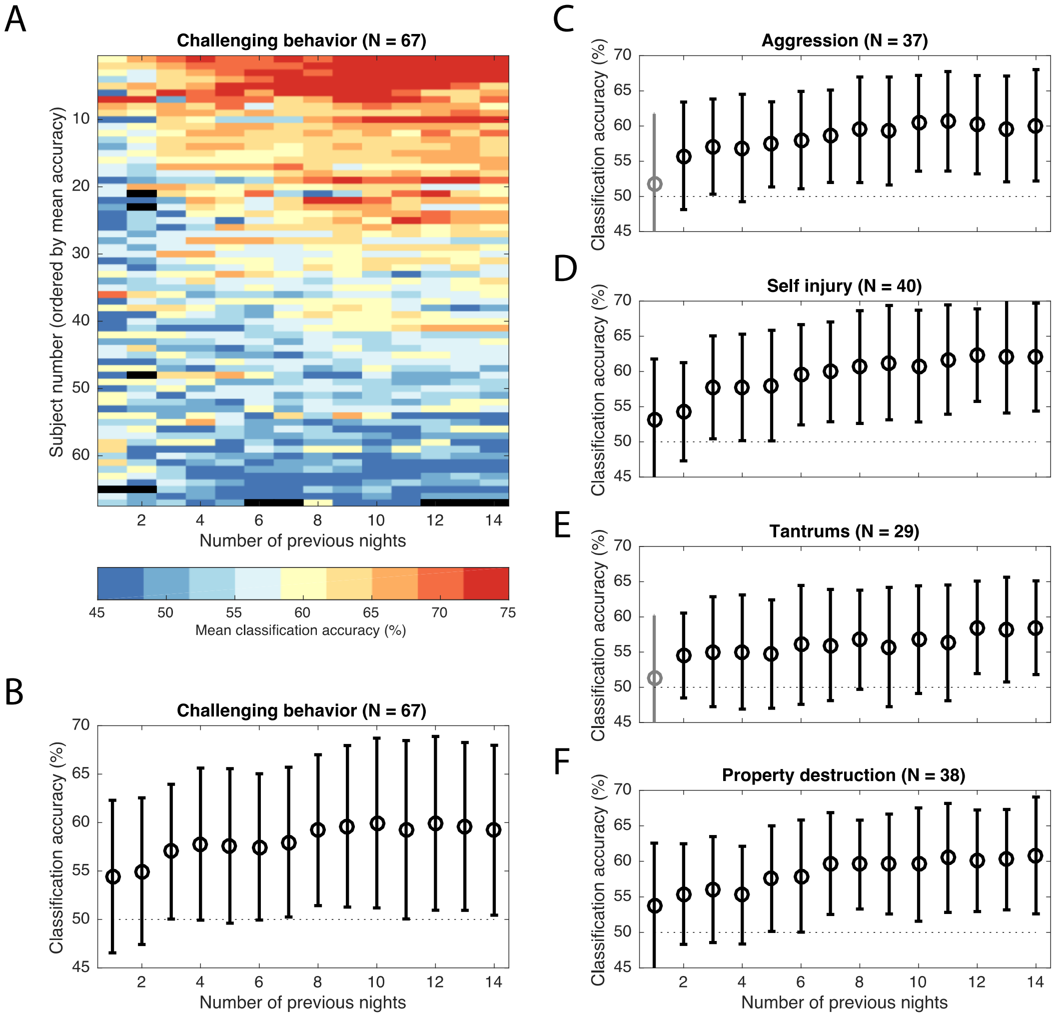

Figure 3: Challenging daytime behaviors can be predicted from prior sleep in individuals with low-functioning autism with an accuracy that increases with the number of prior nights of sleep used to make the prediction. A Color plot showing the mean 10-fold cross validated classification accuracy for 67 individuals (rows), ordered by classification accuracy, using the preceding 1-14 nights of sleep (columns) to predict the presence or absence of a challenging behavior the next day (aggression, self injury, tantrum, or property destruction), shown across the range 45%-75% as indicated in the color bar below. The color bar representing accuracies of 45-75% was imposed to show main trends from high to low accuracies, however accuracies ranged from 27-82%. Note that each point in the plot corresponds to the result of a classification model trained for a given individual and sleep timescale, as shown in Figure 2. **B-F** For each behavior, plots show the mean classification accuracy (standard deviation as error bars) taken across all individuals exhibiting that behavior (*N* listed in title), as a function of the number of prior nights of sleep: challenging behavior index (**B**), aggression (**C**), self injury (**D**), tantrums (**E**), and property destruction (**F**). The dotted line indicates the chance level for binary classification (50%). Mean classification rates that were statistically significant (permutation test, $P < 0.05$) are plotted black, and are otherwise plotted as gray (only two points: aggression and tantrum prediction using one prior night of sleep).

Relevance of sleep features in predicting future behavior

Having demonstrated a significant predictive relationship between prior sleep and daytime behavior across our sample, we next investigated whether particular types of sleep features were prominent in driving the result. For each individual, measures of feature importance were extracted from each classifier as normalized SVM beta weights, which contain a magnitude (providing an estimate of the importance of that feature in distinguishing behaviors from non-behaviors), and a sign (indicating whether high values of the feature were positively associated with either behaviors, +, or non-behaviors, -). For this highly heterogeneous sample, feature importance values exhibited large inter-subject variability, indicating that different aspects of sleep may be driving the successful classification of behavior for each individual. Despite this variability, to determine whether any features were driving successful classification of the sample as a whole, we averaged feature importance values across individuals. Figure 4 shows the average normalized feature importance across subjects, with positive values indicating a positive association between sleep features and behavior, and negative values indicating a negative association between sleep features and behavior. The statistical significance of each mean feature importance value was computed relative to an empirical null distribution using a permutation test, with results with $P < 0.05$ are plotted using black circles. The results demonstrated significant overall roles of different sleep features in predicting challenging behaviors.

Some sleep features were positively associated with challenging behaviors across different durations of prior sleep, including variability in sleep efficiency, variability in sleep onset, and mean sleep efficiency – i.e., high values were associated with a higher probability of challenging behavior the following day. Other sleep features were consistently negatively associated with challenging behavior across different durations of prior sleep, namely earlier mean sleep onset time, mean total sleep time, and variability in sleep offset time – i.e., high values were association with a lower probability of challenging behavior the following day. These key sleep features that consistently drive prediction of behavior were similar when each behavior was analyzed separately. That is, aggression, self-injury, tantrums and property destruction were all associated with overall increases in variability of total sleep time and night awakenings, across different durations of prior sleep, as well as decreases in mean total sleep time (for aggression) and sleep regularity (for self injury and tantrums). Taken together, the sample as a whole, these results suggest a temporal association between increased night-to-night sleep variability and problem daytime behavior.

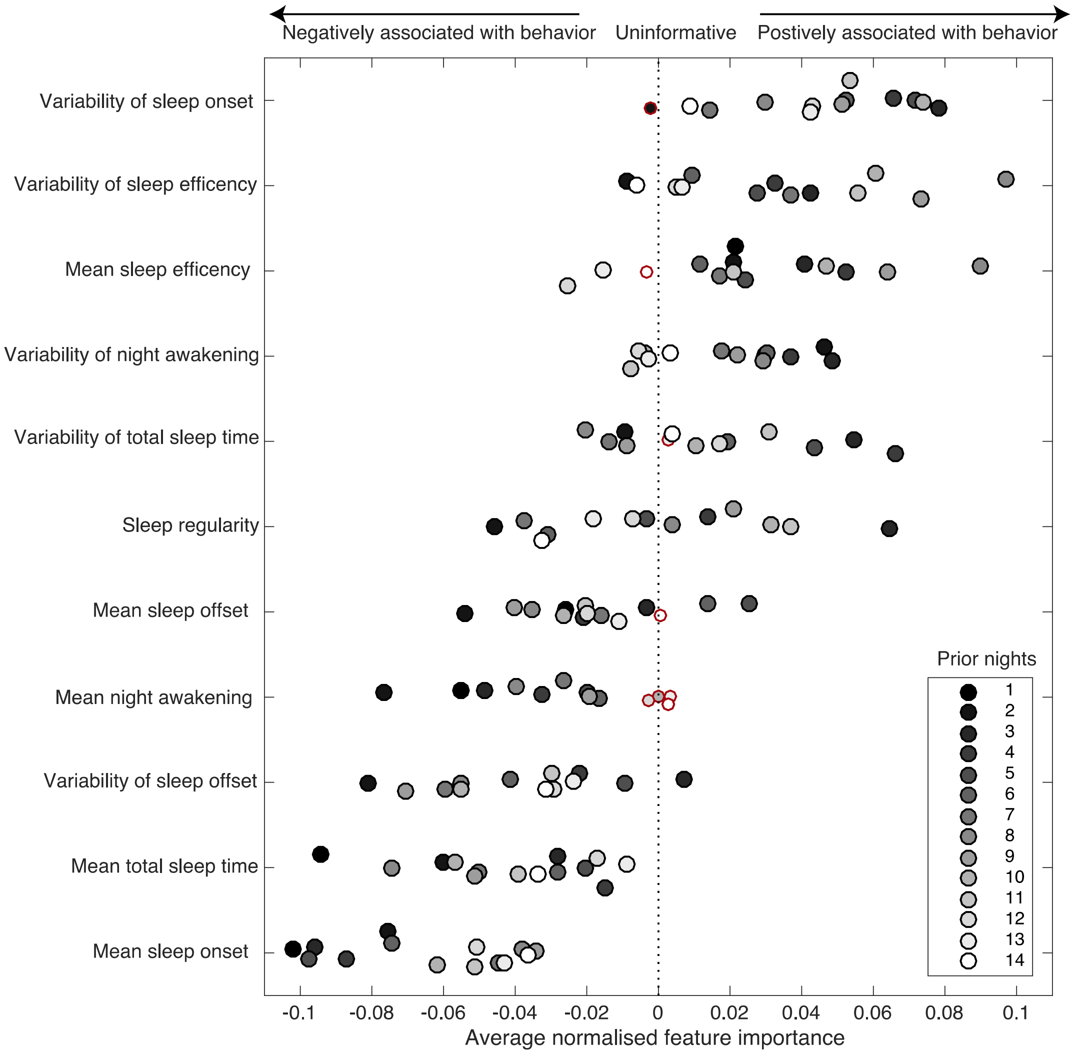

Figure 4: Measures of sleep feature importance averaged across patients reveals features that drive successful prediction of challenging behaviors. For each feature and duration of prior nights, we measured the mean feature importance as the mean (across individuals) of the normalized beta weight obtained from fitted linear SVM models. Values are plotted relative to zero (uninformative), with positive values indicating a positive association with behaviors, and negative values indicating a negative association with behaviors for each duration of prior sleep. The statistical significance of each mean feature importance value was computed relative to an empirical null distribution using a permutation test; results with $P > 0.05$ are plotted using smaller red circles. Variability of sleep features were measured as the standard deviation across a given duration of prior sleep.

Correlation between sleep-behavior relationship and clinical characteristics

Next we investigated whether the variation in the sleep-behavior relationship was associated with other characteristics of individuals. We found statistically significant negative correlations between classification accuracy and adaptive behavior scores for communication (P = 0.01), adaptive composite score (P = 0.01), and socialisation (P = 0.02), as shown in

Figure 5. We also confirmed that classification results were not significantly correlated with confounding individual characteristics, including age (r = -0.19, P = 0.26), duration of recording period (r = -0.21, P = 0.07), and proportion of days with a specific medication: serotonin reuptake inhibitors (n = 17, r = 0.10, P = 0.43), melatonin (n = 10, r = -0.09, P = 0.47), anti-psychotics (n = 45, r = 0.05, P = 0.67), beta-blockers (n = 24, r = 0.03, P = 0.83) or anti-convulsant (n = 20, r = 0.02, P = 0.87).

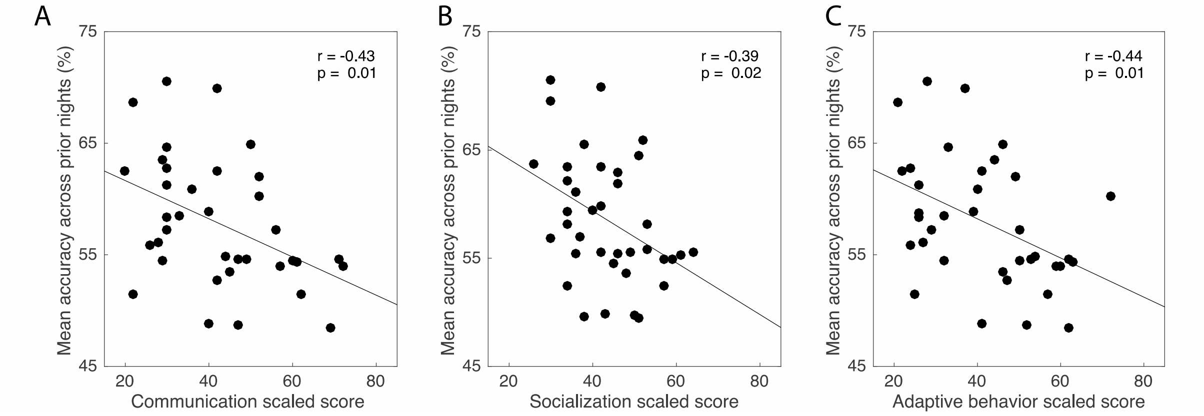

Figure 5: The sleep-behavior relationship is stronger in individuals with more severe adaptive functioning impairment. Pearson correlation coefficients, r, were calculated between **A** communication scaled scores (n = 38), **B** socialization scaled scores (n = 39), and **C** overall adaptive behavior scaled score (n = 40) and the mean accuracy of classifying a challenging behavior from prior sleep (averaged over all durations, from 1-14 nights of prior sleep) across all individuals. The least squares linear fit is shown with a solid line in each plot. Statistical significance was assessed using F-tests with Bonferroni correction for all comparisons

DISCUSSION

In this work, we present the first demonstration of a predictive relationship between prior sleep and subsequent daytime behavior using over 20,000 recorded nights of sleep matched to daytime behavior in 67 individuals with low-functioning autism. This temporal relationship was uncovered despite coarse observational measurements of sleep-wake behavior and a simple binary measurement of the presence or absence of daytime behavior, in individuals that varied in age, sleep patterns, and behavioral profiles. Surprisingly, the previous night of sleep was not strongly predictive of problem behaviors the following day. Rather, consistent with previous findings suggesting a cumulative effect of restricted sleep on daytime cognitive performance (Van Dongen, Maislin, et al., 2003) and mood (Sano et al., 2015), behavior was more accurately predicted from longer durations of prior sleep, achieving optimal prediction using at least ~one week of prior sleep data. This result was reproduced for all behaviors analyzed, suggesting a consistent underlying timescale on which sleep affects daytime functioning in this population. This consistency may be contributed by our finding that increased sleep variability (which require longer timescales to measure reliably) most consistently drove successful classification of behavior, supporting recent literature on the importance of regular sleep patterns for day-time functioning (Clerx et al., 2014; Sano et al., 2015; Taylor, Williams, Farmer, & Taylor, 2015). Finally, we demonstrated that the temporal sleep-behavior relationship was strongest for individuals with the most severe impairments in adaptive functioning, providing evidence for a relationship between symptom severity, sleep, and daytime behavior in individuals with low-functioning autism. By drawing on sleep patterns across time, we demonstrate that sleep continuity (and not just hours of sleep on the past night) impacts daily functioning in individuals with autism. Moreover, the comprehensive data processing and prediction algorithms introduced here constitute the first step in isolating robust sleep-wake relationships in large and complex temporal datasets (that are becoming easier to collect, e.g., with sensors, smartphone or smart ‘bed’ technology), and provides a foundation towards real-time clinical monitoring of sleep to inform patient care.

Investigating the relationship between sleep and behavior is complicated by a mix of external and internal factors that can cause disruptions to sleep and behavior. Individuals with autism exhibit challenging behaviors even when sleep is sufficient (Lambert et al., 2016), and a range of non-sleep-related factors such as interpersonal interactions (e.g., lack of attention, or increasing care-giver demands) or environmental changes (e.g., weather events, transitions from one activity to the next, or loud noises) can trigger behavioral events. In this study, we analyzed individuals who were undergoing constant physiological/developmental change across time, which complicated our task of learning a single relationship between sleep and daytime behavior. Despite the wide range of factors that may be expected to more directly precipitate challenging behaviors in this heterogeneous sample, we nevertheless found a significant predictive relationship between prior sleep and challenging daytime behavior in 75% of our sample. This result indicates that real-time fluctuations in sleep are an important component in understanding behavioral functioning in autism. It is also important to note, however, that in 25% our sample, we did not detect a statistically significant effect between sleep and behavior, with accuracies ranging from 27-48%. One explanation of this is that, we took comprehensive steps to ensure that we captured robust sleep-behavior relationships by removing easy-to-predict periods of data that contained extended stretches of the same type of behavior within a 2-week period. Thus our results provide pessimistic predictions, and actual clinical predictions on these individuals would be expected to be higher than reported here when using their actual clinical data. Additionally, these insignificant findings could have been due to the nature of the dataset (whereby coarse temporal observations may not have accurately captured subtle sleep features such as total sleep time), heterogeneity of the sample (with some individuals having stable sleep patterns), or noise from non-sleep related triggers (such as medications), which may have been a stronger precipitant for a behavioral episode than sleep. Future work could disentangle these effects by conducting the same analysis using more objective measures of sleep such as actigraphy or PSG in a controlled sleep environment and isolating the effects of variables such as medications. This will allow for a more homogenous sample and better quality data that more accurately capture the measurements of subtle sleep features. The classification accuracies presented here, which isolate the effect of sleep, can thus be expected to increase significantly when taking these factors into account.

In our sample, the temporal sleep-behavior relationship was stronger for individuals with greater impairments in adaptive functioning. It is well known that environmental and interpersonal cues tend to serve as more direct triggers than sleep to problem behaviors in autism (Landrigan, 2010). Thus, individuals with impaired social and communication abilities may be less sensitive to environmental and interpersonal cues, rendering them relatively more sensitive to their prior sleep. If this were the case, our classification models would be better able to predict behavior from prior sleep in these individuals, as we find here. Hence, we hypothesize that social awareness and communication ability moderates the strength of the sleep-behavior relationship and that the ability to predict behavior from prior sleep depends on an individual's sensitivity to non-sleep-related external cues. We can also hypothesize that if we utilized higher functioning individuals (such as typical individuals who have reduced sensitivity to interpersonal situations), we may have been better able to predict behavior from several nights of prior sleep using this method. For example, prior studies have shown that prior sleep can be used to predict mood in typical subjects (Sano et al., 2015). Thus when studying these patterns using a wider cohort, we might expect a non-linear pattern of accuracies, with higher accuracies increasing in low and high adaptive functioning individuals. Future work, can address this hypothesis when testing this model on other populations (such an individuals with high-functioning autism or typically developing individuals).

Here we demonstrate a methodological framework for predicting daily behavioral events in real time from coarse observational measures of nightly sleep, a finding with clear translational opportunities for improving patient care in an age of increasing technological monitoring capabilities. The approach demonstrated here shows that sleep could form a key component in an embedded monitoring system for an individual (that could also include a range of other predictive factors, such as medication and behaviors). For example, automated sleep monitoring system could be employed with a movement detection device, which would update and apply the classification model to predict the probability of each behavior type the following day. This would provide a low-cost way of monitoring sleep, which could then be used by a carer to pre-emptively organize appropriate support or implement preventative interventions (such as daytime naps or prophylactic use of sleep medications). Given the relatively robust temporal relationship between sleep and behavior (reaching an mean prediction accuracy of ~60% using features computed from ~7 days of prior sleep), and the large inter-individual variability (accuracies ranging from 27%-82%), the real-world utility of such a monitoring system would benefit from the incorporation of additional, non-sleep-related measurements to improve classification accuracy. It is important to note that our results reflect a unique contribution of sleep during periods of alternating behaviors and non-behaviors, and we would expect a more optimistic prediction of actual day-to-day accuracy if we avoided filtering out strings of repeated behaviors. The current work, however, can be seen as a first step towards an individually tailored monitoring system that learns the unique predictive signatures of problem behaviors on an individual level that could motivate individualized treatment.

In this study, we took comprehensive steps to ensure that our results represent robust temporal relationships between sleep and behavior, however it is not withstanding its limitations. First, sleep recordings are based on coarse observations of sleep or wake behavior (in 15 or 30 min intervals, depending on the school) through the night by caregivers. This coarseness limited our ability to compute subtle sleep features from our data, and is clearly less reliable and accurate than lab-based sleep studies. In future, this approach could be validated against continuous recordings obtained from actigraphy or PSG (although these measures would be difficult to tolerate individuals with low-functioning autism). Other methods, such as bed or room sleep sensors, may be more appropriate for this group due to their difficulty tolerating sensory measures such as actigraphy (Talay-Ongan & Wood, 2000). Furthermore, behaviors measurements could be validated against valid scales of behavior, for example the Child Challenging Behavior Scale (Bourke-Taylor, Law, Howie, & Pallant, 2010). Second, our study group is primarily of Caucasian descent living in a residential facility in the US Northeast and therefore may not be generalizable to outpatient autism samples, or individuals with high-functioning autism. Third, individuals were undergoing regular intervention (including psychopharmacology and behavioral therapy) which is known to moderate both sleep problems and behavior severity (Siegel & Beaulieu, 2012). Although the overall predictive strength of the sleep-behavior relationship for an individual did not correlate with the proportion of nights they were on medications (including SSRI's, anti-psychotics, anti-convulsant, melatonin etc.), the presence of changing medications over time, which was not taken into account in this study, could have affected sleep and behavior. For example, it has been shown that administration of melatonin over a 1-week period improves sleep and behavior in children with autism (Malow et al., 2012). This changing relationship between sleep, behavior and medications over time, including individuals who are in the presence of constant developmental and physiological changes, limits our ability to learn a consistent sleep-behavior relationship, and therefore the classification rates reported here can be considered a conservative estimate of what would be expected in an un-medicated sample or a sample in which medications were constant. Future work using samples with a uniform developmental period (for example, adults) or un-medicated populations is likely to find a stronger relationship. Future longitudinal studies in autism outpatient services, with more accurate sleep and behavior assessments will be critical in supporting the relationship between cumulative sleep and behavioral functioning in autism to ensure the robustness of these findings.

In summary, here we report a robust, real-time predictive relationship between sleep and behavior in individuals with low-functioning autism. Despite analyzing coarsely measured real-world data with high inter-individual variability in complex time-varying sleep patterns, behavioral profiles, ages, and medications, we demonstrate a statistically significant predictive relationship between prior sleep and challenging daytime behavior. Prediction accuracy increases with the number of prior nights of sleep used to make the prediction (up to approximately 7 days), and with the extent of adaptive functioning impairment of the individual. Our results identify a role for sleep in affecting day-to-day functioning of individuals with autism, and suggest that a real-time predictive monitor could be developed to warn caregivers of impending behaviors that result in improvements of functioning and wellbeing.

Conflict of interest

The authors declare no conflict of interests nor any competing financial interests in relation to this work described.

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Declaration for Thesis Chapter 6

Declaration by candidate

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Project design, review of relevant literature, collection of data, analysis of data and writing of manuscript	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Extent of contribution (%) student and co-authors only**
Dr Ben D. Fulcher, Professor Kim Cornish, Dr Russell Conduit, Professor Steven W. Lockley and Professor Shantha M.W. Rajaratnam	Contributed to discussion of theoretical issues, provided expertise on drafting and critically reviewed the manuscript.	
Jason Sullivan, Dr Melissa St Hilaire, Dr Tobias Loddenkemper, Dr Sanjeev Kothare, Dr Kelly McConnell, Dr Paula Braga-Kenyon, Andrew Shelsinger, Dr Jacqueline Potter, Frank Bird, Dr William Ahearn	Critically reviewed the manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidates signature	[redacted]	Date 20/07/16

Main supervisors signature	[redacted]	Date 20/07/16

Chapter 6: The bidirectional associations between daytime challenging behavior and night-time sleep duration in children with low-functioning autism.

<u>6.1. Preamble to empirical paper 4:</u> The bidirectional associations between daytime challenging behaviors and night-time sleep duration in children with low-functioning autism.

The findings from chapter five demonstrate that a machine learning classifier can be used to uncover a significant predictive relationship between prior sleep and subsequent challenging behaviors in individuals with low-functioning autism. The following empirical paper explores these relationships further by examining whether these associations exist in a bidirectional manner, that is, can a prior day of challenging behavior be used to predict the subsequent night's sleep duration? This study takes into consideration the magnitude of these associations, rather than the presence or absence of challenging behavior as per chapter five. Linear mixed regression was used to model the global prediction of i) nightly sleep durations and ii) daily challenging behavior episodes across 66 children with low-functioning autism. We then examined the clinical characteristics of individuals to which these models best apply. No study to date has explored the sleep-behavior relationship on a day-to-day and night-to-night basis, nor explored the magnitude of these relationships and whether they are bidirectional in children with autism. This is an area that has received very little attention in the literature and can be seen as the first step towards implementing a clinical tool to predict both nightly sleep durations and daily challenging behavior in the future in children with low-functioning autism.

Cohen, S., Fulcher, B.D., Rajaratnam, S.M.W, Conduit, R., Sullivan, J., St Hilaire, M., Loddenkepmer, T., Kothare, S., McConnell, K., Braga-Kenyon, P., Shlesinger, A., McConnell, K., Bird, F., Ahearn, W., Cornish, K., & Lockley, S.W. (submitted). The bidirectional associations between daytime challenging behaviors and night-time sleep duration in children with low-functioning autism.

This paper has been submitted to *Journal of Child Psychology and Psychiatry*

ABSTRACT

Although the overall relationship between reduced sleep quality and increased frequency of challenging behaviors has been well established in children with high-functioning autism, it remains unknown whether nightly sleep or daily challenging behavior episodes can be used to make real-time predictions about future sleep-behavior outcomes in children with low-functioning autism. The aim of this study was to model the bidirectional relationship between nightly sleep duration and daily challenging behavior episodes across a 1-year period (22,987 observations) in 66 children (aged between 6.2-17.9 years) with low-functioning autism, living in two U.S. residential facilities. A linear mixed model with random effects to account for individual differences was used to model these relationships. We then investigated whether variation in model performance was associated with subject-specific clinical characteristics. We found a significant bidirectional relationship between average nightly sleep duration and average daily frequency of challenging behavior episodes. Inter-individual differences accounted for approximately 50% of the variance, suggesting a statistically significant degree of variability in these relationships among children with autism. The relative strength of these relationships suggested that nightly sleep duration was more strongly predicted from daily challenging behavior than the inverse relationship. Furthermore, the prediction of nightly sleep duration from daily challenging behaviors was the most accurate in children with greater impairments in adaptive functioning. This study is the first to report an overall bidirectional relationship between nightly sleep and daytime challenging behavior using daily real-time observations in children with low-functioning autism. Our results pave the way for future work in developing real-time monitoring tool to pre-empt daily challenging behavioral events and nightly sleep problems, which will help facilitate prophylactic treatment in children with autism.

INTRODUCTION

Sleep problems and challenging daytime behaviors are one of the most common co-morbidities in individuals with autism, with approximately 50-80% of individuals presenting with sleep difficulties (Rzepecka et al., 2011) and 64-93% presenting with challenging behaviors (Hattier et al., 2011). Prior research investigating the relationship between sleep and behavior in children with autism have examined retrospective global associations between overall sleep and their overall behavior averaged across children with autism (Lambert et al., 2016; Mazurek & Sohl, 2016; Schwichtenberg et al., 2013; Sikora et al., 2012). Studies examining the real-world ecological validity of these relationships are lacking, however, and it remains unknown as to whether sleep or behavior can be used to predict one another in autism. Moreover, no study to date has examined whether night-to-night sleep duration can be used to predict day-to-day episodes of challenging behavior, and whether these relationships are bidirectional. That is, i) does a poor night of sleep lead to an increased likelihood of challenging behavior the next day? or ii) does a day of challenging behaviors (e.g., episodes of aggression or self injury) lead to increased likelihood of reduced sleep that night? Such research questions pave the way for future work in developing real-time monitoring tool to pre-empt daily challenging behavioral events and nightly sleep problems, which will help facilitate prophylactic treatment in children with autism.

The majority of past studies examining the relationship between sleep and behavior in autism have examined intra-individual differences in sleep and behavior in individuals with high-functioning autism (defined as individuals with above average intellectual ability, IQ > 70) at one point in time in either experimental, cross-sectional studies or correlational studies (Fadini et al., 2015; Hirata et al., 2016; Lambert et al., 2016; Mazurek & Sohl, 2016; Mutluer, Karakoc Demirkaya, & Abali, 2016). While cross-sectional studies have found an association between average sleep duration and average frequency of challenging behaviors across a 1-week period (Hirata et al., 2016; Mazurek & Sohl, 2016), correlational studies have found no relationship between parent-reported sleep duration and externalizing problems (such as aggression or self-injurious behaviors) averaged across a 6-week time period (Fadini et al., 2015). Moreover, objective sleep studies using polysomnography (PSG) and actigraphy over a 2-week period have failed to find a relationship between sleep quality and challenging behavior in autism (Goodlin-Jones et al., 2009; Lambert et al., 2016). Thus the association between sleep and behavior in autism is unclear, and studies are currently limited by their retrospective parent reports of sleep and behavior, short duration of sleep monitoring, and a primary focus on individuals with high-functioning autism. Moreover, no study to date has examined these associations in children with low-functioning autism (i.e., defined as individuals with below average intellectual ability, IQ $\leq$ 70) nor tested the reverse pathway corresponding to the effects of challenging behavior on sleep outcomes.

As prior studies have tended to examine the overall relationship between sleep daytime functioning, it remains unknown whether night-to-night sleep-wake patterns can be used to make real-time predictions about subsequent day-to-day behavior in children with autism, or *vice versa*. A study by Cohen et al., (submitted) found that prior sleep can be used to predict the absence or presence of challenging behaviors in the future in individuals with low-functioning autism. However further work needs to be done to examine the magnitude of these associations (i.e., the frequency of challenging behaviors predicted from prior sleep). Similar research questions examining temporal associations have been studied in typical subjects, with evidence that nightly variation in sleep duration predicts daily variations in emotions (Kalmbach, Pillai, Roth, & Drake, 2014; Tavernier & Willoughby, 2014) and daily variations in stress predict subjective reports of subsequent sleep quality (Akerstedt et al., 2012). Moreover, bidirectional associations between night-to-night sleep duration and day-to-day behavior (including mood) have been studied in typical children using daily observations over a 1-week period (Kouros & El-Sheikh, 2015; van Zundert, van Roekel, Engels, & Scholte, 2015). The investigation into the day-to-day associations between sleep and behavior, requires a large volume of data collected over time, which is typically prohibitive in traditional lab-based studies. Large volumes of daily observational data have real-world ecological validity and provide information on the real-time temporal relationship between sleep and behavior.

The present study extends past research by examining the daily and bidirectional relationships between nightly sleep and challenging behavior across a 1-year time period in 66 children with low-functioning autism. The first aim of this study was to examine whether nightly sleep duration predicts daily frequency of challenging behavior episodes and the second aim was to examine whether daily challenging behavior episodes predicts nightly sleep duration. Based on previous research, we hypothesized that shorter nightly sleep duration would predict a higher frequency of challenging behavior episodes the next day, and that higher daily frequency of challenging behavior episodes would predict shorter sleep duration that night. Examining sleep and behavior outcomes are of particular clinical interest because they represent modifiable risk factors for early intervention in children with autism.

PARTICIPANTS AND METHODS

Participants

This study was approved by the Partners Healthcare Institution Review Board (USA) and the Monash University Human Research Ethics Committee (Australia). A waiver of consent was obtained to access de-identified clinical data. The data were collected from Melmark New England (MNE) and the New England Center for Children (NECC), two residential schools in Massachusetts (USA) that provide a 24-hour structured educational and residential environment for 47 and 132 individuals with autism, respectively. Individuals were initially screened for inclusion in this study according to the following criteria: (i) a diagnosis of autism as assessed by Pediatricians or Psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-IV) criteria, with the low-functioning subtype including impairments in communication and adaptive functioning as assessed by the Vineland Adaptive Behavior Scales (VABS) (Sparrow et al., 1984) (ii) at least 1 year of nightly sleep-wake behavior matched to subsequent daily behavior recordings (taken from the earliest section of an individuals recording period) and (iii) children and adolescents less than 18-years of age. We took a restricted range of data (at least 1 year) in order to ensure a uniform developmental period across individuals. Further inclusion criteria were then applied based on the quality of data from each individual (taking into account missing data, unequal distributions of behavior and sleep over time, and ensuring a sufficient number of nightly sleep matched to daily behavior data-points to perform the analysis).

A total of 66 children (54 boys, 12 girls) from the two residential facilities (22 from MNE, and 44 from NECC) aged between 6.2-17.9 years (M = 14.2, SD = 2.8), met the inclusion criteria for this study. Children assessed with the Vineland Adaptive Behavior Scales (n = 37) were considered to be low-functioning (M = 41.39, SD = 14.22) and those with missing VABS recordings (n = 29) were given the criteria for low-functioning autism, according to clinical reports specified by Pediatricians or Psychiatrists. Most of the children in the present study were of Caucasian (n = 59), and the remainder were either Asian (n = 3), Hispanic (n = 3) or Native American (n = 1) ethnicity. Ninety percent of participants (n = 60) were on medications (including serotonin reuptake inhibitors, anti-psychotics, anti-convulsant, melatonin). Medications were taken consistently across the year-long recording period and on average 88% (SD = 3.5%) of days an individual was on at least one medication. For each child we took a maximum of 1 year of nightly sleep and daily behavior data and subsequently filtered the data to meet assumptions for the regression analysis (including linearity, absence of collinearity, homoscedasticity, normality of residuals.). Across all participants, the dataset consisted of 6,954 nights (~30% of the data) of missing recorded sleep data and 7,017 days (~30% of the data) of missing behavior data across children (e.g., due to weekends breaks, holidays, or incomplete observations). After filtering, each child contributed between 120-362 nights/days of data (M = 348, SD = 46) yielding a total of 22,987 matched observations of nightly sleep-wake behavior to daily behavior recordings.

Nightly sleep-wake observations

As part of their clinical care, NECC and MNE conduct frequent assessments of sleep. Sleep-wake behavior was measured every 30 minutes at MNE and every 15 minutes at NECC overnight from 19:00h-7:00h, whereby caretakers conducted frequent bed checks, and observe whether the child was awake (out of bed) or asleep (in bed with eyes closed). Participants residing at MNE had variable 'lights-off' times, between the hours of 19:00-21:00h which could change throughout their stay in the residential facility. Participants at NECC had a standard fixed lights-off time of 21:00h with no prompted night awakenings. Sleep-wake recordings were taken at lights-off and sleep was not permitted outside of this time window at either facility. From the sleep-wake recordings we calculated the sleep duration statistic, which was defined as the total time (in hours) spent asleep from when lights were turned off (~21:00h) until lights were turned on (7:00h). Only nights with complete measured data were included in our analysis.

Daily behavior observations

Daily behavioral observations were taken by one-on-one clinicians throughout the day from 8:00-21:00h. These clinicians rotated hourly between children, and manually recorded hourly counts of 40 different types of behaviors. These hourly counts of behavior were then summed to give a total frequency score of each behavior on each day. Of these 40 behaviors, here we summed the daily frequencies of the most challenging behaviors in the sample: aggression, self injury, tantrums and property destruction. This 'challenging behavior' score was assigned to each subject on each day, which comprised of a total frequency of daily episodes of these behaviors.

Statistical analysis

The goal of the present study was to examine the bidirectional relationships between nightly sleep duration and daily frequency of challenging behavior and their temporal order in children with low-functioning autism. For example, we investigated whether sleep duration at different time-lags (i.e., sleep duration one night earlier S_{t-1} sleep duration two nights earlier;

S_{t-2}), predicted challenging behavior episodes that day (B_t), or whether frequency of challenging behavior episodes across different time lags (behavior frequency on one day; B_t, behavior frequency two days earlier; B_{t-1}) predicted sleep duration that night (S_t) (see Figure 1 for explanation of analysis plan).

Prior to the analysis, the distribution of the sleep durations and challenging behavior frequencies were examined for each of the 66 individuals to ensure assumptions of regression analysis were met (Montgomery, Peck, & Vining, 2012). Residual plots (deviations of the observed data points from the predicted values) were used to check assumptions. Visual inspection of residual plots for sleep duration data for all individuals did not show any obvious deviations from homoscedasticity (constant variance of residuals over time) or normality after removing outliers (~2% entries were removed to make data normal). Visual inspection of residual plots for frequency of challenging behaviors for all individuals showed significant deviations from homoscedasticity and normality (positive skewed distribution) for 52/66 individuals. For individuals who had these violations we applied a series of corrections to the data, including removal of outliers (>2 standard deviations above the mean), and resampled the data to allow for an even distribution of behavior and non-behavior days through time. We then applied an outlier-robust sigmoidal normalizing transformation to all individuals' challenging behavior data (Fulcher, Little, & Jones, 2013) which helped meet the assumptions of the regression analysis (including normal distributions, homoscedasticity etc). This transformation normalized scores according to the median and interquartile range (iqr), adjusted for outliers in the data and allowed children with variable behavior measurements to be compared meaningfully (Fulcher et al., 2014). This transformation gives the data a value from 0 – 1 representing low-high frequencies of the challenging behavior index. All comparative analyses were conducted on transformed data.

The data collected in this study involved repeated observations of both sleep and behavior. In order to account for the time-series structure of the data, serial dependencies in measurements (~365 data points per individual) and individual differences in the relationships between predictors, a series of linear mixed regression models were used. Linear mixed regression allows for random effects to be specified for the intercept (i.e., each individual has their own intercept) and a slope to be estimated for each predictor against the outcome variable (Montgomery et al., 2012). As such, this analytic approach estimates the population average rate of change while allowing quantifiable variability to be fitted to individuals. This approach also allows each individual contribute the same weight to the model and is robust to missing data, common in repeated measures studies (Singer & Willett, 2003). Two separate lagged linear models were reported. The reported models are the result of several considered models, including addition of sleep and behavior predictors across longer time lags, added individually (in a univariate analysis) or concurrently (in a multivariate analysis). The final model was that which minimized the Bayesian Information Criterion (BIC), which penalized models for having greater number of predictors. In all models, interaction terms were assessed through sequential addition to the main effects and the results of the analysis demonstrate the effects of each variable with all other variables held constant.

Once we had established models that predicted nightly sleep duration and daily episodes of challenging behavior, next we investigated whether the variation in model performance was associated with specific individual characteristics such as adaptive functioning, age and proportion of nights on medications. To this end, we tested the models against an independent set of nightly sleep durations and daily episodes of challenging behavior data from each child (using data from their subsequent year). We evaluated model performance using the mean absolute error (mean absolute difference between the actual and predicted sleep and behavior data). We then computed Pearson correlations between each individual's mean absolute error and their clinical characteristics including adaptive behavior scores (such as communication, socialization and overall adaptive behavior composite), age and proportion of nights on medications. Statistical significance of correlations was estimated using an F-test.

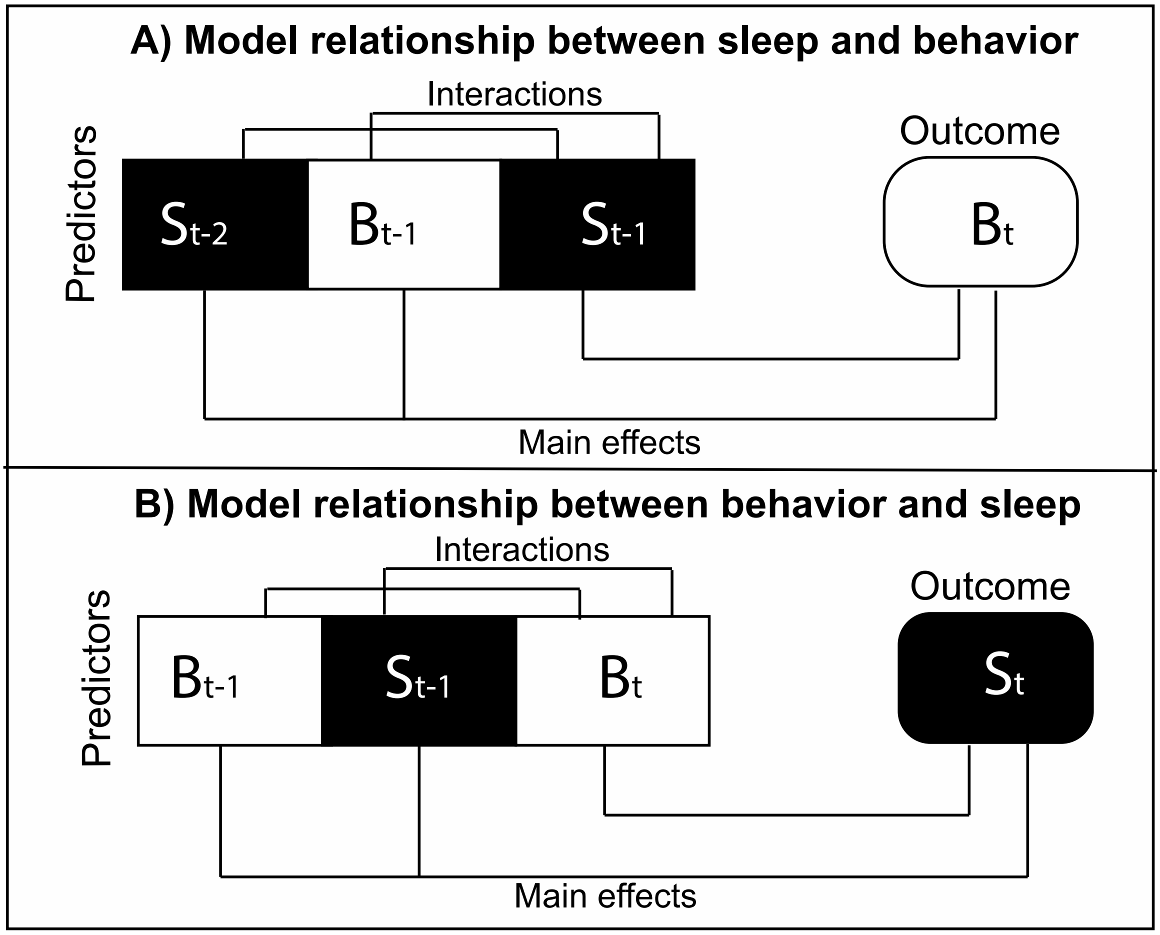

Figure 1: Explanation of analysis plan examining the bidirectional association between nightly sleep duration and daily frequency of behavior across different time lags. S_t represents a vector of sleep durations for a single night, and B_t represents a vector of frequencies of challenging behavior episodes for a single day. We were interested in the bidirectional association between nightly sleep duration and daily frequency of behavior episodes at different time lags ($_{t-n}$, where $_t$= current time, and $_n$ = number of days/nights back). (**A)** For the behavior model we were interested several main effects including the ability to use nightly sleep duration and daily frequency of challenging behavior episodes across different time lags ($_{t-n}$), and their association to the current day of challenging behavior episodes (B_t) **(B)** For the sleep model, we were interested several main effects including the ability to use nightly sleep duration and daily frequency of challenging behavior episodes across different time lags ($_{t-n}$), and their association to the current night of sleep duration (S_t). We were also interested in the interactions of these variables in predicting nightly sleep duration and daily episodes of challenging behavior.

RESULTS

Modeling the prediction of challenging behavior in autism

The first goal of this study was to examine whether nightly sleep duration across different time-periods could be used to predict daytime challenging behavior in children with low-functioning autism using linear mixed regression. The final model was chosen as it minimized both the Bayesian Information Criterion (BIC) and was selected after several models were tested ($n = 6$) considering linear versions of various lags of sleep (i.e., sleep durations from the previous 1-7 nights), frequency of challenging behaviors (i.e., challenging behavior frequencies from the previous 1-7 days) and several interaction terms (i.e., different combinations of sleep durations and frequencies of challenging behaviors across 1-7 days/night).

Table 1 presents the main results for the linear mixed model analysis, which was the best fitting model to predict daily-challenging behaviors based on the BIC. The table shows the results of several main effects on the outcome variable (challenging behavior frequency on one day), which included i) challenging behavior one day earlier, ii) sleep duration one night earlier, and ii) sleep duration two nights earlier. The model also shows interactions between predictors on the outcome variable which included i) sleep duration one night earlier and sleep duration two nights earlier, ii) sleep duration one night earlier and challenging behavior one day earlier. The output for the model included a mean regression coefficient (*B*) from the individual coefficients, their standard errors (*SE*) and its *p*-value. All inferences were two-tailed and point estimates are presented with 95% confidence intervals.

The final model included several statistically significant relationships. The model demonstrated that higher frequency of challenging behavior episodes on one day was positively associated with a higher frequency of challenging behavior episodes one day earlier ($b = 0.47$, $SE = 0.03$, $p < 0.001$). Moreover, sleep duration one night earlier (S_{t-1}) was negatively associated with the frequency of challenging behavior episodes the following day ($b = -0.10$, $SE = 0.05$, $p = 0.04$). Similarly sleep duration two nights earlier (S_{t-2}) was negatively associated with the frequency of challenging behavior episodes the following day ($b = -0.16$, $SE = 0.05$, $p < 0.00$). The final model also demonstrated a statistically significant interaction effects between sleep duration one night earlier and sleep duration two nights earlier ($b = -0.00$ $SE = 0.00$, $p < 0.00$). The interaction terms in the model indicate that recent sleep durations combine in unique ways to influence frequency of challenging behaviors.

Figure 2 shows a comparison between the actual data (left panel) and model predictions (right panel). The similarity between plots reflects the strong fit between predicted and observed frequency of challenging behaviors when using this model, with a mean absolute error of 2.4. The actual and predicted frequency of challenging behavior was interpolated from nightly sleep durations from two different time lags (S_{t-1}, S_{t-2}) that were agglomerated across individuals included in the models. As illustrated, there was a large degree of variability between sleep durations and frequencies of challenging behavior (with episodes of challenging behavior occurring during periods of short-long sleep duration). These results should be interpreted in the context of the high inter-individual variability as the random subject-to-subject variance in this model was 57% (SD = 2.5). This suggests that there was significant variability in the ability to predict challenging behavior frequencies across individuals. Nevertheless we were able to interpret overall trends in the data. This plot shows that if sleep duration one night earlier (S_{t-1}), and sleep duration two nights earlier (S_{t-2}) were short, the model predicts a higher frequency of challenging behavior episodes the following day (B_t). Conversely, if sleep duration one night earlier (S_{t-1}), and sleep duration two nights earlier (S_{t-2}) were long, the model predicts a lower frequency of challenging behavior episodes the following day (B_t). Moreover, if sleep duration one night earlier (S_{t-1}), and sleep duration two nights earlier (S_{t-2}) was variable (i.e., long on one night and short on the other night), the model predicted a higher frequency of challenging behavior episodes the following day (B_t).

Table 1: Modeling the prediction of challenging behavior today using mixed model analysis

Outcome	Predictor	B	SE	95% CI		P value
				Lower	Upper	
$Behavior_t$	Intercept	3.03	0.44	2.16	3.90	0.00
	$Behavior_{t-1}$	0.47	0.03	0.41	0.54	0.00
	$Sleep_{t-1}$	-0.10	0.05	-0.20	-0.00	0.04
	$Sleep_{t-2}$	-0.16	0.05	-0.26	-0.06	0.00
	$Sleep_{t-1}$: $Sleep_{t-2}$	0.01	0.00	0.00	0.02	0.00
	$Sleep_{t-1}$: $Behavior_{t-1}$	-0.00	0.00	-0.01	0.00	0.07

Behavior = frequency of daily challenging behavior episodes, Sleep = nightly sleep duration, t = time, B = estimate, SE = standard error, CI = confidence interval. The colon (:) demonstrates the interactions between predictor variables.

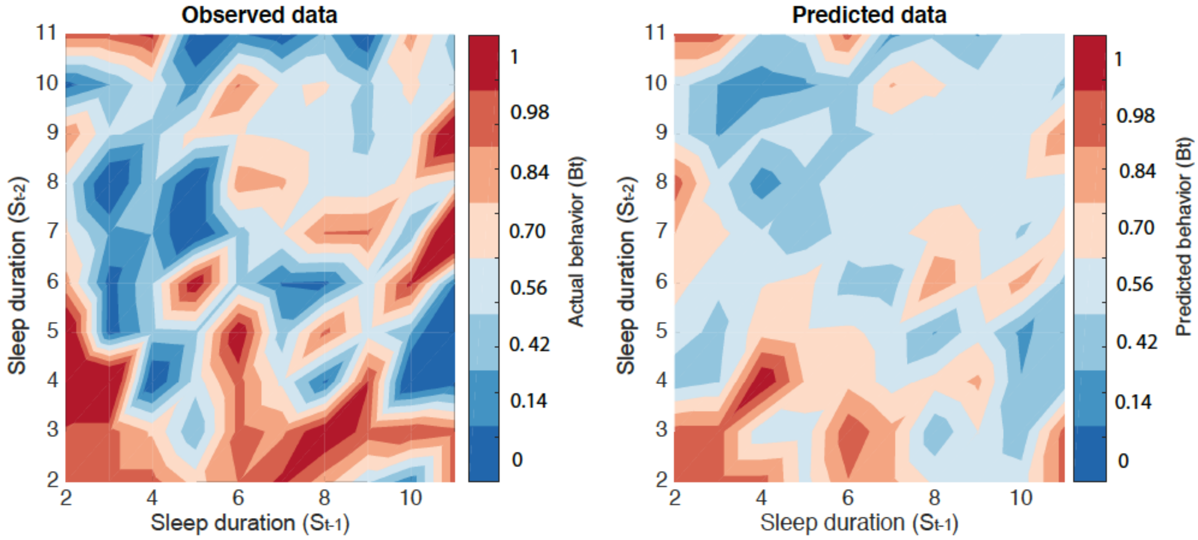

Figure 2: Contour plot depicting the average actual (left) and average predicted (right) normalized frequency of challenging behavior episodes the following day as a function of sleep duration one night earlier (x-axis), and the sleep duration two nights earlier (y-axis). The actual and predicted values of challenging behavior are shown using color from (red-blue) with a higher frequency of challenging behavior relative to the distribution of each individual shown in red and lower frequency of challenging behavior relative to the distribution of each individual shown in blue. This model reflects the high degree of inter-individual variability in the nightly sleep and daily challenging behavior relationships.

Modeling the prediction of sleep duration in autism

Next we modeled the inverse relationship that is, the ability to use daily challenging behavior episodes to predict the subsequent nights' sleep duration. Table 2 presents the main results of the linear mixed model analysis, which was the best-fitting model to predict nightly sleep duration according the BIC. The model shows the results of several main effects on the outcome variable (sleep duration on one night) which included i) sleep one night earlier, ii) challenging behavior frequency that day, iii) challenging behavior frequency one day earlier. The model also shows interactions between predictors on the outcome variable, which included i) challenging behavior frequency that day and sleep duration one night earlier, ii) challenging behavior frequency that day and challenging behavior frequency one day earlier. The output for the model included a mean regression coefficient (*B*) from the individual coefficients, their standard errors (*SE*), p-values as well as 95% confidence intervals.

The final model demonstrated several statistically significant main effects. The frequency of challenging behavior episodes that day (B_t) was negatively associated with short sleep duration that night (S_t) (b = -0.53, SE = 0.15, p < 0.001). The magnitude of this relationship suggested that the relationship between daily challenging behavior and subsequent night's sleep duration was stronger than the relationship between a night's sleep duration and a subsequent day of challenging behavior (b = -0.10). There was no relationship between sleep duration that night and sleep duration one night earlier (b = 0.01, SE = -0.00, p

= 0.26) and behavior one day earlier (*b* = 0.06, *SE* = 0.03, *p* = 0.08). The final model also demonstrated a statistically significant interaction between sleep duration one night earlier and challenging behavior that day in predicting sleep duration that night (*b* = -0.00 *SE* = 0.00, $p < 0.00$).

Figure 3 shows a comparison between the actual data (left panel) and model predictions (right panel) with the similarity between plots reflect the strong fit between predicted and observed sleep durations with the mean absolute error (in hours) of 0.8. The actual and predicted sleep durations was interpolated from sleep and behavior data that was agglomerated across individuals included in the model. This plot showed several notable relationships. Firstly, if sleep duration one night earlier (S_{t-1}) was short and there was a high frequency of challenging behavior episodes that day (B_t), the model predicted shorter sleep duration that night (S_t). Conversely, if sleep duration one night earlier (S_{t-1}) was long, and there was a higher frequency of challenging behaviors that day (B_t), the model predicted longer sleep duration that night (S_t). These results should be interpreted in the context of the high inter-individual variability as the random subject-to-subject variance was 50% (SD = 1.5). Nevertheless, the results reflect that sleep duration the previous night has an impact on future nights sleep duration, regardless of recent episodes of challenging behaviors.

Table 2: Modeling the prediction of sleep duration tonight using mixed model analysis

Outcome	Predictor	B	SE	95% CI		P value
				Lower	Upper	
$Sleep_t$	Intercept	8.56	0.13	8.30	8.82	<0.001
	$Sleep_{t-1}$	0.01	-0.00	-0.00	-0.02	0.26
	$Behavior_t$	-0.53	0.15	-0.83	-0.22	<0.001
	$Behavior_{t-1}$	0.06	0.03	-0.00	0.14	0.08
	$Behavior_t$: $Sleep_{t-1}$	0.06	0.01	0.02	0.09	<0.001
	$Behavior_t$:$Behavior_{t-1}$	-0.04	0.07	-0.19	0.10	0.56

Behavior = frequency of daily challenging behavior episodes, Sleep = nightly sleep duration, t = time, B = estimate, SE = standard error, CI = confidence interval. The colon (:) demonstrates the interactions between predictor variables.

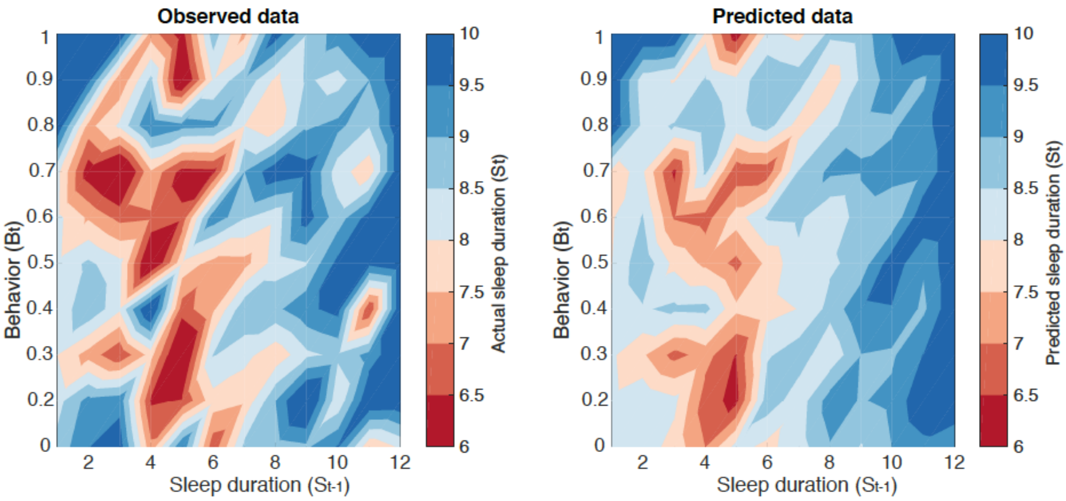

Figure 3: **Contour plot depicting the average actual (left) and predicted (right) sleep duration (hours) as a function of sleep duration one night earlier (x-axis), and normalized frequency of challenging behaviors that day (y-axis).** The actual and predicted sleep duration values are shown using color with short sleep durations shown in red, and long sleep duration shown in blue. The values for challenging behavior episodes (y-axis) are shown from 0-1, where 0 represents a low frequency of challenging behavior episodes, and 1 represents a high frequency of challenging behavior episodes (relative to the distribution of each individual). The sleep duration range from 6-10 hours and was imposed to show main trends from short to long sleep durations, however actual sleep duration ranged from 2-11 hours.

Correlations between individual model performance and clinical characteristics

Having established global models of the prediction of nightly sleep duration and daily frequency of challenging behavior, we next investigated whether the variation in model performance was associated with individual characteristics such as adaptive functioning, age and proportion of nights on medications. That is, the best fitting models (as described above) were used to predict an independent dataset from each individual (1-year of subsequent sleep duration and challenging behavior data). The mean absolute error for each individual was calculated to measure how accurate their predicted sleep/behavior data were from their actual sleep/behavior data when using the models. When examining the prediction of daily challenging behaviors, the mean absolute error across individuals was not correlated with communication (r = -0.03, p = 0.88), socialization (r = 0.03, p = 0.88), and overall adaptive functioning scores (r = 0.06 p = 0.75). When examining the prediction of nightly sleep duration, there were positive correlations between the mean absolute error across individuals and communication (r = 0.33, p = 0.06), socialization (r = 0.36, p = 0.04), and overall adaptive behavior composite (r = 0.38, p = 0.03) which were statistically significant as shown in Figure 4. This suggests that the sleep model was best fitted to individuals with impaired adaptive functioning. We also examined whether other individual characteristics such as age, and proportion of nights on medications distinguished the predictive ability of these models. We computed the linear correlations between mean absolute error for an individual against age and proportion of nights on medications. The mean absolute error of an individual was not correlated with age in both the behavior ($r = 0.11$ $p = 0.42$) and sleep model ($r = -0.07$, $p = 0.58$) nor proportion of days on medication use in both the behavior ($r = 0.07$, $p = 0.59$) and sleep model ($r = 0.08$, $p = 0.53$).

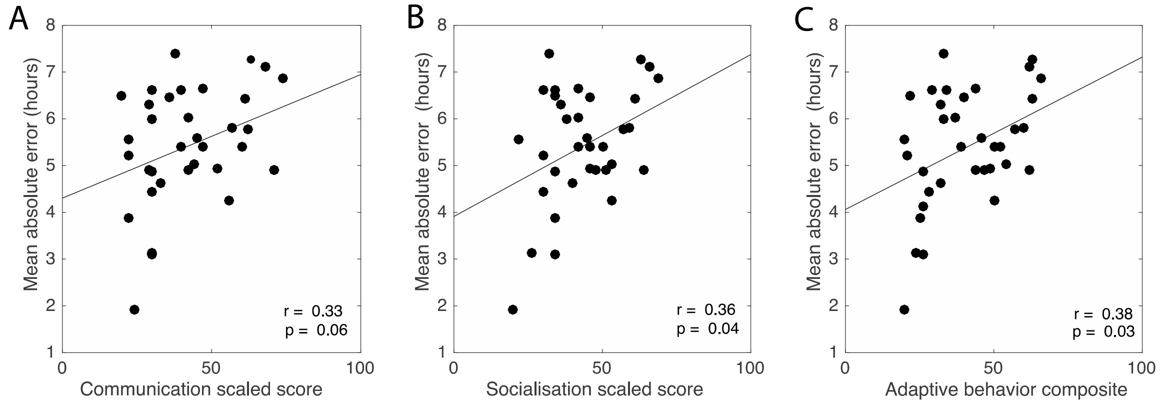

Figure 4: The global model used to predict nightly sleep duration was best fitted to children with severe impairments in adaptive functioning. Pearson correlation coefficients, *r*, were calculated between (**A)** communication scaled scores, (**B)** socialization scaled scores and (**C**) overall adaptive behavior scaled score and the mean absolute error (absolute difference between actual and predicted sleep duration) as predicted from the sleep model across individuals with available adaptive functioning data ($n = 37$). Higher scaled scores mean greater functioning in adaptive scale measures. The least squares linear fit is shown with a solid line in each plot. Statistical significance was assessed using F-tests with $p < 0.05$.

DISCUSSION

We investigated the bidirectional relationship between nightly sleep duration and daily frequency of challenging behavior events, using over 20,000 recorded nights of sleep matched to daytime behavior in 66 children with low-functioning autism. This study is unique in its daily data collection and data analytic plan that afforded quantification of both temporal relationships and intra-individual differences. Consistent with recent research in typically developing children (Kouros & El-Sheikh, 2015; van Zundert et al., 2015), we found evidence in support of a bidirectional relationship between nightly sleep and daily behavioral outcomes in children with low-functioning autism. That is, short sleep duration on one night was associated with higher frequency of challenging behavior episodes the next day, and a higher frequency of daily challenging behavior episodes was associated with short sleep duration the following night. The relationship between daily challenging behavior and subsequent night's sleep duration was stronger than the inverse relationship. These findings suggest that daytime challenging behaviors may serve a potential modifier for a subsequent night's sleep in children with low-functioning autism. In contrast, while sleep duration on one night may act as a potential modifier to challenging behavior the next day, other environmental and interpersonal cues may serve as more direct triggers than sleep to problem behaviors in autism (Landrigan, 2010). It is important to note that there was a significant degree of variability across individuals with inter-individual differences accounting for approximately 50-57% of variance in these relationships. Thus despite the significant bidirectional sleep-behavior relationships found across children with autism, there was a significant degree of variability that existed within individuals when examining these associations. Nevertheless, the models introduce here, constitutes the first step in isolating global bidirectional relationships between sleep and behavior in individuals with low-functioning autism.

The results of this study indicated that the prediction of daily challenging behavior episodes across individuals was modified by recent sleep history. That is across individuals, short sleep duration across two consecutive nights was associated with subsequent higher frequency of daily challenging behavior episodes. Moreover, long sleep duration across two consecutive nights was associated with subsequent lower frequency of daily challenging behavior episodes. From this we can conclude that cumulative short sleep increases the frequency of challenging behavior episodes in autism. These findings are consistent with previous studies highlighting the role of sleep in behavioral functioning in autism (Hirata et al., 2016; Lambert et al., 2016; May, Cornish, Conduit, Rajaratnam, & Rinehart, 2015), and further expand on these studies by considering that night-to-night sleep duration (rather than overall sleep duration or prior night of sleep duration) has a measurable impact on daily functioning in children with low-functioning autism.

The results of this study also demonstrated that the prediction of nightly sleep duration across individuals was also modified by recent sleep history, regardless of the recent frequency of challenging behavior episodes that day. Specifically, overall short sleep duration the previous night and an overall higher frequency of daily challenging behavior episodes the next day was associated with short sleep duration that night. Moreover, overall long sleep duration the previous night and an overall higher frequency of daily challenging behavior episodes the next day was associated with long sleep duration that night. These results suggest that adequate prior sleep is protective against future sleep disruption regardless of the frequency of challenging behaviors that day. Interestingly, there was no association between sleep durations across two time lags (i.e., sleep duration on one night was not associated with sleep duration the previous night), despite our expectation that these variables would be negatively associated, in line with the theory of sleep homeostasis (Borbely, Achermann, Trachsel, & Tobler, 1989). One theoretical explanation for this, may be due to associated neurological deficits experienced by children with severe autism may disrupt mechanisms responsible sleep-wake regulation (Glickman, 2010; Patzold, Richdale, & Tonge, 1998). Interestingly, we found that the prediction of sleep duration from prior behavior was most accurate when applied to children with severe autism symptoms (i.e., more severe deficits in communication and social skills). Hence, alongside previous studies demonstrating a positive relationship between sleep deficits and autism symptom severity (Adams et al., 2014; Schreck et al., 2004), these findings suggest that daily challenging behavior and nightly sleep duration are more strongly associated in individuals with the greater impairments in adaptive functioning. Individuals with severe deficits in social-communication may have difficulty regulating their emotional responses and hyper-arousal following a challenging behavior episode may disrupt a subsequent night of sleep (Kahn, Sheppe & Sadeh, 2013). This study can be seen as the first step towards real-time predictions of sleep duration based on previous sleep-behavior history, which can assist in the facilitating intervention (such as a daytime nap or pharmacology) to prevent sleep disruption in autism.

While the present study adds to the literature on sleep and behavior in autism, our findings must be interpreted in the context of certain limitations. These models provide preliminary support for the uncovered bidirectional relationships between sleep and behavior in children with low-functioning autism and therefore future investigation is warranted. Firstly, sleep recordings are based on relatively coarse observations of sleep or wake behavior (in 15 or 30 min intervals, depending on the school), and behaviors were based on hourly observations of behavior, manually recorded by carers at the facilities. This methodology, while providing a large quantity of real-world data, limited our ability to compute subtle sleep features and behavioral properties from our data, and may be less reliable and accurate than controlled laboratory-based studies. In future, this approach could be validated against continuous recordings obtained from actigraphy or PSG although these methods are problematic in this population (Hodge et al., 2012). Other methods, such as bed or room sleep sensors, or validated scales such as the Child Sleep Habits Questionnaire may be more appropriate for this group due to their difficulty tolerating sensory measures such as actigraphy (Talay-Ongan & Wood, 2000; Veatch et al., 2016). The impact of daily medications on sleep and behavior was also not considered in this study, although we found that the overall predictive strength of the sleep-behavior bidirectional relationship when applied on an individual level did not correlate with the proportion of nights an individual was on medications. While most children were on a stable medication regimen across the maximum 1-year recording period selected, this may have increased the variability between individuals therefore future studies could consider medication as a potential confounder. A range of other potential modifiers might have also impacted the uncovered associations (for example, hormones, psychiatric and medical co-morbidities), as well as environmental variables (such as changing schedules, intrusions of digital technologies, and sleep environment and routines); however these factors were not available to take into account in the present study. Our study group was also primarily of Caucasian descent living in a residential facility in the US and therefore may not be generalizable to outpatient autism samples, or individuals with high-functioning autism. Thus the extent to which these findings can be generalizable to other individuals with autism is unknown. Lastly, while linear mixed models take into account variability between individuals, it sets a global gradient that is consistent for all individuals and therefore fails to take into account subtle individual differences. The findings demonstrated that there was a significant degree of variability between individuals and therefore future studies could apply a linear regression on an individual level to model individual rather than group differences for these sleep-behavior relationships.

In summary, we report the first examination into the bidirectional relationship between sleep and behavior in children with low-functioning autism. We used linear mixed regression to model the relationship between 20,000 nights of sleep matched to subsequent challenging behavior days in 66 children with low-functioning autism. Despite high inter-individual variability of sleep patterns, behavioral profiles, ages, and medications, we found a statistically significant bidirectional relationship between nightly sleep duration and daily challenging behavior in children with low-functioning autism. Moreover, our results present the case for a robust role of cumulative sleep in affecting night-to-night sleep quality and day-to-day behavioral functioning in children with autism. These results suggest that a real-time predictive monitor could be developed to warn care-givers of impending behaviors or disrupted subsequent sleep that may result in improvements in the functioning and wellbeing of individuals and carers with autism.

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Chapter 7: General Discussion

The aim of this thesis was to identify systematically the nature of sleep difficulties and its relationship with daytime problematic behavior in an understudied population of individuals with low-functioning autism. To achieve this overall aim, this thesis examines an unprecedented dataset of nightly sleep-awake recordings and daily behavioral recordings across a 6 month to 6 year time range collected from a cohort of over 100 individuals with low-functioning autism living in two U.S residential facilities in Boston. Chapter two of this thesis offers a systematic investigation into the nature of the sleep-behavior relationship in autism, and specifically highlights the gaps in the research, including the lack of investigation of these associations in individuals with low-functioning autism. In lieu of this gap in the research, chapter four offers an investigation into the nature of sleep profiles in individuals with low-functioning autism, and relates behaviorally determined sleep phenotypes to clinical characteristics in autism including adaptive functioning. The findings from chapter five further contribute to the literature by demonstrating that prior sleep can be used to make real-time predictions about future challenging behavior events in individuals with low-functioning autism. Lastly, the findings from chapter six, demonstrate that the relationship between daily challenging behavior episodes and nightly sleep duration is bidirectional in children with autism, with a significant degree of inter-individual variability in these associations.

This thesis contributes to the growing body of literature and highlights the need for this area of research to be considered more seriously in individuals with low-functioning autism. Although the findings need further validation in independent samples, the results from this thesis pave the way for future work in i) profiling sleep problems as a standard part of treatment in autism, and ii) the development of a real-time monitoring tool to pre-empt behavioral and sleep problems in individuals with autism. This chapter integrates the main findings across the studies presented in this thesis, highlights theoretical implications for understanding the relationship between sleep and behavior in autism, and discusses clinical implications. Finally, the limitations and future directions arising from this thesis will be discussed.

7.1. General overview of findings

Chapter four provides an investigation into the nature of sleep phenotypes and their relation to adaptive functioning in individuals with low-functioning autism. Using cluster-analysis performed on sleep summaries calculated from 60,000 nights of sleep-wake observations for 129 individuals with low-functioning autism, we found two clusters of individuals with clearly distinguishable sleep phenotypes. The clusters were summarized as ‘stable’ (cluster 1) and ‘unstable’ (cluster 2) sleep phenotypes, with two further ‘unstable’ sleep clusters (cluster 2a, and cluster 2b) that were distinguished by the severity of their sleep disruption (including mean sleep duration, mean sleep offset, and sleep stability). Moreover, consistent with previous research highlighting the relationship between severity of sleep problems and severity of autism symptoms (Adams et al., 2014; Tudor, Hoffman, & Sweeney, 2012), the findings from this study demonstrate that sleep phenotypes are robustly associated with differences in symptom severity in individuals with low-functioning autism. That is, the ‘stable’ and ‘unstable’ sleep clusters displayed significant differences in properties that were not used for clustering, such as intellectual functioning, communication and overall adaptive functioning, demonstrating that sleep phenotypes are associated with symptom severity in individuals with autism. Given the lack of insight into the nature of sleep problems in individuals with low-functioning autism (see chapter two), these findings suggest that a significant proportion of individuals with low-functioning autism experience sleep disruptions, which is intrinsically linked to the severity of their disability. The findings from this study provide foundational evidence for profiling sleep difficulties in routine assessments for individuals with low-functioning autism.

Chapter five provides the first investigation into the real-time predictive relationship between sleep and behavior in individuals with low-functioning autism. The main finding from this study was that problematic daytime behaviors can be robustly predicted from prior sleep in individuals with low-functioning autism and that classification accuracies increased with the number of days of prior sleep used to make the prediction, up to one week. Importantly, despite the large inter-individual variability, increased sleep variability was the most consistent predictor of problematic behavior. Furthermore, individuals with stronger predictive relationships between prior sleep and behavior had greater impairments in adaptive functioning. These findings are consistent with the studies examining the overall relationship between sleep and behavior in autism (Hirata et al., 2016; Lambert et al., 2016) and expand on these studies by demonstrating a robust, real-time relationship between sleep and behavior, which is moderated by the severity of autism symptoms. This study is the first to provide a foundation of a real-time monitoring tool to pre-empt behavioral problems and facilitate intervention for individuals with low-functioning autism living in residential facilities.

Chapter six provides the first investigation into the bidirectional relationship between nightly sleep duration and daily challenging behavior episodes across a 1-year period (22,987 observations) in 66 children with low-functioning autism, and offers a number of important contributions. Firstly, despite the inter-individual variability, there was a significant bidirectional association between nightly sleep duration and daily challenging behavior episodes across children with low-functioning autism. The relative strength of these relationships suggested that nightly sleep duration was more strongly predicted from daily challenging behavior than the inverse relationship. Moreover, this bidirectional relationship was moderated by prior nights sleep duration, suggesting that sleep history has a meaningful impact on future outcomes in children with autism. Furthermore, children with greater impairments in adaptive functioning had more accurate predictions when using daily challenging behavior episodes to predict the following nights sleep duration. Alongside the findings of chapter five, results from this study offers the foundation of a global real-time monitoring tool to pre-empt both future challenging behavior episodes and sleep duration, which will help facilitate prophylactic treatment in children with autism living in residential settings.

7.2. Theoretical implications

7.2.1 Implications for the etiology of sleep problems in individuals with autism

Findings from this thesis add to existing theoretical models addressing the etiology of sleep difficulties in autism, by providing a framework for understanding the nature of sleep difficulties in individuals with low-functioning autism. Several theories have been put forward to propose that sleep problems frequently seen by individuals with autism are underlined by a complex interaction between neurobiological abnormalities (i.e., imbalance in melatonin), psychological factors (i.e., anxiety), behavioral factors (i.e., challenging behaviors), environmental factors (i.e., family stress, child’s sleep environment) and medications (Cortesi et al., 2010; Malow et al., 2016; Richdale & Schreck, 2009, Veatch et al., 2015). It has also been proposed that underlying neurophysiology intrinsic to individuals with autism may predispose chronic sleep-wake disturbances in this population, however this theory has yet to be tested empirically (Glickman, 2010). Specifically, theories suggest that individuals with autism have difficulty perceiving environmental time cues (or ‘zeitgebers’) to permit appropriate entrainment with the 24-hour day (i.e., the synchronization of the internal biological clock to external time cues) due to their social-communication deficits (Glickman, 2010). To date, the theoretical understanding of the etiology of sleep difficulties in autism are still under review and are primarily based on findings from outpatient samples of children with mixed autism diagnoses (high and low-functioning individuals). While these theories provide a broad understanding of the etiology of sleep problems, they fail to integrate the nature of sleep difficulties specifically in individuals with low-functioning autism.

The findings from this thesis inform pre-existing theoretical models in several ways. Firstly, the result that individuals with 'unstable' sleep phenotypes (i.e., characterized by increased sleep variability in the measured sleep features) had greater impairments in intellectual functioning, communication and socialization supports the theoretical framework that factors intrinsic to autism contribute to sleep disturbance in this disorder. Secondly, all individuals had good sleep hygiene (including consistent sleep schedules, and routines around bedtime), which supports the idea that environmental variables might moderate the severity of sleep deficits in this population. That is, a significant proportion of individuals in the sample had stable sleep despite having a diagnosis of low-functioning autism. Thirdly, the inter-individual variation in sleep profiles as presented here suggests that numerous dynamic and interacting factors may be driving sleep difficulties in individuals with autism. These factors include medical co-morbidities, psychiatric co-morbidities, changing medications and physiological changes. Although not studied in this thesis, a range of factors needs to be considered when understanding sleep phenotypes in individuals with low-functioning autism.

7.2.2. The relationship between sleep disruption and challenging behavior in autism

The findings from this thesis also provide a theoretical framework to understand the relationship between sleep and behavior in individuals with low-functioning autism. An existing framework has been proposed which suggests that the combined effects of autism severity, internalising behavior and externalising behavior predispose the development of sleep difficulties and hence further behavior problems in children with autism (Hollway & Aman, 2011). To date, theoretical frameworks have neglected to understand the sleep-behavior relationships in individuals with low-functioning autism and this is the first study to propose a model to understand these relationships in this population.

Figure 1 combines findings from this thesis to incorporate it into a framework to understand the relationship between sleep-behavior in individuals with low-functioning autism. The model starts by demonstrating that level of intellectual functioning (IQ) moderates autism symptom severity, as lower IQ has been know to contribute to the severity

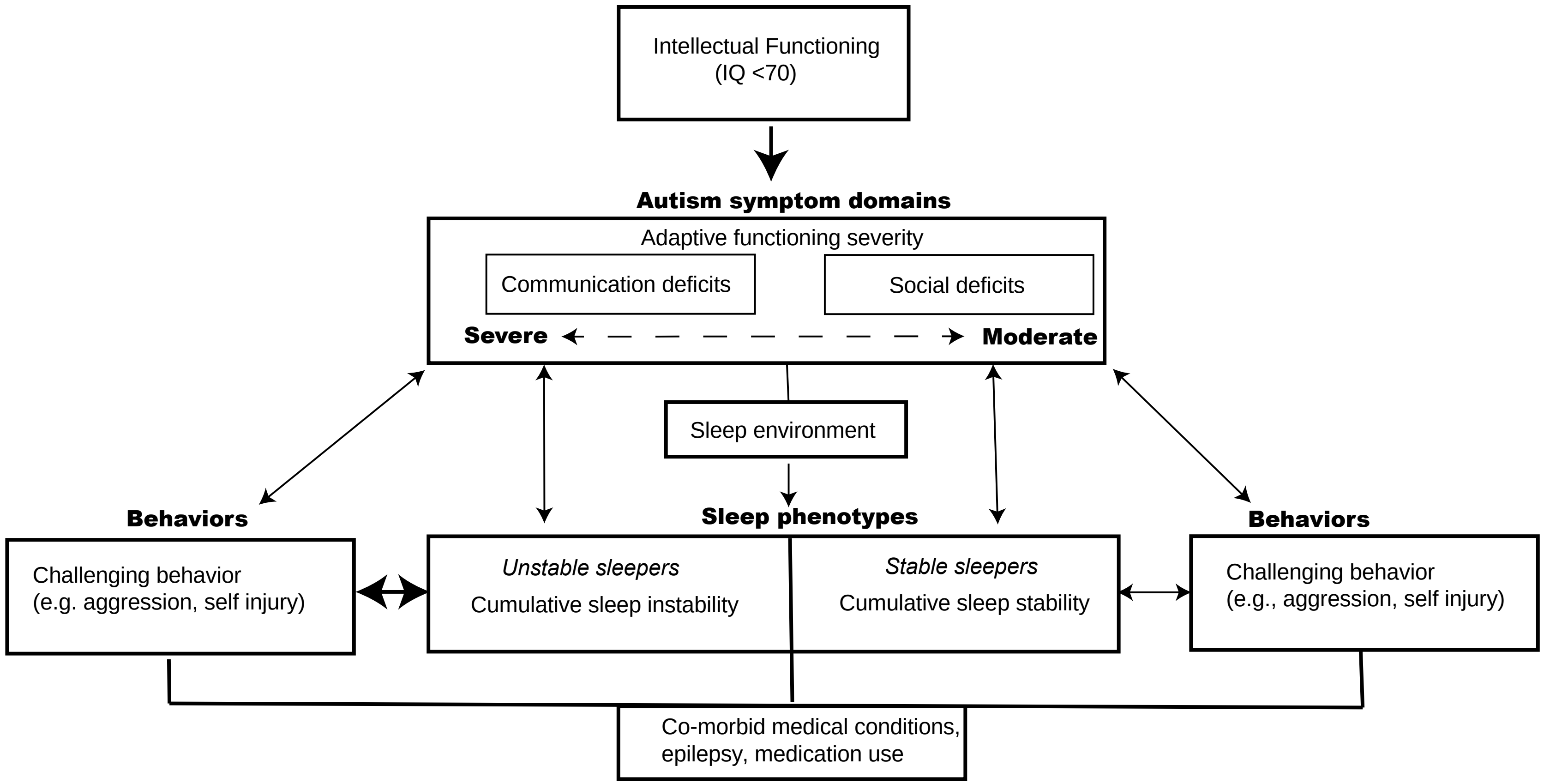

Figure 8: A preliminary theoretical framework to propose the development of sleep difficulties and associated behavioral symptoms in individuals < 20 years of age with low-functioning autism. The model takes into account autism symptom severity in the development of sleep profiles (stable or unstable phenotypes) in individuals with low-functioning autism. The model explains that the strength of the bidirectional relationship between sleep and behavior is stronger for individuals with unstable sleep phenotypes (as shown by bold arrow) compared to individuals with stable sleep phenotypes due to their impaired social and communication deficits. The model also takes into account co-morbid medical conditions and medication use that are known to impact both sleep and behavior and their relationship.

of autism symptoms (Elrod & Hood, 2015). The model then demonstrates how autism severity, including deficits in communication and social skills, serve as vulnerability factors in the development of sleep phenotypes. That is, individuals with severe deficits are more likely to match an 'unstable' sleep profile, which is distinguished by reduced stability of sleep including greater variability in total sleep time, sleep onset, sleep offset etc. These findings support research that suggests that increased autism symptom severity is associated with severity of sleep difficulties (Hollaway et al., 2013; Hollway & Aman, 2011). This may be due to the overlapping mechanisms between sleep regulation and biological functions implicated in autism (see Veatch et al., 2015 for review). Furthermore, the model highlights the role of sleep environment, as adequate sleep hygiene has been shown to be protective against sleep difficulties in individuals with moderate autism symptoms (Weiskop, Richdale, & Mathews, 2005). Thus individuals with severe autism symptoms may not respond to traditional to sleep hygiene approaches due to their neurological deficits, which may impair sleep regulation.

The model then demonstrates how individuals with severe social and communication deficits (and unstable sleep profiles) have stronger predictions when using prior sleep to predict behavior (and vice versa) when compared to individuals with moderate deficits (and stable sleep profiles). The social-communication deficits experienced by these individuals may render them more prone to behavioral dysregulation and the hyper-arousal associated with these regulation difficulties may subsequently impair sleep, which may subsequently impair daytime behavior. This then may cause a vicious cycle of sleep-behavior difficulties, despite adequate sleep hygiene. Hence, we propose that overall level of adaptive functioning moderates the strength of the sleep-behavior relationship and that the ability to predict behavior from prior sleep (and vice versa) depends on an individual's sensitivity to non-sleep-related external cues. Thus individuals with moderate levels of adaptive functioning may be better able to regulate their behavioral responses and therefore an episode of challenging behavior may not impair sleep and consequently have no impact on daytime behavior. Lastly, the theoretical model specifies that sleep-behavior interfering correlates need to be considered including medical conditions and medications, as they are known to impact the strength of the sleep-behavior relationship (Malow et al., 2016, Veatch et al., 2015).

The study of sleep in individuals with low-functioning autism is an understudied area, and this theoretical framework may be useful to assist in the development of future studies. Moreover, the theoretical framework introduced, provides the impetus to study the sleep-behavior relationship in other clinical groups and could be applied to broader clinical groups with intellectual delays such as individuals with Downs Syndrome, Fragile-X or Retts

Disorder. The framework proposed here highlights areas, which require consideration when examining sleep and behavioral difficulties in individuals with low-functioning autism and other clinical populations, and identifies areas that are yet to receive research attention in these populations, including the examination of sleep over time.

7.3. Clinical implications

The findings from this thesis have several clinical implications, which can assist in the prophylactic treatment in individuals with autism or other clinical populations. The empirical studies presented in this thesis validate the severity of sleep disruption in a significant proportion of individuals with low-functioning autism, suggesting that uniform screening for sleep difficulties should form an essential treatment component in this population. Moreover, the findings point to the importance of sleep stability or regularity in daily functioning, and provide a means to assess the stability of sleep so that clinicians can understand the regularity and consistency of sleep patterns in individuals with autism and broader clinical populations. Here we also demonstrate that there are unique and heterogeneous sleep profiles in individuals with autism, which can inform clinicians when assessing, diagnosing and treating sleep difficulties in children with autism. Furthermore, in chapter five we demonstrate a methodological framework for predicting daily behavioral events in real time from coarse observational measures of nightly sleep, and in chapter six we provide a framework for predicting nightly sleep duration from daily challenging behavior episodes. Both studies have clear translational opportunities for improving patient care in an age of increasing technological monitoring capabilities. The approach demonstrates that prior sleep could form a key component in an embedded monitoring system for an individual (that could also include a range of other predictive factors, such as medication and prior behaviors). For example, an automated sleep monitoring system could be employed with a movement detection device, which would update and apply the model to predict the probability of a behavior occurring the following day or a subsequent night of poor sleep. This would provide a low-cost way of monitoring sleep, which could then be used by a carer to pre-emptively organize appropriate support or to implement preventative interventions (such as daytime naps or prophylactic use of sleep medications). Moreover, this model could also be applied to other clinical populations, which have characteristic difficulties in sleep and behaviors. For example studies have shown that sleep problems are intrinsically linked to the cause and maintenance of psychotic symptoms in schizophrenia (Waters et al., 2011; Waters et al., 2012). The algorithms introduced here, could also form part of a real-time clinical monitoring tool that could be used to predict episodes of psychosis based on prior sleep in this clinical population. The current work, however, can be seen as a first step towards an individually tailored monitoring system that learns the unique predictive signatures of problem behaviors and sleep patterns on an individual and a group level, which could motivate individualized treatment in autism and other clinical populations.

7.4. Limitations

In this thesis, we took comprehensive steps to ensure that our results represent robust sleep phenotypes and a true relationship between sleep and behavior, however it is not withstanding its limitations. First, sleep recordings are based on coarse observations of sleep or wake behavior (in 15 or 30 min intervals, depending on the school) through the night by caregivers. This coarseness limited our ability to compute subtle sleep features from our data, and is clearly less reliable and accurate than lab-based sleep studies, which use actigraphy and polysomnography. Whilst, we acknowledge the quality of sleep measurement in our study is less accurate than traditional lab-based studies this limitation was overcome by the uniqueness of this dataset in that it comprises an unprecedented volume of real world data. Moreover, a recent study by Veatch et al., (2016) found that actigraphy measured sleep duration was correlated with subjective parent report measures in children with autism, which challenges the notion that sleep recordings need to be objectively measured in order to be validated. The clinicians at both residential facilities were well educated about sleep in autism and therefore sleep-wake observations may have been as accurate as objective measures. Second, our study group is primarily of Caucasian descent living in a residential facility in Boston, USA and therefore may not be generalizable to outpatient samples, or individuals with high-functioning autism. Third, individuals were undergoing regular intervention (including psychopharmacology and behavioral therapy), which are known to moderate both sleep problems and behavior severity (Malow et al., 2016). Most individuals were taking prescription medications to remediate either sleep or behavior difficulties which poses as a potential limitation. This changing relationship between sleep, behavior and medications over time, including individuals who are in the presence of constant developmental and physiological changes, may have limited our ability to understand sleep-behavior relationships. Fourth, several individuals were missing adaptive functioning and IQ measures and for individuals with available data, their scores were only determined at one point in time when they were initially enrolled at the residential facilities. This poses as a potential limitation as later intervention may have moderated these scores (although this is not likely as these measures are considered to be stable measure across time (Freeman, Del'Homme, Guthrie, & Zhang, 1999)), and the findings linking sleep phenotypes to adaptive functioning were only based on a subset of individuals from the sample. Fifth, a diagnosis of autism was not confirmed by the 'gold-standard' diagnostic such as the Autism Diagnostic Observation Schedules (ADOS). Although the potential impact of this significant limitation was minimized by reviews of all individuals' original Pediatrician or Psychiatric diagnostic reports to ensure criteria was met for DSM-IV criteria of autism (specifically low-functioning subtype), it is possible that participants in our low-functioning sample could have met criteria for other disorders that took precedence (e.g., Fragile X syndrome, or Retts syndrome). Lastly, a range of other potential effect modifiers might have impacted uncovered associations (for example, hormones, psychiatric and medical co-morbidities), as well as environmental variables (such as changing schedules, weekends or holiday breaks, intrusions of digital technologies, and sleep environment and routines), however these confounds were not taken into account in this thesis.

7.5. Directions for future research

This thesis presents the first step in investigating the nature of sleep difficulties and its relationship to behavior in individuals with low-functioning autism and therefore further studies are warranted. Whilst the current thesis supports the notion that long-term sleep difficulties in individuals with low-functioning autism are due to deficits in neurological pathways, which disrupt the sleep-wake cycle, this assumption remains untested and requires empirical support from future studies. Specifically, further investigation into the nature of sleep disruption in this population as well as the underlying mechanism, which predispose sleep instability, is interesting and requires further investigation. Moreover, the behaviorally determined sleep phenotypes identified in this thesis were based on coarse temporal observations of sleep-wake behavior, which requires further validation against continuous recordings obtained from actigraphy or PSG, although bed or room sleep sensors, may be more appropriate for this group due to their difficulty tolerating sensory measures such as actigraphy (Hodge et al., 2012). Moreover, the finding that autism severity (as measured by the VABS) is linked to unstable sleep phenotypes requires further validation by examining adaptive behavior at concurrent data points and measuring these scores against sleep phenotypes across time. Further validation of sleep phenotypes in independent cohorts, including a wider variety of demographics, outpatient samples and levels of autism severity, is needed to allow for generalizability of findings.

Previous studies in the field of sleep and autism have been cross-sectional, focusing on overall relationships between sleep and behavior, and yet to investigate whether these associations hold in real-time. This is the first study to examine the real-time relationship between sleep and behavior in individuals with autism, as well as their bidirectional relationship. It is also the first study to date to investigate the effects of cumulative sleep on daytime functioning in autism. The methods introduced here therefore present the first step towards the development of a real-time predictive modeling tool that can help pre-empt sleep and behavioral episodes in this population. Hence future investigations are warranted, including the use of these methodologies to uncover the sleep-behavior relationship in healthy populations (i.e., typical adults and children), child clinical populations (i.e., children with high-functioning autism, ADHD or Fragile-X) and adult clinical populations (i.e., schizophrenia, depression). These findings also require independent replication in outpatient samples of individuals with low-functioning autism. Future studies are also needed to investigate the role of cumulative sleep on behavioral functioning in autism and in other populations, as this is the first study to date to investigate the role of sleep history in daytime functioning. This thesis did not to take into account age-related changes in sleep and behavior (as we restricted our dataset to a 12-18 month time period), which requires further examination as no study to date has examined how the sleep-behavior relationship changes over time. Future longitudinal studies, which collect real-time data on sleep and behavior from early childhood to adolescents, should be studied in order to understand developmental trajectories of these difficulties over time in individuals with low-functioning autism. Lastly, most individuals included in this thesis were on medications, which may have influenced the sleep-behavior relationship (or lack thereof). Therefore, studies of this nature should be replicated in order to isolate the effects of variables such as medications, which are known to have an impact on both sleep and behavior.

7.6. Conclusions

The aim of this thesis was to identify the nature of sleep difficulties and its relationship to behavior in an understudied population of individuals with low-functioning autism. Collectively, this thesis builds on the research to date by profiling the nature of sleep deficits and modeling the relationship between sleep and behavior in individuals with low-functioning autism, delving beyond cross-sectional designs that are the traditional focus of research in the area of autism. Importantly we were able to uncover relationships, despite coarse observational measurements of sleep-wake behavior and daytime behavior observations, in individuals that varied in age, medications, sleep patterns and behavioral profiles. Moreover, the comprehensive data processing and prediction algorithms introduced here constitute the first step in isolating robust sleep-wake relationships in large and complex temporal datasets (that are becoming easier to collect with sensors and smartphone technology). Given the annual societal cost of autism with recent predictions estimated at $126 billion in the US (Buescher et al., 2014), there is a compelling need to develop prophylactic treatments which moderate the severity of autism symptoms. This thesis provides the first foundation towards developing a real-time clinical monitoring tool, which can be used pre-empt behavioral and sleep difficulties so that appropriate interventions can be placed to improve the functioning and wellbeing of 1 in 68 individuals diagnosed with autism.

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