THE MEASUREMENT OF SLEEP IN CHILDREN WITH NEUROGENETIC SYNDROMES

by

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OVERVIEW

This thesis is submitted by Natalie Knight for the Clinical Psychology Doctorate at the University of Birmingham. The thesis contains three chapters which comprise the research component of the doctorate. The first chapter is a systematic review of the concordance between objective and subjective sleep assessment methods in rare neurogenetic syndromes. The second chapter is an empirical paper which uses an existing actigraphy dataset to explore the impact of sleep assessment methodologies on sleep parameter estimates across neurogenetic syndromes. The final chapter is in the form of a press release for both the review and empirical chapters. The press releases will be used to disseminate findings.

Declaration of contribution

Chapter Two presents a secondary analysis of data originally collected by Dr Jayne Trickett in part fulfilment of her own PhD. Dr Trickett designed the original study and collected the data. The chapter presented here reflects an independent research question and novel analysis of the data. Published papers using all or part of the original data set;

Agar, G., Oliver, C., Trickett, J., Licence, L., & Richards, C. (2020). Sleep disorders in children with Angelman and Smith-Magenis syndromes: The assessment of potential causes of disrupted settling and night time waking. *Research in developmental disabilities*, *97*, 103555.

Surtees, A., Richards, C., Clarkson, E., Heald, M., Trickett, J., Denyer, H., Crawford, H., & Oliver, C. (2019) Sleep problems in autism spectrum disorders: a comparison to sleep in typically developing children using actigraphy, diaries and questionnaires, *Research in Autism Spectrum Disorders, 67,* 101439.

Trickett, J., Oliver, C., Heald, M., Denyer, H., Surtees, A., Clarkson, E., Gringras, P., & Richards, C. (2019) Multi-Method Assessment of Sleep in Children With Angelman Syndrome: A Case-Controlled Study. *Frontiers in psychiatry*, *10*, 874.

Trickett, J., Oliver, C., Heald, M., Denyer, H., Surtees, A., Clarkson, E., Gringras, P., & Richards, C. (2020) Sleep in children with Smith-Magenis syndrome: a case-control actigraphy study. *Sleep*, *43*(4), zsz260.

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TABLE OF CONTENTS

CHAPTER 1 – THE USE AND CONCORDANCE OF OBJECTIVE AND SUBJECITVE SLEEP MEASUREMENT IN NEUROGENETIC SYNDROMES: A SYSTEMATIC REVIEW

Page

CHAPTER 2: DO DIIFERENT METHODS OF SLEEP DATA COLLECTION AND DATA MANAGEMENT AFFECT SLEEP PARAMETERS ACROSS NEURGENETIC SYNDROMES?

CHAPTER 3: PRESS RELEASES

LIST OF TABLES

LIST OF FIGURES

APPENDICES

CHAPTER ONE

The Use and Concordance of Objective and Subjective Sleep Measurement in Neurogenetic Syndromes: a systematic review

1.1 Abstract

Background: The consequences of poor sleep are wide ranging for people with neurogenetic syndromes, warranting accurate and robust sleep assessment strategies. Varying levels of concordance between assessment methods have been reported in typically developing populations. However, this area is under-researched within rare neurogenetic syndromes and no systematic reviews of concordance between objective and subjective sleep measurement have been conducted.

Methods: A systematic literature search was undertaken to identify papers using both an objective and subjective measure of sleep. Quality criteria were developed and applied to papers to inform an evaluation of the methodological strengths and limitation of the literature. The search returned 26 papers for inclusion, drawing data from nine neurogenetic syndromes. Data were extracted and summarised where possible and estimates of potential concordance correlations for each paper were calculated.

Results: Actigraphy was the predominant objective measure used. As rated, the quality of its application was mixed, with inconsistency across the use of a concurrent sleep diary, reporting on data cleaning and the number of nights of data included in analysis. Eight studies reported correlational concordance data, across four syndromes. It was not possible to draw any meaningful conclusions of concordance from these limited findings. Across all papers, the literature showed much greater potential for the exploration of concordance with only 6% of possible correlations between subjective and objective measurement computed in the 26 papers.

Discussion: Results are discussed in relation to the need for more research in this area, more comprehensive reporting of data sets with consideration for Open Science and robust actigraphy guidelines for the field. Both clinical and research recommendations are provided.

1.2 Introduction

Sleep is as a biopsychosocial process, often with multiple mechanisms interacting to underpin both normal and atypical sleep. Biologically, humans have a 24 hour rhythmic cycle, regulated by an intrinsic 'clock' (Brainard, Gobel, Scott, Koeppen & Eckle, 2015). This circadian system is driven by the release of melatonin, a hormone secreted from the pineal gland (Cajochen, Krauchi, & Wirz-Justice, 2003). Psychologically, atypical sleep is considered a symptom of many psychiatric conditions and here the literature also suggests a complex bidirectional relationship. Studies have found that both anxiety and depression are concurrently associated with reduced quality and duration of sleep (e.g., Fuligni & Hardway, 2006) in addition to sleep difficulties in childhood being shown to confer risk for depression (e.g., Danielsson, Harvey, MacDonald, Jansson-Frojmark & Linton, 2013). Socially, multiple contextual factors have been linked to sleep. For example, in some cultures an afternoon nap is encouraged and has become an integrated component of daily life (Lin, 2018) with some studies suggesting that a nap may help adolescents achieve greater total sleep over the course of a day (Lazaratou et al 2005). For a comprehensive discussion of contextual factors related to sleep see Becker, Langbery and Byars, (2015). In summary, sleep can be considered as a complex interaction between observed biological processes and both psychological and social factors.

The importance of sleep

Sleep is an essential biopsychological process implicated in a range of daytime functions. The consequences of poor sleep in typically developing adults and children are well documented. In adults, poor sleep affects memory consolidation (Frank & Bennington, 2006), effective immunological response (Besedovsky, Lange & Born, 2012) mood (Blaxton,

Bergeman, Whitehead, Braun, & Payne, 2017) and cellular development (Gilad & Shapiro, 2020). In paediatric populations, the consequences of poor sleep include poor cognitive functioning (Touchette, Petit, Séguin, Boivin, Tremblay, & Montplaisir, 2007), emotion dysregulation (Mindell, Leichman, DuMond, & Sadeh, 2016) and attentional deficits (Sadeh, Marcas, Guri, Berger, Tikotzky & Bar-Haim, 2015). For people with neurodevelopmental conditions, sleep and the consequences of poor sleep are less well understood, though such groups are arguably additionally disadvantaged given pre-existing difficulties and differences in these areas of daytime functioning. Problems with sleep in children with neurodevelopmental conditions are associated with an increase in behaviours that challenge (Rzepecka, McKenzie, McClure, & Murphy, 2011) and adverse effects on parental wellbeing (Didden, Korzilius, van Aperlo, van Overloop, & de Vries, 2002; Quine, 1991). In summary, the effects of poor sleep are multisystemic but remain understudied in people with neurodevelopmental conditions.

One sub-population at increased risk of poor sleep is people with rare genetic syndromes, which are often associated with intellectual disability. A recent meta-analysis of sleep in 19 rare genetic syndromes placed the prevalence of general sleep disorders[1] in these groups at 10 to 95% (Agar, Brown, Sutherland, Coulborn, Oliver, & Richards, 2021). The upper range of these estimates is considerably higher than those for typically developing populations, estimated at 6-47% for children (Calhoun, Fernandez-Mendoza, Vgontzas, Liao, & Bixler, 2014; Johnson, Roth, Schultz, & Breslau, 2006; Liu, Liu, Owens, & Kaplan, 2005; Owens, 2008) and 23-56% for adults (Léger, Poursain, Neubauer & Uchiyama, 2008). In broader intellectual disability populations, prevalence of poor sleep is estimated at 16-84% for children (Johnson et al., 2006; Quine, 1991; Wiggs & Stores, 1996) and 9-34% for adults (Brylewski & Wiggs 1998; Espie & Tweedie, 1991; van de Wouw, Evenhuis, & Echteld, 2012). Ultimately,

[1] In Agar et al. (2021) papers describing 'general' sleep disorders were those where the sleep difficulty lacked a clear definition of the aspect of sleep that was assessed.

these data demonstrate that people with rare genetic syndromes are a high-risk group and given the wide-ranging consequences of poor sleep, it is essential that targeted research is done to ensure sleep assessment tools are effective, accurate and ecologically valid for this group.

Methods of sleep assessment

Sleep can be measured using both objective and subjective methods and both assessment approaches feature in research conducted with people with neurodevelopmental conditions. The most widely used objective measures are polysomnography (PSG) and actigraphy, and the most common subjective methods are sleep diaries and informant questionnaires. Each of these measurement approaches have differing strengths and limitations, particularly in their ability to capture habitual sleep parameters in people with neurodevelopmental conditions.

Polysomnography (PSG) is considered the 'gold standard' in sleep assessment, endorsed by the American Academy of Sleep Medicine (AASM, 2020). PSG is an objective sleep measurement that provides data on sleep parameters and sleep stages by measuring electrical activity of the brain alongside cardiography, limb movement and pulse oximetry (Esbensen & Schwichtenberg, 2016). Unfortunately, PSG is expensive and often not well-tolerated owing to its intrusive nature. This is particularly pertinent for children with intellectual disability and rare syndromes, for whom sensory needs may make it difficult to tolerate the necessary placement of electrodes and wires. In cases where PSG has been used (e.g., Arens et al.,1998; Breslin, Spanò, Bootzin, Anand, Nadel, & Edgin, 2014; Bruni, Cortesi, Giannotti, & Curatolo, 1995; Goldman, Bichell, Surdyka, & Malow, 2012; Gimenez et al., 2018; Kaplan, McCool, Lupski, Glaze, & Potocki, 2019; Levanon, Tarasiuk, & Tal, 1999; Maris, Verhulst, Wojciechowski, Van de Heyning & Boudewyns, 2016; Mason et al., 2011 & Tawfik et al., 2009), data are often limited to a single night within a sleep laboratory, limiting ability to capture longitudinal variability and habitual sleep patterns, and reducing ecological validity. In

summary, despite being well-endorsed, the nature of PSG often makes it an unsuitable choice for the groups of interest here and alternatives have been sought.

Actigraphy is an alternative approach to objective sleep assessment. It is a small watch-like device, worn on the wrist or ankle. Data can be collected over longer periods of time, capturing habitual variability in sleep parameters. Acebo et al., (1999) recommend collecting a minimum of five nights of data to ensure adequate estimates of sleep parameters citing reliability estimates for mean values aggregated over five nights at ≥.70. Actigraphy is a proxy measure, and whilst some devices will capture light data scoring algorithms typically use the presence or absence of movement via accelerometer to denote periods of sleep or wake. This can be a particular issue for parameters such as 'Onset Latency', where the actigraph may code time the child is laying still as sleep, leading to an underestimation of both 'Onset Latency' and 'Night Waking', with a concomitant overestimation of parameters such as 'Total Sleep Time'. Research examining concordance between actigraphy and PSG has produced a mixed picture. For example, a recent review of papers examining healthy adults (k = 20) highlighted notable variance in the strength of correlations between the two objective methods ranging from r = .19-.98 for 'Total Sleep Time' (Conley et al., 2019). As shown, actigraphy has many beneficial attributes for use in a broader range of populations though is not without its limitations warranting caution in data interpretation.

As a subjective measure of sleep, questionnaires have been widely used within rare genetic syndrome research. They are an accessible method using both self and informant report, the latter being particularly useful when intellectual disability and communication difficulties are present. Questionnaires often measure both sleep parameter values and the presence of overall sleep difficulties or disorders, which may map onto sleep disorder taxonomy as specified in the International Classification of Sleep Disorders (American Academy of Sleep Medicine,

2014). Two commonly used questionnaires in rare syndromes are the Modified Simonds and Parraga Sleep Questionnaire (MSPSQ; Simonds & Parraga, 1982; Wiggs & Stores, 1996) and the Child Sleep Habits Questionnaire (CSHQ; Owens, Spirito, & McGuinn, 2000). The informant reported MSPSQ gives an overall measure of sleep from 51 items, separated into seven subscales. In a sample of children with intellectual disability, test-rest reliability ranged from .83 to 1.0 (Wiggs & Stores, 1996). Moore, Evans, Hanvey, & Johnson (2017) commended the MSPSQ for being able to inform treatment planning and being sensitive to change. The CSHQ examines childhood medical and behavioural sleep difficulties across 33-items completed by a caregiver. Esbensen & Hoffman (2017) found it to have strong psychometric properties when applied to a population of children with Down syndrome. However, use of questionnaire measures is vulnerable to threats to validity, such as informant error and bias. For example, parents are often required to appraise their child's sleep habits retrospectively, which can lead to recall bias. It is also difficult for subjective methods to capture night by night variability when informants are asked for total estimates, reducing precision and subsequent validity as an accurate measure of sleep parameters. Finally, co-occurring conditions may lead to informant over- or under-estimation of sleep difficulties, for example, parents whose children display behaviours that challenge when they wake in the night are more likely to inadvertently overestimate sleep difficulty (Esbensen, Hoffman, Stansberry & Shaffer, 2018b). Both the CSHQ and MSPSQ are useful subjective tools for sleep research in neurogenetic syndromes when potential biases and validity threats are accounted for.

Sleep diaries are also commonly deployed subjective measurement tools, providing daily records of multiple parameters related to sleep scheduling, from which sleep quality parameters can be derived. Diaries can be completed on a self-report basis or by informant. They are used to capture night-by-night data in contrast to overall perceptions of sleep quality

and as such are potentially less affected by recall bias. However, when completed by parents, the parent may not be in consistent proximity to their child during the sleep period and subsequently may estimate several parameters based on their own limited interactions with the child overnight. For the most useful data it is important for informants to show a good level of adherence to the completion of a sleep diary. Additionally, Moore et al., (2017) suggest that some informants may find diaries demanding, particularly those already facing a challenging bedtime. While the completion of a daily diary may reduce some of the biases associated with questionnaires, the required investment in time may lead to reduced adherence and accuracy.

Neither objective nor subjective methods of sleep assessment fit an 'ideal' and differing approaches used to assess sleep will vary in their capacity to describe the biological, psychological and social components the 'biopsychosocial' sleep process. A clear picture of how both subjective and objective approaches compare is vital if researchers and clinicians alike are to know to what extent the data from such methods can be generalised. In addition to guiding clinical decision making, an evaluation of concordance between subjective and objective sleep measurement tools in rare syndromes would enhance comparisons between studies and improve description of sleep in these high-risk populations. Improved understanding of concordance could also translate to intervention studies, enhancing consistency of sleep measurement to afford more conclusive estimates of intervention efficacy.

Concordance between objective and subjective sleep measures in typically developing populations

Concordance between objective and subjective measures of sleep has been well-researched in both child and adult typically developing populations. In children, Matricciani (2013) aimed to review evidence for subjective report validity, with a focus on elements of phrasing in questions. From 11 studies, correlations between objective and subjective measures

for the parameters of 'Bedtime' and 'Wake Time' were high. Matricciani (2013) also investigated whether the definition used for 'Total Sleep Time' influenced the strength of concordance correlation for this parameter. When the definition was given as the difference between sleep start and sleep end, correlations were strong. However, when additional parameters such as 'Wake After Sleep Onset' were included, correlations were weaker. Mild to moderate correlations were reported in cases where no definition was provided. Included in this review, a detailed examination by Werner et al., (2008) highlighted different concordance rates dependent on the type of subjective measure included in the comparison to actigraphy. The level of agreement between diaries and actigraphy was marked as acceptable, but agreement between questionnaire data and actigraphy was not. This may be due to the potential bias and validity threats with questionnaires discussed above. Additional studies report that parents tend to overestimate sleep in terms of increased duration, earlier bedtimes and later wake times compared to actigraphy in data collected from both sleep logs and questionnaires (Iwasaki et al., 2010; Short, Gradiasar, Lack, Wright, & Carskadon, 2012), though findings from Iwasaki et al., (2010) also reported stronger correlations between sleep logs and actigraphy compared with questionnaires. Overall, in typically developing children concordance between subjective and objective assessment is fair to good, and varies dependent on the type of sleep measurement, sleep parameter and specificity of definition of sleep parameter.

In a recent review of the relationship between objective and subjective sleep measurement in healthy adults, Cudney, Frey, McCabe, & Green, (2022) identified 13 studies. The authors reported the PSG variables most often significantly associated with subjective measurement were 'Total Sleep Time' and 'Sleep Efficiency'. It is interesting that both positive and negative relationships between the measurement types were observed. The authors took this to indicate that sleep problems can be associated with varying extremes in sleep duration.

Interestingly, evidence for subjective measures overestimating 'Total Sleep Time' relative to actigraphy has been evidenced in both child and adult studies (Guedes, Abreu, Rodrigues, Teixeira, Luiz & Block, 2016; Jackson, Patel, Jackson, Lutsey & Redline, 2018; Mazza, Bastuji, & Rey, 2020; Perpetuo, Fernandes & Verissimo, 2020; Short et al., 2012). In summary, these reviews demonstrate high variability in concordance between subjective and objective measures in both typically developing children and adults. Given the heightened risk for sleep disorders and more heterogenous sleep profiles in people with neurodevelopmental conditions generally and rare syndromes more specifically, an examination of concordance within this population is warranted.

Concordance in Neurodevelopmental conditions

Concordance between sleep assessment methods in neurodevelopmental conditions has received considerably less research attention than typically developing populations with few studies aiming to examine this. Of the available literature, findings are also mixed.

Hodge, Parnell, Hoffman, & Sweeney, (2012) reported correlations between objective and subjective sleep measures in children with autism on 'Total Sleep Time' ranging between .16 and .78, whilst studies of both children and adults have reported consistent results between objective and subjective measurement across the parameters of 'Total Sleep Time' (r = .75), 'Sleep Efficiency', 'Sleep Onset Latency' (r = .83), and 'Wake After Sleep Onset' (r = .7), (Cortese, Faraone, Konofal, & Lecendreux, 2012; Morgan, Nageye, Masi, & Cortese, 2020). In a study of children with ADHD, Wiggs, Montgomery, & Stores (2005) reported a positive correlation for 'Wake-up Time' between objective and subjective methodology but poor correspondence on the variable of restlessness. Further Choi, Yoon, Kim, Chung, & Yoo (2010) reported significant differences between children with ADHD and typically developing

children on several CSHQ subscales which were then not replicated when compared to results of PSG indicating a lack of concordance between the methodologies. Given this variability, the literature would suggest that a combined use of objective and subjective measurement tools is best placed to inform sleep research and clinical practice in neurodevelopmental conditions. What remains unknown however is whether these findings are replicated for people with rare genetic syndromes.

Why look at concordance for sleep assessment tools in neurogenetic syndromes?

Both within and between rare syndrome groups exists substantive heterogeneity, particularly in the domains of communication and severity of intellectual disability. In part this means some groups will be more able to tolerate objective sleep measurement methods whereas other groups may find this more challenging and will find subjective informant report tools more accessible. If we are therefore to make inferences about sleep using a combination of assessment measures, we need to know where there lies agreement and where there are areas requiring a more careful interpretation. Further, knowledge of concordance is vital in enabling an accurate interpretation of data both for the purposes of research and clinical practice. Such information will help us learn more about sleep difficulties in these groups and put in place the most effective interventions. It is also vital that we obtain a robust picture of whether the support we put in place is helpful and working and currently we do not know if the conclusions we draw will be different based on sleep assessment method used. Therefore, the present systematic review will examine concordance between objective and subjective measurement methods in rare neurogenetic syndromes to inform both future research studies and clinical practice.

1.3 Methods

1.3.1 Search Strategy

A list of rare syndromes associated with intellectual disability in which to investigate concordance of subjective and objective sleep measurement was derived from Stores (2014), as used previously in a meta-analysis of sleep disorders in rare genetic syndromes (Agar et al., 2021). This focused the systematic search on syndromes most associated with sleep difficulties. In total, 21 syndromes were selected for review.

Searches were conducted in Ovid MEDLINE, Ovid PsychINFO, Ovid Embase and Web of Science databases. Searches combined search terms for sleep and measurement with all variations of each syndrome as used in Agar et al.,'s (2021) meta-analysis, using the strategy presented in Table 1.1. Backward searching of reference lists for included papers was also completed. Table 1.2 lists details of syndrome groups, search dates, inclusion dates and search terms for the syndromes.

Table 1. 1 Overview of search terms

Search line	Search terms
A	"sleep"
B	(measure* OR actigraph* OR actimeter OR actometer OR "wrist actigraphy" OR "rest actigraphy" OR "sleep wake" OR diary OR record OR log OR objective OR subjective OR questionnaire OR PSG OR polysomnograph* OR monitor OR detect OR assess OR device OR wearable)
C	*search terms listed in Table 1.2*
D	A + B + C (repeated for each individual syndrome)

Table 1. 2 Syndromes, search details and search terms

	Embase		PsychINFO		MEDLINE		Web of Science		
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Search terms**
Angelman syndrome (AS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Angelman*" OR "Angelman* syndrome" OR "Happy puppet syndrome" OR "Happy puppet"
CHARGE syndrome (CS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"CHARGE" OR "CHARGE syndrome" OR "CHARGE association" OR "Hall-Hittner* syndrome" OR "Hall* Hittner* syndrome" OR "Coloboma"
Cornelia de Lange syndrome (CdLS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Cornelia de Lange* syndrome" OR "CDLS" OR "De Lange* syndrome" OR "Branchmann-De Lange* syndrome" OR "BDLS" OR "Brachmann* syndrome" OR "Amstelodamensis typus degenerativus" OR "Amsterdam dwarf syndrome" OR "Amsterdam dwarfism" OR "Typus degenerativus amstelodamensis"

	Embase		PsychINFO		MEDLINE		Web of Science		
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Search terms**
Cri du Chat syndrome (CdC)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Cri-du-Chat" OR "Cat cry syndrome" OR "5p minus syndrome" OR "Chromosome 5p deletion syndrome" OR "5p- syndrome; Monosomy 5p" OR "5p deletion syndrome" OR "Chromosome 5p- syndrome"
Down syndrome (DS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Down* syndrome" OR "Trisomy 21" OR "Trisomy G" OR "47,XX,+21" OR "47,XY,+2"
Fragile X syndrome (FXS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Fragile X" OR "Fragile-X" OR "Fragile X syndrome" OR "FXS" OR "FRAXA syndrome" OR "AFRAX" OR "Martin-Bell* syndrome" OR "Marker X syndrome" OR "fraX syndrome" OR "fra(X) syndrome" OR "X-linked mental retardation" OR "Macroorchidism" OR "Escalante* syndrome" OR "Escalante*"

	Embase		PsychINFO		MEDLINE		Web of Science		Search terms
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	
Hurler Syndrome (Hurler)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Hurler*" OR "Mucopolysaccharidosis Ih" OR "MPS1-H" OR "MPS1H" OR "Mucopolysaccharidosis type 1H" OR "Mucopolysaccharidosis type IH" OR "Hurler disease" OR "MPSIH"
Jacobsen syndrome (JS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Jacobsen syndrome" OR "Jacobsen*" OR "JBS" OR "Chromosome 11q deletion syndrome" OR "Partial 11q monosomy syndrome"
Juvenile neuronal ceroid-lipofuscinosis (JNCL)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"juvenile neuronal*" OR "JNCL" OR "Neuronal ceroid lipofuscinosis 3" OR "Juvenile neuronal ceroid lipofuscinosis" OR "Vogt Spielmeyer disease" OR "Spielmeyer Sjogren disease" OR "CLN3 disease"

	Embase		PsychINFO		MEDLINE		Web of Science		Search terms
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	
Lesch-Nyhan syndrome (LNS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Lesch-Nyhan syndrome" OR "LNS" OR "HPRT deficiency" OR "HPRT1 deficiency" OR "HPRT deficiency, complete" OR "Hypoxanthine guanine phospho-ribosyltransferase 1 deficiency" OR "Lesch-Nyhan syndrome" OR "Lesch Nyhan disease"
Mucopolysaccharidosis Type II (MPS II)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Hunter*" OR "Mucopolysaccharidosis type II" OR "MPS II" OR "Attenuated MPS" OR "Severe MPS II" OR "Hunter syndrome" OR "Iduronate 2-sulfatase deficiency" OR "I2S deficiency" OR "MPS 2"
Mucopolysaccharidosis Type IIIB (MPS IIIB)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"sanfilippo*" OR "Mucopolysaccharidosis type III" OR "Mucopoly-saccharidosis type 3" OR "Sanfilippo syndrome" OR "MPSIII" OR "Mucopolysaccharidosis type 3" OR "Sanfilippo disease"

	Embase		PsychINFO		MEDLINE		Web of Science		Search terms
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	
Mucopolysaccharidosis Type IVA (MPS IVA)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Morquio*" OR "Morquio syndrome B" OR "Mucopolysaccharidosis type IVB" OR "MPS IVB" OR "MPS 4B"
Neurofibromatosis (NF)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Neurofibromatosis" OR "Neurofibromatosis type 1" OR "Neurofibromatosis 1" OR "NF1" OR "Peripheral Neurofibromatosis" OR "Recklinghausen* disease" OR "Neurofibromatosis type 2" OR "Neurofibromatosis 2" OR "NF2" OR "Central neurofibromatosis" OR "Bilateral acoustic neurofibromatosis" OR "BANF" OR "Familial acoustic neuromas"
Norrie disease	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Atrophia bulborum hereditaria" OR "Pseudoglioma" OR "Episkopi blindness" OR "Norrie*" OR "Norrie-Warburg syndrome" OR "Anderson-Warburg syndrome" OR "NDP" OR "Fetal iritis syndrome"

	Embase		PsychINFO		MEDLINE		Web of Science		Search terms
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	
Prader-Willi syndrome (PWS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"PWS" OR "Prader-Willi*" OR "Willi-Prader syndrome" OR "Prader-Labhart-Willi syndrome"
Rett Syndrome (Rett)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Rett*" OR "Rett* syndrome" OR "Rett* disorder" OR "RTS" OR "RTT" OR "Cerebroatrophic hyperammonemia" OR "Autism-dementia-ataxia-loss of purposeful hand use syndrome"
Smith-Lemli-Opitz syndrome (SLOS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Smith Lemli Opitz syndrome" OR "SLO syndrome" OR "7-Dehydrocholesterol reductase deficiency" OR "RSH syndrome" OR "SLOS" OR "Rutledge lethal multiple congenital anomaly syndrome" OR "Polydactyly, sex reversal, renal hypoplasia, and unilobular lung" OR "Lethal acrodysgenital syndrome"

	Embase		PsychINFO		MEDLINE		Web of Science		Search terms
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	
Smith-Magenis syndrome (SMS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Smith-magenis*" OR "smith magenis" OR "Chromosome 17p11.2 deletion syndrome" OR "17p- syndrome" OR "17p11.2 monosomy" OR "chromosome 17p deletion syndrome" OR "deletion 17p syndrome" OR "partial monosomy 17p" OR "SMS"
Tuberous Sclerosis Complex (TSC)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"Tuberous sclerosis" OR "Tuberous sclerosis syndrome" OR "Bourneville* disease" OR "Bourneville* phakomatosis" OR "Cerebral sclerosis" OR "Cerebral sclerosis syndrome" OR "Epiloia" OR "Sclerosis tuberose" OR "Tuberose sclerosis" OR "Tuberose sclerosis syndrome" OR "Tuberous sclerosis complex" OR "TSC" OR "TSS"

	Embase		PsychINFO		MEDLINE		Web of Science		Search terms
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	
Williams syndrome (WS)	25.01.20	1974 to 24th January 2020	25.01.20	1967 to January week 3 2020	25.01.20	1946 to January 24th 2020	26.01.20	1900 to 26th January 2020	"William*" OR "William* syndrome" OR "Beuren* syndrome" OR "Elfin Facies syndrome" OR "Hypercalcemia-Supravalvar Aortic Stenosis" OR "Infantile hypercalcemia" OR "Supravalvar aortic stenosis syndrome" OR "WBS" OR "Williams-Beuren* syndrome" OR "WMS" OR "WS" OR "WBS"

1.3.2 Selection Strategy

The searches identified a total of 3,153 articles following the removal of 2,962 duplicates. The articles were then subjected to a three-stage process to determine suitability for inclusion of screening, title and abstract review, and full text eligibility review.

1.3.2.1 Screening

Abstracts and titles for articles were screened against the inclusion and exclusion criteria presented in Table 1.3.

Table 1. 3 Inclusion and exclusion criteria for screening

Inclusion Criteria	Exclusion Criteria
Peer reviewed journal	Not peer reviewed, e.g., conference abstract, thesis publication
Includes both an objective and subjective measure of sleep parameter(s) or sleep quality applied to the same sample	Does not include both an objective and subjective measure
Reports a sample ($n \geq 5$) of adults or children with a named confirmed diagnosis of a rare genetic syndrome	Sample size $n < 5$
Not a dulplicate	Duplicates
Full paper	Not a full paper (abstract only)
Written in the English language	Not in English
Reports on primary data	Does not report primary data
Syndrome is reported and is included on predefined list	Does not measure sleep
Human sample	Syndrome not reported or syndrome not on list of those assigned for review
	Review paper
	Not human sample

1.3.2.2 Eligibility

The inclusion and exclusion criteria presented in Table 1. 3 were also used at screening, title and abstract review and full-text eligibility review.

Figure 1.1. developed using the PRISMA model adapted from Moher, Liberati, Tetzlaff, & Altman (2009), shows the number of papers excluded at each stage of the selection process.

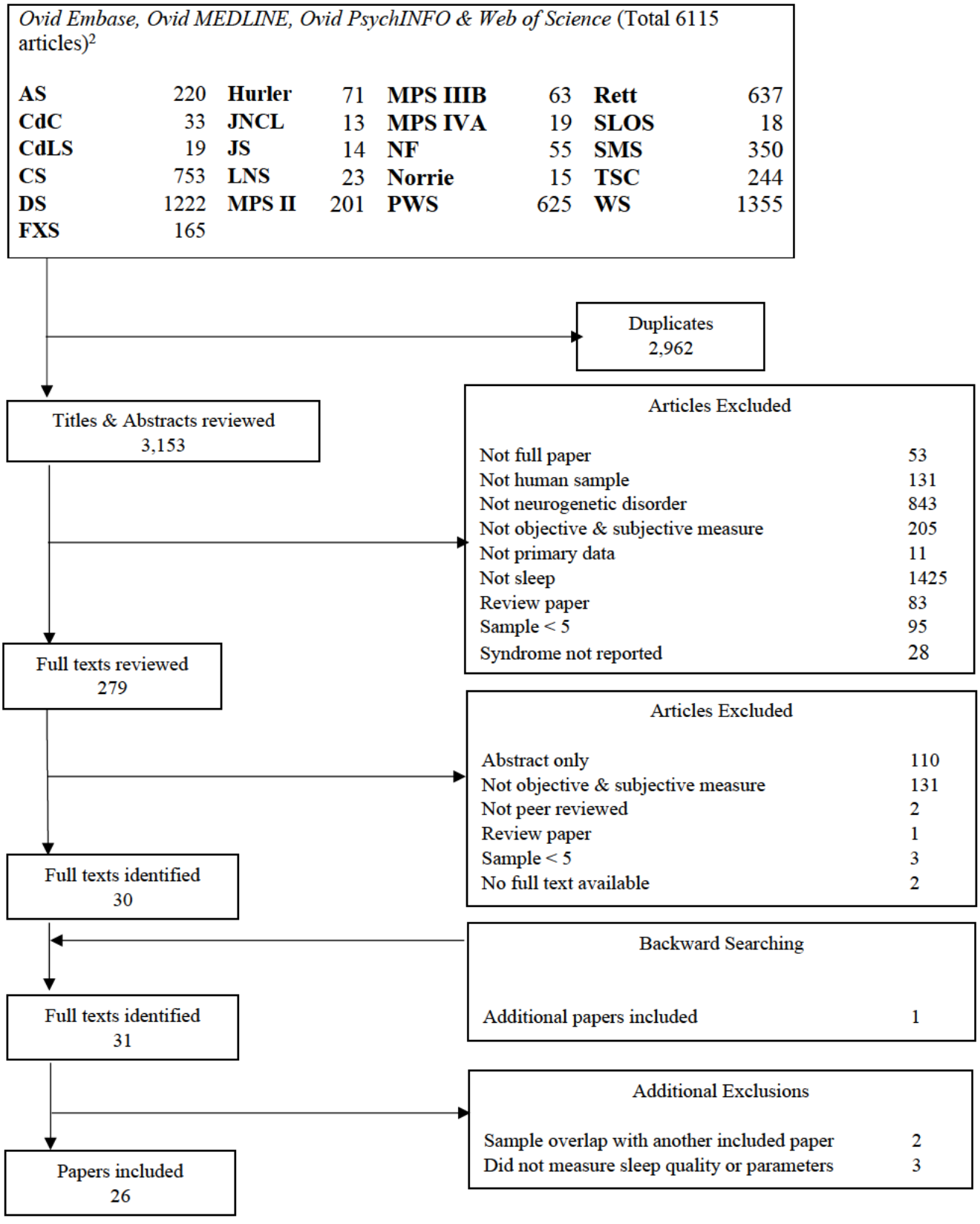

Figure 1. 1 PRISMA diagram outlining number of papers excluded at each stage of review

[2] Acronym definitions given in Table 1.2

1.3.3 Quality

Studies were appraised for quality using criteria designed for the purposes of this review (See Table 1.4). All criteria were rated on a four-point scale: 'poor', 'adequate', 'good' and 'excellent'. All papers were rated on criteria of sample identification and confirmation of syndrome, adapted from Richards, Jones, Groves, Moss & Oliver (2015). Sample identification appraised how well the sample could be considered to reflect the syndrome population(s) under investigation to establish threats to external validity. Given the focus here on sleep measurement within rare syndromes, the level of confidence in the accuracy of syndrome diagnosis was also appraised. As per Richards et al., (2015) and Agar et al., (2021) the highest quality criteria was assigned where the most appropriate method of confirmation of genetic syndrome was undertaken. Typically, genetic testing was considered the 'gold standard' diagnostic tool. However, it was recognised that in some syndromes, current guidance does not indicate the use of genetic testing for confirmation of diagnosis. In such cases, papers were rated as 'excellent' if the commonly accepted diagnostic criteria were met based on a review of National Health Service information webpages and individual syndrome organisation information. For example, for both Tuberous Sclerosis Complex and Rett syndrome a rating of 'excellent' was awarded if the diagnosis was given based on clinical assessment by an 'expert' e.g., a specialist paediatrician.

Additional method-specific criteria were also applied. For subjective measurement, several papers administered more than one questionnaire. Here, only the questionnaire most relevant to examining sleep parameters was rated to avoid an overly complex rating system which would include questionnaires looking at other sleep related factors not captured by objective sleep tools (e.g., daytime sleepiness and sleep hygiene). Therefore, in instances where the study used more than one questionnaire, the measure that provided data on sleep parameters

or sleep quality most closely aligned to the types of sleep parameter or quality data obtained via objective measures was preferentially selected for both quality rating and data extraction. Following this process, the CSHQ and MSPSQ were often selected over other measures. No studies used *both* the CSHQ and the MSPSQ. For all commonly used questionnaires, the quality rating of the questionnaire was pre-assigned and all papers using that questionnaire were allocated this rating for questionnaire quality. Given the scarcity of research within rare genetic syndromes, it was uncommon for measures to be validated specifically for use in these populations. Therefore, a questionnaire was assigned a rating of 'excellent' if validated for use within intellectual disability or at least one neurogenetic syndrome.

Existing literature was unclear on what was important regarding data gleaned from sleep diaries. Here, a rating of 'good' was awarded if the paper cited completion of a sleep diary for a minimum of five nights in line with actigraphy best practice (Acebo et al., 1999). Data were also required to be reported with means and standard deviations at a group mean level for extraction purposes. Definitions of parameters for which data were collected were required owing to known variability within existing literature. It was necessary for diary data to be collected concurrent to the objective measure in order that meaningful information regarding concordance could be gathered. A paper was awarded a rating of 'excellent' if an example copy of the diary was provided within the paper.

Within the quality framework, sub-criteria for actigraphy were compiled (See Appendix A) based on guidelines derived from Acebo et al., (1999), Meltzer, Montgomery-Downs, Insana, & Walsh (2012), Sadeh (2011) and Fawkes et al., (2015). Each paper using actigraphy received a percentage score for applicable criteria; these were then equally distributed between the four-point primary framework scale. To avoid an overly complex criteria for polysomnography, and in line with reporting conventions within the literature, papers received

a rating of ‘excellent’ if a statement was provided citing adherence to recognised guidelines available at the time of paper publication. Such guidelines include methodological considerations such as the use of a habituation night and the placement of electrodes for both adult and paediatric populations. The absence of a reference to such guidance defaulted to a rating of ‘poor’. Table 1.5 gives an overview of ratings assigned to each paper.

Table 1.4 Quality criteria ratings for included papers, coded as 'poor' (red), 'adequate' (yellow), 'good' (amber) and 'excellent' (green).

	Poor	Adequate	Good	Excellent
Sample Identification	Not specified/reported	Single restricted or non-random sample e.g., a specialist clinic or previous research study Single regional sample e.g., a regional parent support group	Multiple restricted or non-random samples e.g., multi-region specialist clinics National non-random sampling e.g., national parent support groups	Random or total population sample
Confirmation of syndrome[1]	Not confirmed/reported Clinical diagnosis only suspected	Clinical diagnosis by 'generalist' e.g., General Practitioner or Paediatrician	Clinical diagnosis by 'expert' e.g., Clinical Geneticist or Specialist Paediatrician	Molecular/Cytogentic/ Metabolic confirmation of diagnosis
Questionnaire[2]	Response to a single question Telephone survey developed by research team Screening tool developed by research team Child Sleep Habits Revised Scale (CSHRS)	Questionnaire validated for use in TD population. Paediatric Sleep Quality Index (PSQI)	Is considered gold standard measure for use in typically developing populations and is widely used within the fields of ID and neurodevelopmental populations.	Questionnaire validated for use in ID or at least one neurodevelopmental syndrome Modified Simmonds & Parraga Sleep Questionnaire (MPSQ) Child Sleep Habits Questionnaire (CSHQ)
Sleep diary	Copy of diary not given. Data are not reported Parameters not reported. Less than 7 nights of data.	Partial reporting of data, i.e. vague descriptive reference. Parameters are reported but definitions are missing.	Diaries have been completed for a minimum of 5 nights AND Data have been reported with group means and standard deviations as a minimum AND Parameters recorded are reported, with descriptive definition AND Diaries have been completed concurrent with objective measure.	Diaries have been completed for a minimum of 5 nights AND Data have been reported with group means and standard deviations as a minimum AND Parameters recorded are reported, with descriptive definition AND Diaries have been completed concurrent with objective measure AND A copy of the diary is provided.

	Poor	Adequate	Good	Excellent
Actigraphy See Appendix A for full criteria.	0-25% of applicable criteria met	26-50% of applicable criteria met.	51-75% of applicable criteria met.	76-100% of applicable criteria met.
Polysomnography Statement that administration and scoring adhered to recognised guidelines at the time of publication[3]	Not present	NA	NA	Present.

[1] For syndromes where current opinion does not indicate genetic testing for confirmation of diagnosis the study will be rated as "excellent" if the commonly accepted diagnostic criteria have been met.
MPS/MPS III = Enzyme assays.
Rett = Clinical assessment by 'expert' e.g. specialist paediatrician
TSC = Clinical assessment by 'expert' e.g. specialist paediatrician
[2]For papers which have utilised more than one questionnaire, only that which is most relevant to examining sleep quality ought to be rated.
[3] e.g. American Association of Sleep Medicine (AASM) or Rechtschaffen & Kales (1968)

1.3.4 Inter-rater reliability

To examine whether the quality criteria were clearly operationalised, nine (30%) papers were assigned to a second rater. Given the small sample, as not all criteria were applicable to all papers, formal calculations on interrater reliability were not considered to be sufficiently robust to draw a meaningful conclusion. However, 82% of ratings were identical across raters suggesting that the criteria were both interpretable and useable for the purposes of this research question. Discussion between raters clarified differences in interpretation and any remaining discrepancies were resolved.

1.3.5 Data analysis

Data extracted from the studies included the following; syndrome group, number of participants, type of objective and subjective measure and any concordance correlation findings[3]. Definitions of sleep parameters used in studies which reported correlations were extracted and are provided in Table 1.6. Where correlation analyses were reported, these data were extracted and are reported in Table 1.8. For each remaining study the number of possible correlation analyses between objective and subjective measures were calculated where their methods made it clear these data had been collected but concordance between methods was not reported, see Tables 1.5 & 1.7.[4]

[3] In cases where the reporting or relevant correlational data was considered 'partial' e.g., non-significant findings not reported in full, lead authors were contacted by email with a request to provide these data directly.
[4] Potential within measure analyses were not included here, nor were subjective x subjective or objective x objective putative analyses as these were not the focus of the review.

1.4 Results

This review will firstly set out paper level characteristics. There will then be a review of overall literature quality, followed by a brief specific commentary on the use of actigraphy. A description of studies actively reporting concordance via correlational data between objective and subjective measurement will follow and finally there will be a summary of papers where it was clear from the presented data that concordance analyses were possible, but these were not reported.

1.4.1 Identified papers

The literature search returned 31 articles which included both an objective and subjective measure of sleep within a genetic syndrome population. Five studies were further excluded (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2015; Esbensen, Hoffman, Beebe, Byars & Epstein, 2018; Stores & Stores, 2014; Sudarasan, Paramasivan, Arumugam, Murali, & Kameswaran, 2014; Tawfik, Hashem, Zaki, El-Shazly, Hegazt, El-Maguid, & Hashem, 2009). Esbensen et al., (2018) was clarified to have 100% sample overlap with Esbensen & Hoffman, (2018a) whilst Ashworth et al., (2015) was clarified by the lead author to have 'majority' sample overlap with Ashworth, Hill, Karmiloff-Smith, & Dimitriou (2013) and was also excluded. Stores & Stores (2014), Sudarasan et al., (2014) and Tawfik et al., (2009) on closer inspection of the full texts were found not to include data relating to sleep quality or sleep parameters, so were therefore also excluded leaving 26 papers for review. Table 1.5 presents an overview of each study that reported concordance correlations between objective and subjective data, alongside their quality criteria ratings. The table also includes the number of possible correlation analyses that could have been undertaken between subjective and objective data for sleep parameters and sleep quality, derived from the data the study collected. Table 1.7

presents an overview of each study that *did not* report concordance correlations between their collected objective and subjective data, alongside their quality criteria ratings, and the number of possible correlations that could have been undertaken.

All studies were published between 1995 and 2019. The sample size ranged from 5 - 130 participants and covered a total of eight different genetic syndromes.

Table 1.5 Study characteristics, quality ratings and number of completed and possible (N/N) concordance correlations reported for each paper that undertook correlational[1] analyses.

Study	Syndrome (*n*)	Participant information[4]	Objective measure	Subjective measure	Quality				No. of possible correlations
					Sample identification	Syndrome confirmation	Objective measure	Subjective measure	
Ashworth et al. 2013	Williams (24) Down (22)	Williams 1. 9.5 (6.1-12.6) 2. 50% Down 1. 9.4 (6.1-12.2) 2. 50%	Actigraphy	CSHQ Sleep diary*				CSHQ Diary	5/130
Esbensen & Hoffman (2018a)	Down (30)	1. 11.7 (6 -17) 2. 60%	Actigraphy	CSHQ Sleep diary*				CSHQ Diary	4/22
Esbensen & Hoffman (2018b)	Down (47)	1. 10.9 (6 – 17) 2. 62%	Actigraphy	CSHQ Sleep diary*				CSHQ Diary	45/70
Goldman et al. 2012	Angelman (15)	1. 6.5 (2-16) 2. 40%	Actigraphy PSG	CSHQ Sleep diary*			Actigraphy PSG	CSHQ Diary	7/99[3]
Merbler et al. 2018	Rett (13)	1. 9.4 (1-17) 2. 0%	Actigraphy	CSHQ Sleep diary**				CSHQ Diary	5/70
Gimenez at al. 2018[1]	Downs (54)	1. 39.6 (20-62) 2. 62%	Actigraphy PSG	PSQI ESS Sleep diary**			Actigraphy PSG	PSQI Diary	0[1]/80
Stores (2004)	Down (46)	1.2.6 (.6 – 4.8) 2. 48%	Actigraphy	MSPSQ					9/72[2]
Mason et al. (2011)	Williams (35)	1. 9.3 (2-18) 2. 43%	PSG	Parental sleep questionnaire					3/24

*diary data not reported, ** diary data reported at participant means, [1] mANOVA analyses performed by Gimenez at al. (2018), [2]Composite CSPS variable with actigraphy, [3]at a minimum, diary parameters not reported, [4] 1 = mean age in years & (range), 2 = % male
Abbreviations: Child Sleep Habits Questionnaire (CSHQ), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Modified Simmonds & Parraga Sleep Questionnaire (MSPSQ),

Table 1.6 Definitions by study of actigraphy variables included in Table 1.5

	Esbensen & Hoffman (2018a)	Esbensen & Hoffman (2019b)	Ashworth et al. (2013)	Goldman et al. (2012)	Merbler et al (2013)
Time in bed	-	Not given.	-	From lights out until lights on the next morning	-
Total sleep time	'Sleep period'. The time from when the child fell asleep to when the child woke up, ignoring waking times within that period.	Minutes asleep after onset.	-	'Sleep duration' The sum of all sleep epochs within the interval between the time set on the actogram for night-time sleep and morning wake time	Total sleep between sleep onset and offset once a person was in bed
WASO	-	Total wake time after sleep onset.	'Night waking duration'	The sum of all wake epochs during the sleep period	-
Total wake episodes	-	The number of blocks of contiguous wake epochs (30 second intervals).	'Night waking' Number of.	-	-
Sleep efficiency	The percent of the sleep period that the child spent in sleep.	Not given.	-	-	The percent of time in an interval that the person is sleeping, calculated as [time asleep/ (total interval time—invalid time) × 100]
Assumed sleep time	-	-	Time from sleep onset to offset.	-	-
Sleep latency	-	-	Time from bedtime to sleep start.	The time required for sleep onset after lights out (first attempt to go to sleep)	The time it takes to fall asleep from lights out
Fragmentation	-	-	An indication of restlessness where a higher figure denotes increased restlessness	Captures all movement regardless of the intensity of the movement.	-
Daytime sleep	-	-	-	-	The amount of time spent asleep when parents report a nap of at least 10 min
Sleep onset	-	-	-	-	Not given.

Wake After Sleep Onset (WASO)

Table 1.7 Characteristics and quality ratings of additional literature where concordance analyses were not undertaken, with the number of possible concordance correlations.

Study	Syndrome (*n*)	Participant Information[2]	Objective measure	Subjective measure	Quality				Possible correlative analyses
					Sample identification	Syndrome confirmation	Objective measure	Subjective measure	
Allen et al. 2013	Angelman (5)	1. 5.6 (2 – 11) 2. 40%	Actigraphy	CSHQ Sleep diary*				CSHQ Diary	0/56
Arens et al. 1998	Williams (7)	1. 3.9 (2-9) 2. *	PSG	Telephone survey					0/4[4]
Breslin et al. 2014	Down (38)	1. 9.6 (7-12) 2. 40%	PSG	CSHQ					0/9
Bruni et al. 1995	Down (10)	1. 11 (2-17) 2. 10%	PSG	Interview Sleep diary				Interview Diary	0/40[1]
De Leersnyder et al. 2001	Smith-Magenis (7)	1. 9.8 (4-17) 2. 56%	Actigraphy	Sleep diary*					0/3[1]
Edgin et al. 2015	Down (29)	1. 3.5 (2.3-5.3) 2.72%	Actigraphy	CSHQ Sleep diary*				CSHQ Diary	0/45[1]
Gibbs et al. 2013	Prada-Willi (8)	1. 8.8 (7.1-10.7)[3] 2. 75%	Actigraphy	CSHQ Sleep diary* Daytime sleepiness questions				CSHQ Diary	0/104
Goldman et al. 2009	Williams (23)	1. 25.5 (17 – 35) 2. 52%	Actigraphy	ESS Sleep diary*				Diary	0/18

Study	Syndrome (*n*)	Participant Information[2]	Objective measure	Subjective measure	Quality				Possible correlative analyses
					Sample identification	Syndrome confirmation	Objective measure	Subjective measure	
Kaplan et al. 2019	Potocki-Lupski (23)	1. Not given. 2. 61%	PSG	CSHQ (n = 11)					0/18
Levanon et al. 1999	Down (23)	1. 4.8 (1-10) 2. 61%	PSG	Sleep quality q'aire*					0/5[1]
Mahon et al. 2014	MPS III (18)	1. 9.25 (2-15) 2. 63%	Actigraphy	CSHRS					0/54
Maris et al. 2016	Down (54)	1. 7.5 (5.4 – 11.6) 2. 55%	PSG	CSHQ					0/9[1]
McArthur et al. 1998	Rett (9)	1. 10.1 (4-17) 2. 0%	Actigraphy	Sleep diary					0/16
Sniecinska- Cooper et al. 2015	Williams (25)	1. 7.3 (4-11) 2. 48%	Actigraphy	CSHQ Sleep diary*				CSHQ Diary Diary	0/55
Stotko et al. 2017	Down (130)	1. 5.6 (3-24.4) 2. 60%	PSG (n = 102)	CSHQ					0/18
Trickett et al. 2019a	Angelman (20)	1. 9.43 (not given) 2. 40%	Actigraphy	MSPSQ, ESS FISH, Sleep diary				MSPSQ Diary	0/91
Trickett et al. 2019b	Smith Magenis (20)	1. 8.7 (4-15) 2. 45%	Actigraphy	MSPSQ, ESS FISH, Sleep diary				MSPSQ Diary	0/91
Zhdanova et al. 1999	Angelman (13)	1. 6.5 (2-10) 2. 30%	Actigraphy	Sleep diary*					0/6

*data not reported, [1] at a minimum, questionnaire/diary/PSG variables not given, [2] 1 = mean age in years & (range), 2 = % male, [3] Median & IQR [4]only items relating to sleep parameters included

Abbreviations: Child Sleep Habits Questionnaire (CSHQ), Epworth Sleepiness Scale (ESS), Children's Sleep Habits Rating Scale (CSHRS), Modified Simmonds & Parraga Sleep Questionnaire (MSPSQ), Pediatric Daytime Sleepiness Scale (PDSS), Family Inventory of Sleep Habits (FISH)

1.4.2 Measures

1.4.2.1 Objective

Within the studies identified, 69% used actigraphy (k = 18) and 38% used polysomnography (k =10) as an objective measure of sleep. Two studies (Goldman et al., 2012 & Gimenez et al., 2018) employed the use of both techniques.

1.4.2.2 Subjective

Half of the studies used the CSHQ (50%, k = 13) as a subjective measure of sleep quality. Sleep diaries were almost exclusively used alongside actigraphy (k = 18), with the exception of Bruni et al., (1995), who combined a sleep diary with PSG data. The use of diary was frequently referenced as a tool to clean artifact from the actigraphy data, and, as such the majority (79%) of studies did not report their sleep diary data. Some partial reporting of diary data was observed in six of the studies which included group-level means and some individual parameters.

1.4.3 Overall quality of the literature

In most studies (k = 18), participants were recruited from a single non-random sample, achieving a rating of 'adequate'. Six of the studies used multiple non-random samples and the remaining two studies did not report how participants were identified. Where reported, most studies (k = 15) were rated 'excellent' in their methods of confirming syndrome diagnoses, either by means of genetic testing or commonly accepted diagnostic criteria, strengthening internal validity. Three studies achieved an 'adequate' rating for reporting a clinical diagnosis confirmed by a generalist. The remaining studies (k = 8) either did not confirm or report a clinical diagnosis.

1.4.3.1 Quality of subjective measurement

Most studies (*k* =16) used a subjective measure which had been validated for use in intellectual disability or syndrome population(s). Five studies were assigned a rating of 'poor' for their use of unvalidated surveys or singular focussed questions. Of those studies using sleep diaries, most received a 'poor rating' (*k* = 8) owing to these data not being reported within the published study. Four studies received an 'adequate' rating for their inclusion of some partial data report. Four studies met the criteria for being of 'good' quality and no studies using sleep diaries were rated as 'excellent'.

1.4.3.2 Quality of objective measurement

All studies using PSG measurement were assigned a rating of 'excellent' for their adherence to recognised PSG guidelines. However, quality of actigraphy studies was more variable. Across all studies, 18 used actigraphy as an objective measure of sleep. Appendix A provides the specific actigraphy criteria against which each study was rated with their corresponding scores. Most studies were rated as 'poor' (*k* = 8). Seven studies were awarded an 'adequate' rating and the remaining three were rated as 'good'. Most studies used either wrist or ankle placement for the actiwatch, provided definitions of the actigraphy variables and placed watches on participants at least one hour prior to bedtime. Only four studies explicitly stated that a minimum of five nights of data had been included in analysis for all participants (Gibbs, Wiltshire, & Elder, 2013; Mahon et al., 2014; Esbensen et al., 2018b & Trickett et al., 2019a). Two of the studies (Trickett et al., 2019a & Trickett et al., 2019b) reported using a concurrent sleep diary with actigraphy which included recommended parameters. Similarly, few studies described when participants were instructed to press the activity marker (Gibbs. Wiltshire, & Elder, 2013; Trickett et al., 2019a & Trickett et al., 2019b) or used manual scoring (Goldman, Malow, Newman, Roof, & Dykens, 2009; Goldman et al., 2012 & Mahon et al.,

2014). Six studies included some description of how data were cleaned. None of the studies provided a clear definition of how missing data were handled and most studies did not refer to interrater reliability of actigraphy scoring.

1.4.4 Studies reporting correlational data

A small number of studies *(k* = 7) included correlational data between an objective and subjective measure of sleep, insufficient for statistical meta-analysis. The characteristics of these studies alongside quality ratings are presented in Table 1.5 with a summary of concordance findings between actigraphy and CSHQ data from five studies provided in Table 1.8. The first finding of note is that the reporting of data across these studies was highly varied, possibly reflective of concordance between measures of sleep not being the primary research aim of the studies. Goldman et al., (2012) conducted Spearman rank correlations between actigraphy variables and the CSHQ, only values with $r > .50$ and $p < .001$ were reported by the authors. Merbler, Byiers, Garcia, Freyma, & Symons, (2018) limited their correlations to actigraphy with CSHQ total score, omitting CSHQ subscales and only presenting statistical data from their single significant finding[5]. Ashworth et al., (2013) presented five correlations between analogous actigraphy and CSHQ variables, again not reporting those that were non-significant. However here, Ashworth et al., did report their data for 'Sleep Latency', highlighting a trend towards agreement and noting their hypothesis that the variables would correlate. Esbensen & Hoffman (2018a) reported all available data for concordance analyses between actigraphy and the CSHQ but of note chose only to include two of the CSHQ subscales in their analysis; duration and parasomnias. The only study to report correlations for all

[5] When directly contacted the lead author provided statistics for non-significant correlations.

subscales of the CSHQ with each actigraphy parameter was Esbesnsen & Hoffman (2018b) who reported their data in full.

The second finding of note is the absence of any clear patterns of agreement across the datasets. There were three variable pairs where one study reported a significant positive correlation and one or more of the other studies reported a non-significant finding. These were 'Actigraphy WASO x CSHQ Sleep Duration', 'Actigraphy Total Sleep Time x CSHQ Night Waking' and 'Actigraphy Total Sleep Time x CSHQ Parasomnias'. There were however several variable pairs where two of the studies report non-significant correlations, as shown in Table 1.8. There were also some differences in the ways each study defined their sleep parameters, detailed in Table 1.6. A visual inspection of Table 1.6. also makes it clear that several definitions were not reported.

In addition to the studies presented in Table 1.8, three additional papers reported correlational data using other measures. Gimenez et al., (2018) used a mANOVA analysis to report diary data showing significantly shorter estimates of both 'Sleep Latency' and 'WASO' compared to PSG whereas 'Time in bed', Total Sleep Time' and 'Sleep Efficiency' were estimated as significantly longer (or higher in the case of latency) by sleep diaries. In comparing diary data to actigraphy, diary data was found to give a significantly longer estimate of 'Total Sleep Time' and increased 'Sleep Efficiency' but a shorter estimate of WASO. Stores (2004) used the MSPSQ to quantify difficulties with settling, night waking, early waking and sleeping with parents into a Composite Sleep Problem Score (CSPS) which was not found to correlate significantly with any of their included actigraphy variables (inc. Total Sleep Time, Efficiency, & WASO) Finally, Mason (2011) reported a non-significant correlation between parental reports of both restlessness and arousal via a sleep questionnaire and 'Sleep Efficiency' as measured by PSG.

In summary, the data reported on concordance between objective and subjective sleep variables did not provide a clear or consistent indication of concordance for these methods in people with neurogenetic syndromes.

Table 1.8. Summary of correlational findings between actigraphy variables and CSHQ subscales, coded as correlation of zero (0), positive correlation (+), negative correlation (-).

		Actigraphy								
		Time in Bed (min)	Total Sleep Time (min)	Total WASO (min)	Total Wake Episodes (#)	Sleep Efficiency (%)	Assumed Sleep Time (min)	Sleep Latency	Fragmentation	Daytime Sleep	Sleep Onset
CSHQ	**Bedtime Resistance**	0[1]	NS[1]	NS[1]	NS[1]	NS[1]					
	Sleep Onset Delay	0[1]	NS[1]	NS[1]	NS[1]	NS[1]		NS[3]	–[4a*]		
	Sleep Duration	NS[1]	NS[1,2]	+[4a*] NS[1]	NS[1]	NS[1,2]	+[3*]		+[4b*]		
	Sleep Anxiety	–[4a*] NS[1]	NS[1]	–[4a*] NS[1]	NS[1]	NS[1]					
	Night Waking	NS[1]	+ [4b*] NS[1]	NS[1,3]	NS [1,3]	NS[1]					
	Parasomnias	NS[1]	+[4b*] NS[1,2]	+[1*]	+[1*]	NS[1, 2]					
	Sleep Disordered Breathing	NS[1]	NS[1]	NS[1]	NS[1]	NS[1]					
	Daytime Sleepiness	NS[1]	NS[1]	NS[1]	NS[1]	NS[1]					
	Total score	NS[1]	NS[1,5]	NS[1,5]	NS[1]	NS[1,5]		NS[5]		+[5*]	

*p <.05, NS = non-significant finding

[1] Esbensen & Hoffman (2018b)
[2] Esbensen & Hoffman (2018a)
[3] Ashworth et al,. (2013) (all three groups)
[4a] Goldman et al., (2012) Actigraphy on PSG night. *Only values with $r_s > .5$ and $p < 0.001$
[4b] Goldman et al., (2012) Actigraphy- in home. *Only values with rs > .5 and p < 0.001
[5] Merbler et al., (2018)

1.4.5 Possible concordance correlation analyses

Tables 1.5 and 1.7 show the number of potential concordance correlation analyses that could have been performed, derived from the data each study reported to have collected. Of a total 1,209 possible correlations, only 71 were reported, equating to 6% of total available concordance analyses. In summary, only a very small proportion of the possible correlations were conducted and reported.

1.5 Discussion

This review aimed to examine concordance between objective and subjective measures of sleep in people with neurogenetic syndromes, groups at particularly high risk for sleep difficulties and thus warranting attention in areas of both sleep assessment and intervention (Agar et al., 2021; Johnson, 1996; Quine, 1991; Rzepecka at al., 2011; Wiggs & Stores, 1996). A comprehensive, systematic search of the literature was undertaken. Where possible, completed concordance correlation analyses were extracted. The literature was considered for its overall quality and application of subjective and objective sleep measures. The results from a small group of studies reporting correlation data gave an incomplete and mixed picture of concordance between CSHQ subscales and actigraphy parameters. The number of additional correlation analyses possible based on data collected in each study was also explored, demonstrating that there were substantial data available to inform concordance, but that studies had not consistently explored or reported these analyses. A detailed examination of each study showed the potential for a much broader examination of concordance between measures based on the data collected. Actigraphy was the more favoured objective measure, though the quality of its application as reported was predominantly rated as less than 'good' based on the quality criteria applied.

Summary of findings

The search returned a relatively small number of papers, supporting the assertion that sleep and sleep assessment methods are a relatively under-researched area in neurogenetic syndromes. Most of the studies (68%) used actigraphy as the objective measure, likely demonstrative of it being a more accessible and better-tolerated method than PSG for use with these populations. In terms of quality, all the studies using PSG received an 'excellent' rating, likely owing to the existence of standardised guidelines available to reference and guide

practice in research. For actigraphy, quality was much more mixed with studies falling across the categories of 'poor', 'adequate' and 'good'. No studies achieved a rating of 'excellent'. Three studies were rated as 'good' (Gibbs et al., 2013; Goldman et al., 2009; McArthur et al., 1998) and here the specific criteria met to achieve this also varied. It is important to acknowledge however that assigned ratings of 'poor' quality may have been due to reporting omissions, possibly due to assessment methodology not being the primary aim of most studies. Sleep diaries were primarily used as an adjunct to actigraphy and in most studies these data were not reported, possibly seen as irrelevant when used to support an objective method viewed as more robust. However, diaries can be a useful tool by which to capture night by night subjective perception of sleep (Mazza, Bastuji, & Rey, 2020). Reporting of diary data would also have allowed for meta-analytic calculations of concordance between methods. As such, future studies should seek to report diary data fully when collected in sleep assessments.

The search criteria used in this review were broad; however only six studies were found to have reported any data where concordance analyses had been applied. This creates a problem for clinicians and researchers alike who are striving for the best understanding of sleep in these groups, in order to implement the most effective treatments and interventions. At present, a reliance on findings from typically developing cohorts exists, such as a general trend for subjective methods to overestimate 'Total Sleep Time' relative to actigraphy, when relationships could be quite different for syndrome groups where varying sleep profiles and causal mechanisms of poor sleep exist (Agar et al., 2021). Interestingly, it is clear from the remaining studies included in this review that the possibility within this body of literature exists to be able to give a much more comprehensive understanding of concordance than that which can be presented here.

Of the six studies in which correlational data were reported between actigraphy and CSHQ, across only four genetic syndromes, it was difficult to draw any conclusions owing to the variability in reporting and incomplete data sets. Only a very small number of significant correlations were reported, and there were no instances where these findings were replicated by a significant result in any other study. As a tentative suggestion in line with a biopsychosocial model of sleep, it is possible that a lack of concordance between assessment methods here and in the broader literature is representative of the fact that different assessment methods are capturing different, albeit related aspects of sleep. For example, objective methods such as PSG are likely to have higher accuracy in delineating biological aspects of sleep, such as circadian driven sleep timing, whereas subjective methods may provide more insight into psychological or social aspects of sleep assessing elements of parenting practice and subjective wellbeing. Such variability in this review may relatedly be due to actigraphy recording numerical data whereas CSHQ subscales elicit parental perceptions of their child's sleep. In addition, there were a small number of participants included, a range of syndromes with varying sleep profiles, subtle differences in parameter definitions, variance in the methods with which actigraphy was applied and data were potentially collected over different time periods. In addition, whilst the samples here were broadly comparable in terms of participant sex, five of the six data sets were drawn from child samples and are as such not representative of sleep data across the life span. Of the possible concordance correlations across the data sets, only 6% were computed. In addition, a substantive amount of data reported to have been collected was not reported. The provision of these correlations, or even the full sets of raw data would allow for important meta-analytic work in rare syndromes.

Strengths and limitations

This systematic review was conducted with rigour and in line with PRISMA guidelines, with the exception that, due to the scope of the research and available resources, search results were not double screened for eligibility which would have strengthened confidence in the review accurately capturing all available evidence. The current review can be merited for its novelty, no other reviews to date have systematically examined concordance between sleep measures across neurogenetic groups and this review highlights the lack of research attention this area has received. The search criteria were robust and the broad term of 'sleep' was selected to be overly inclusive and minimise the risk of omitting relevant literature, notably only one additional study was yielded from backward searching. However, it is acknowledged here that additional sleep related search terms search as 'circadian rhythm' and 'nocturnal' may have produced additional papers for inclusion. Within the quality criteria, PSG was evaluated in terms of adherence to established guidelines, distilling these into individual sub criteria may have allowed for a more detailed examination of quality more in line with the approach taken to the actigraphy quality.

Recommendations for future research

It is clear from the data available here that much more research is needed to establish concordance between the range of objective and subjective methods of sleep assessment that are used within neurogenetic syndrome groups. As such, future research should be considered.

First, a greater volume of research examining concordance between objective and subjective measures of sleep would be an asset to the field. In particular, researchers would be well-placed to continue looking at a range of neurogenetic syndromes across the life span before moving towards between-group comparisons, given existing research has already shown that

sleep profiles differ across syndromes. Of the 21 syndromes included in the searches here, only nine were represented in the reported literature. Research conducted in Down syndrome was disproportionately over-represented, featuring in 12 papers, more than double that of the second most featured syndrome, Williams syndrome (k = 5). There was also a heavy skew towards paediatric samples, with only three of the studies included here drawing from an adult sample. Larger sample sizes would also increase statistical power and reduce the probability of concordance studies incorrectly accepting null hypotheses. In this review, sample sizes for studies reporting correlations were small (n = 13-54).

Second, there was significant variation in how actigraphy was applied across the studies. Areas of inconsistency were whether the study used a concurrent sleep diary, whether actigraphy data were reported to have been cleaned and whether the study clearly reported how many nights of data were included in analysis. Clearer, more detailed reporting of actigraphy application would contribute towards the development of standardised guidance for the use of actigraphy in rare syndrome groups, the existence of which may promote a more consistent application of actigraphy as an assessment tool. Combined research and clinical practise guidelines on the use of actigraphy with genetic syndromes would enable clinicians to have confidence that actigraphy was being applied with consistent methods across both domains. This would allow clinicians to generalise from research findings more fully and contextualise their own clients' assessment results. The development of such guidelines is a research priority for the field. Guidelines for actigraphy may also support the adoption of standardised definitions for sleep parameters. Currently, one challenge for researchers investigating sleep is the range of ways in which sleep parameters are defined as evidenced in the variation in definitions observed in this review. For example, for 'Sleep Latency', Merbler et al., (2018) defined this as 'time it takes to fall asleep from lights out' whereas Goldman et al., (2013) add 'first attempt

to go to sleep' suggesting that latency was calculated from the first-time lights are turned out, a detail missing from Merbler et al., which could lead to ambiguity as to when 'Sleep Latency' starts from. In defining 'Total Sleep Time', the definitions of Esbensen & Hoffman (2018a), Goldman et al., (2012) were broadly comparable whilst both Esbensen & Hoffman (2019b) and Merbler et al., (2018) omitted to detail how periods of waking were treated in relation to 'Total Sleep Time'. For variables to be considered truly analogous and for concordance estimates to be valid, there is a need for standardised definitions of sleep parameters which are operational across groups.

Finally, it would be of benefit for authors to offer more transparency and detailed reporting of sleep assessment methods and sleep datasets. This would allow for robust replicability and would support further reviews to make accurate quality interpretations. Standardising the inclusion of diary data in publishing would also provide additional useful information. Where studies did compute correlation analyses, reporting was often limited to a statement of 'non significance' with exact *p* values and effect sizes absent. It would be useful for researchers here to align with open science and move towards open datasets that can be shared and combined. Concordance estimates could then be calculated in secondary analysis and pooled across studies, strengthening the current knowledge base. This is particularly useful and important here given the rarity of some neurogenetic syndromes. In the context of current scientific debate over the usefulness of *p,* Di Leo & Sardanelli (2020) reiterated the American Statistical Association's position that authors should provide the exact value of *p,* treating it as a continuous quantity. Reporting statistical results in full would allow trends for significance to be identified and future studies to focus their attention in these areas to establish further clarity. Effect sizes are also crucial for meaningful interpretation of data with the American Statistical

Association (2016) also warning firmly against basing conclusions solely on statistical significance.

Recommendations for clinical practice

Clinicians should acknowledge that objective and subjective measures may not have good concordance, in part due to their measuring different facets of 'sleep' in line with an understanding of sleep as a biopsychosocial process. There is no concrete universal definition of 'sleep', and its definition is therefore typically defined by the measure which is being used. For example, actigraphy is considered a proxy measure given that it looks to accelerometer and light data to denote various 'sleep' parameters. Subjective measures of sleep, particularly in the field of neurodevelopmental research, are most often completed by informant and can therefore be better thought of as measuring parental/caregiver perceptions of sleep. With a larger number of studies, future reviews have the potential to take a more detailed look at concordance, beyond the scoping data provided here. Given the lack of data available to evidence concordance, and the successful application of actigraphy in these groups, clinicians may also wish to augment their subjective measurement of sleep with actigraphy. Clinicians need to be mindful of this potential for poor concordance when selecting measures for assessing for sleep disorders and implementing subsequent support until a much clearer picture can be established.

To summarise, this review examined concordance between objective and subjective measures of sleep assessment. The results highlighted that the computing or correlation analyses between these data types is scarce in the field of rare genetic syndromes though the potential for a more detailed picture exists. Where present, findings vary considerably. Actigraphy was found to be the dominant objective measure with considerably variability in its reported application. Additional research across the lifespan from a wider pool of syndromes is

warranted. This, alongside enhanced reporting would allow for both research and clinical guidelines for actigraphy to be developed alongside a better understanding of sleep assessment. It is only with a robust and thorough assessment that we can accurately formulate a given difficulty, that is what is driving and maintaining the problem with sleep. With this knowledge we can then select and tailor the most appropriate interventions in line with a given formulation and aim to better the lives of these groups and their families.

CHAPTER TWO

Do different methods of sleep data collection and data management affect sleep parameters across neurogenetic syndromes?

2.1 Abstract

Background: Sleep has important implications for wellbeing. For children with neurogenetic syndromes, sleep difficulties are highly prevalent. Here, actigraphy is an accessible means by which to measure sleep. Cleaning artefact from actigraphy data using adjunctive diary data is common. No previous research has looked at the impact of such data management processes in neurogenetic syndrome populations, or whether the data cleaning processes produce differential impacts across groups. Previous reports of concordance between parental reported diaries and actigraphy datasets in these groups have been inconsistent.

Methods: In a secondary analysis, a two-way mixed ANOVA of diary vs. autoscored actigraphy vs. cleaned actigraphy was completed across three groups of children: children with Angelman syndrome, children with Smith-Magenis syndrome and Typically Developing children.

Results: Overall differences between autoscored and cleaned actigraphy data were observed on a number of sleep parameters. Some preliminary data for the cleaning protocol having a differential impact across groups were also returned. Diary data did not concord well with actigraphy data for several parameters but here differences appeared broadly static across groups.

Discussion: Hypotheses for the causes of the identified differences are provided. The implications for both research and clinical settings are discussed. Additional research with larger sample sizes will enable a clearer picture of the impact of cleaning actigraphy data to emerge.

2.2 Introduction

The importance of sleep

Sleep is essential for both cognitive performance and physical health. Cognitively, sleep has been shown to impact on learning, memory, behaviour, mood, attention and impulse control (Harvey, 2009; Stickgold, 2005; Stores, 2014; Vriend, Davidson, Corkum, Rusak, Chambers, & McLaughlin, 2013). From a physical health perspective, insufficient sleep can lead to problems with both metabolism (Sharma & Kavuru, 2010) and immune function (Beccuti & Pannain, 2011; Besedovsky, Lange, & Born, 2012). Poor sleep has also been linked to risk for cardiac problems (King, Knutson, Rathouz, Sidney, Liu, & Lauderdale, 2008) obesity (Hart, Cairns, & Jelalian, 2011) and Type II diabetes (Knutson, Ryden, Mander, & Van Cauter, 2006).

Although the impacts of poor sleep for children with neurodevelopmental disorders are less well understood than for typically developing children, it is evident that in such groups, poor sleep may result in a higher frequency of behaviours that challenge (O'Reilly, 1995) and increased carer stress (Chu & Richdale, 2009). Despite the clear, negative consequences of poor sleep, the finer details of how to assess, formulate and intervene for sleep difficulties remains to be explored in sufficient detail.

Prevalence of poor sleep

The prevalence of sleep disorders in typically developing children is estimated at 6-47% (Agar, Oliver, Trickett, Licence, & Richards, 2020; taken from Calhoun, Fernandez-Mendoza, Vgontzas, Liao, & Bixler, 2014; Johnson, Roth, Schultz, & Breslau, 2006; Liu, Liu, Owens, & Kaplan, 2005; Owens, 2008) and here difficulties are often temporary, specifically in relation to bedtime resistance and sleep initiation (Jenni, Fuhrer, Iglowstein, Molinari, & Largo, 2005). Variation in observed prevalence of sleep disorders can be attributed to varying definitions of 'sleep' and the use of varying methods of sleep assessment. For children with intellectual disability, prevalence estimates rise to 16-84% (Johnson, 1996; Quine, 1991; Wiggs & Stores, 1996). Recent evidence suggests that this may be largely driven by these groups including children with rare genetic syndromes. In a meta-analysis of sleep in those with and without intellectual disability, Surtees, Oliver, Jones, Evans, & Richards (2018) reported that prevalence differences between these two groups were only significant when specific genetic or developmental disorders were included within the intellectual disability population. In sum, children with intellectual disability are at increased risk of sleep difficulties and the inclusion of children with genetic disorders within this group may explain this increase, signalling the need for closer inspection of these groups.

A recent meta-analysis placed the prevalence of general sleep difficulties at 10-95% and specific sleep disorders at 25 – 39% across genetic syndromes associated with intellectual disability (Agar, Brown, Sutherland, Coulborn, Oliver, & Richards, 2021). Two syndromes with strong evidence for pronounced difficulties are Angelman Syndrome and Smith-Magenis Syndrome. In a systematic review, Tietze et al., (2012) cited Smith-Magenis syndrome and Angelman syndrome as being most at risk for sleep disturbance when compared to children with other genetic syndromes (prevalence of 100% and 48-70% respectively). In Agar et al.'s

2021 meta-analysis, evidence for 70% prevalence of sleep difficulties in Angelman syndrome was found across many published articles (n = 20) and prevalence for general sleep difficulty in Smith-Magenis Syndrome was placed at 95%, the highest of nineteen syndromes included in the review. In addition to the high prevalence estimates for sleep difficulties, there is also evidence that these syndromes confer risk for unique profiles of sleep disorder.

Sleep in Angelman Syndrome

Angelman syndrome is caused by abnormalities of the chromosome 15q11-13 region (Clayton-Smith & Laan., 2003). The behavioural phenotype includes frequent laughter which can occur out of 'appropriate' context, hyperactivity, and sleep difficulties (Clayton-Smith & Laan, 2003). Difficulties with communication are also prominent (Jolleff & Ryan, 1993), as is severe intellectual disability (Clayton-Smith & Laan., 2003). Consensus guidelines for Angelman syndrome cite unusual sleep-wake cycles and a reduced need for sleep as key features (Williams, 2005). In an actigraphy study, Trickett et al., (2019) reported that children with Angelman syndrome who had parentally reported sleep difficulties had earlier bedtimes and poorer 'Sleep Efficiency' than a typically developing control group, despite no between group differences in sleep hygiene. Attempts to understand such a unique profile of sleep difficulties within Angelman syndrome have led researchers to consider aspects of the behavioural phenotype including the association between sleep and movement of the body and high epilepsy prevalence (Bruni, Ferri, D'Agostino, Miano, Roccela, & Elia, 2004; Miano, Bruni, Elia, Musumeci, Verillo, & Ferri, 2005; Williams, 2005). In a recent review, Winsor, Richards, Bissell, Seri, Liew, & Bagshaw, (2021) further highlighted findings that children with epilepsy have reduced 'Total Sleep Time' and 'Sleep Efficiency' compared to those without epilepsy. However, what remains unclear is how these features may be impacting on the data

we derive from sleep assessment methods and the validity of subsequent conclusions we infer regarding sleep parameters in this group.

Sleep in Smith-Magenis Syndrome

Similarly to Angelman syndrome, Smith-Magenis syndrome is a rare genetic syndrome associated with very high levels of sleep difficulty. It is typically associated with a de novo deletion on chromosome 17p11.2, with a smaller number of cases attributable to a mutation of the RAI1 gene (Onesimo et al., 2021). Broadly speaking, Smith-Magenis syndrome is characterised by several features. Most individuals will have a mild to moderate intellectual disability (Greenberg et al., 1996), alongside defined facial features, speech delay, impulsivity, repetitive behaviours, and attention deficits (Smith, Dykens, & Greenberg, 1998). Research has also described difficulties with behaviours that challenge; Arron, Oliver, Moss, Berg, & Burbidge, (2011) placed prevalence of aggression and self-injurious behaviour in children with Smith-Magenis syndrome at 72.8% and 92.9% respectively. When looking at the specificity of sleep problems within Smith-Magenis syndrome, Trickett et al., (2019) concluded that 92% of children with Smith-Magenis syndrome experienced some form of severe sleep disturbance and argued it should therefore be considered part of the phenotype for this syndrome. In describing these sleep difficulties, Trickett et al., (2019) found children with Smith-Magenis syndrome experienced increased night waking and earlier morning waking than their typically developing peers. This pattern of variation in sleep parameters supports findings that children with Smith-Magenis syndrome experience an atypical circadian rhythm, attributed to an altered pattern of melatonin release (Chik, Rollag, Duncan, & Smith, 2010; De Leersnyder et al., 2001; Nováková, Nevsímalová, Príhodová, Sládek, & Sumová, 2012). De Leersnyder et al., (2001) report that for most children with Smith-Magenis syndrome, peak melatonin release occurs at

around 12pm. This has led to the suggestion that it is the pattern of melatonin release that is atypical, as regulated by circadian genes in this group, rather than an inversion of the circadian rhythm itself (Smith, Morse, Introne, & Duncan, 2019). Further suggestions for the drivers of poor sleep in Smith-Magenis syndrome are the presence of pain (Agar et al., 2020) and a desire for caregiver attention (Agar et al., 2020; Wilde, Silva, & Oliver, 2013), although the precise mechanisms are less well understood here and in need of further research.

People with both Angelman and Smith-Magenis syndromes display sleep profiles which are particularly divergent from typical sleep compared with individuals with more generalised intellectual disability. In addition, heterogeneity of these groups can be seen as held constant by the syndrome itself as opposed to other neurodevelopmental conditions such as Autism Spectrum Disorder. The profiles of sleep difficulty are divergent between Angelman Syndrome and Smith Magenis Syndrome and therefore likely attributable to different aspects of the physical and behavioural phenotypes. This, coupled with high prevalence of sleep difficulty provides risk-saturated exemplars within which to explore data cleaning and concordance within sleep measurement robustly, providing the rationale for the inclusion of these groups in the present study.

Sleep measurement

In considering sleep measurement, robust approaches are essential for describing sleep effectively across populations and advancing sleep research. Supporting those with neurogenetic syndromes and producing the best clinical outcomes requires implementing effective interventions which target poor sleep. Such interventions will combine a full

understanding of sleep characteristics with an effective means to evaluate whether an intervention is working satisfactorily. Both also require robust measurement methods.

Sleep measurement - Polysomnography

Polysomnography (PSG) as an objective tool is considered the 'gold standard' sleep assessment method across sleep disorders and robust, well-cited guidelines exist for its implementation from the American Academy of Sleep Medicine (2020). Polysomnography combines data from electroencephalogram (EEG) used to measure electrical activity of the brain, electrooculography, electromyography, cardiography and pulse oximetry (Esbensen & Schwichtenberg, 2016) to derive information of sleep stages and parameters such as latency, waking, and duration.

Engagement with polysomnography carries significant challenges for individuals with neurodevelopmental conditions, often taking place in an unfamiliar environment and requiring the use of equipment likely to trigger existing sensory difficulties. A single night of PSG may also not produce sufficient data to accurately inform on the variability of sleep quality within these groups. It is therefore particularly pertinent for these groups to have alternative assessment measures which are well understood with rigorous application and robust, replicable methods for handling data which are appropriate for the target population(s).

Sleep measurement – subjective questionnaires

Questionnaires, as a much less invasive subjective method, are often felt to be an accessible tool with which to assess sleep, particularly in the fields of intellectual disability and neurodevelopmental conditions. Subjective methods can as such be thought of as capturing sleep-related behaviours and the wider impacts of sleep difficulties, most often from an

informant perspective. Commonly applied questionnaires for people with neurodevelopmental conditions include the Modified Simonds and Parraga Sleep Questionnaire (Simonds & Parraga, 1982; Wiggs & Stores, 1996), the Epworth Sleepiness Scale (Johns 1991; Williams, Scheimann, Sutton, Hayslett, & Glaze, 2008) and the Child Sleep Habits Questionnaire (CSHQ) (Owens, Spirito, & McGuinn, 2000).

Sleep measurement - actigraphy

Actigraphy is a commonly used objective measure for sleep difficulties with people with neurodevelopmental conditions. Actigraphy is considered a proxy measure of sleep, in that it measures movement and light via an accelerometer, typically placed within a watch-like device and worn on the wrist or ankle. The proxy nature of actigraphy dictates that procedures must be implemented to address inevitable artefacts arising in data. Actigraphy data 'cleaning' is a process by which sleep periods, as produced by the actigraphy software, are manually adjusted based on additional sources of data, with artefacts removed. Typically, this comes in the form of a concurrent sleep diary and the requirement of parents/caregivers to press an event marker on the device as specified time points e.g., lights out. Such subjective data are then used to 'clean' the actigraphy output in a process commonly considered best practice (Fawkes et al., 2015). Follesø, Austad, Olsen, & Saksvik-Lehouillier, (2021) additionally note that sleep analysis within actigraphy data is performed within set rest intervals and it is therefore vital that such intervals are accurately defined. This is difficult with actigraphy, as its reliance on movement and light data make it hard for sedentary behaviour, rest and sleep to be distinguished. Subsequently, event markers and sleep diaries are used to corroborate or adjust the actigraphy data.

Concordance between objective and subjective sleep assessment methods

Objective and subjective sleep measurement are often used in conjunction. As described above, parental reported diary data is often used to remove artefact and 'clean' actigraphy data. In addition, both across and within neurogenetic syndrome populations there will be individual differences in how suitable a particular method is for a person. It is therefore important that there exists a robust understanding of where concordance between measures lies and where more caution must be exercised in interpreting and comparing assessment data. At present, concordance between objective and subjective sleep assessment methods has been scarcely researched in neurogenetic populations, though existing literature from broader neurodiverse populations gives a varied picture (Hodge, Parnell, Hoffman, & Sweeney, 2012; Wiggs, Montgomery & Stores, 2005). Findings discussed in Chapter One indicate that existing concordance data in neurogenetic syndromes are insufficient to derive robust conclusions about the concordance between subjective and objective sleep measurement in these groups.

Rationale for the present study

There are no best practice guidelines on how actigraphy should be implemented or consensus within the field, supported by Follesø et al.'s (2021) review which cited inconsistencies in how actigraphy data are managed. Indeed, a very small number of published articles acknowledge this process at all (See chapter one, section 1.4.3.2) or provide information as to the protocol followed. The exception is the recent paper from Follesø et al., (2021). Here, the authors developed and tested a graded method for defining rest intervals in the data. Their findings included statistically significant changes across all sleep parameters following application of the procedure which was found to have high agreement between scorers (ά =

.975 - .998). However, the data in Follesø et al.,'s work was sourced from healthy adult participants. Given the unique profile of sleep difficulties within neurodevelopmental populations it would not be appropriate to extrapolate such procedures without additional investigation.

The absence of routine reporting regarding data cleaning can lead us to infer that there is limited or no consistency with this process. This is problematic for researchers. Further, we know that there are differences between syndrome groups in terms of sleep profile which raises the possibility that actigraphy cleaning may have differential impact on sleep parameter data. For example, children with Angelman syndrome showing increased movement in sleep may be misinterpreted by actigraphy algorithms as wake whereas for children with Smith-Magenis syndrome, early morning waking may be missed by parents when recording concurrent diary information. If the ways in which we adjust data are differentially affecting some groups, then this may indicate that we are either under- or over-estimating variance between groups. Subsequently we may not be getting as accurate an understanding of the way sleep is operating as we could be. Clearly this then has repercussions for the types of support we put in place for those experiencing sleep difficulties. For children at increased risk of sleep difficulty, implementation of effective interventions for sleep difficulties is particularly reliant on precise clinical description of their already complex aetiology, which is in turn dependent on having robust assessment methods, including clear protocols for the handling of data which is already likely atypical and a solid understanding of the differences that may exist in parameter estimates derived from objective and subjective methodologies. This leaves us with the following question which forms the basis of the present study.

Research question

Does the application of an actigraphy data cleaning protocol differentially affect sleep parameters across different groups of children, and how do subjective diary data concord with both Autoscored and Cleaned objective actigraphy estimates?

Study objectives

Using data collected for a previous study of Typically Developing children, children with Smith Magenis Syndrome and Angelman Syndrome, this study has two sets of objectives.

Objective 1: To understand the impact of cleaning on actigraphy data

1.1 To determine if and how the cleaning protocol had an overall impact on the actigraphy data.

1.2 To identify if the impact of the cleaning protocol differed between children with Angelman Syndrome, Smith Magenis Syndrome and Typically Developing children.

1.3 To characterise the nature of any differences identified in 1.2.

Objective 2: To examine concordance between diary and actigraphy data

2.1 To identify overall concordance between diary and actigraphy estimates.

2.2 To identify differences in concordance between diary and actigraphy estimates between children with Angelman Syndrome, Smith Magenis Syndrome and Typically Developing children.

2.3 To describe the nature of any differences identified in 2.2.

2.3 Methods

Data were obtained from a larger pre-existing data set acquired as part of an ongoing programme of sleep research in children with neurodevelopmental conditions. This work has described sleep difficulties over time using a combination of actigraphy, questionnaires, biomarkers, and radio-frequency identification methods. Here, secondary analysis of the original actigraphy and diary data was conducted, to explore the impact of a cleaning protocol on the actigraphy data. For published works from this project and original descriptions of methods used see Trickett et al., (2019; Smith-Magenis Syndrome, SMS) and Trickett et al., (2020; Angelman Syndrome, ANG).

2.3.1 Participants

During the original data collection, participants with Angelman syndrome and Smith-Magenis syndrome were recruited in part from family support groups, via Angelman UK and through the Smith-Magenis Syndrome Foundation UK. Additional participants were recruited from an existing participant database held at the Cerebra Centre for Neurodevelopmental Disorders. The typically developing (TD) cohort were recruited using both social media and through the personal contacts of the research team. Demographic characteristics for all participants are reported in Table 1. Significant differences were noted in Vineland Adaptive Behaviour Scale (VABS) scores (Sparrow, Cicchetti, & Balla, 2005) and ability to walk unaided. The Smith-Magenis group showing a higher level of adaptive functioning compared to the Angelman group who also had significantly reduced mobility. The Typically Developing group had a higher proportion of males than either of the syndrome groups. There were no significant age differences between the groups.

Table 2.1 Demographic characteristics

	AS	SMS	TD	T/F/χ^2	df	P value
N	21	18	47	-	-	-
Age mean (SD)	8.62 (3.87)	8.61 (2.62)	7.77 (3.34)	.545	2	.582
Males n (%)	8 (38.1)	8 (44.4)	30 (63.8)	4.612	2	.100
Adaptive Behaviour Composite score VABS standard score mean (SD)	46.43 (9.13)	65.12 (10.43)	-	-5.887	36	<0.001
Able to walk unaided n (%)[a]	7 (35)	17 (100)	47 (100)	49.22	2	<0.001
Ever experienced tonic-clonic seizures	11 (52.4)	1 (5.6)	-	-	-	-
Ever experienced absence seizures	21 (100)	4 (22.2)	-	-	-	-
Ever experienced clonic seizures	4 (19)	-	-	-	-	-
Ever experienced myoclonic seizures	9 (42.9)	-	-	-	-	-
Ever experienced tonic seizures	3 (14.3)	-	-	-	-	-
Ever experienced atonic seizures	10 (47.6)	-	-	-	-	-
Ever experienced focal seizures	7 (33.3)	-	-	-	-	-
Ever experienced unknown classification of seizures	4 (19)	1 (5.6)	-	-	-	-
Using medication to aid sleep n (%)	12 (57.1)	12 (66.6)	1 (2.1)	-	-	-
Medication helpful to aid sleep[b]	10 (47.6)	10 (55.6)	1 (2.1)	-	-	-
Caregiver education[c]						
Fewer than 5 GCSEs or O Levels (Grades A-C), NVQ 1 or, BTEC First Diploma	2 (9.5)	2 (11.1)	1 (2.1)	-	-	-
5 or more GCSEs or O Levels (Grades A-C), NVQ 2, or equivalent	2 (9.5)	4 (22.2)	8 (17)	-	-	-
3 or more "A" Levels, NVQ 3, BTEC National, or equivalent	1 (4.8)	4 (22.2)	2 (4.3)	-	-	-
Polytechnic/university degree, NVQ 4, or equivalent	12 (57.1)	4 (22.2)	21 (44.7)	-	-	-
Masters/doctoral degree, NVQ 5, or equivalent	4 (19)	2 (11.1)	14 (29.8)	-	-	-
Family income [d]						
Less than £15,000	2 (9.5)	1 (5.6)	1 (2.1)	-	-	-

	AS	SMS	TD	T/F/χ^2	df	P value
£15,001 to £25,000	2 (9.5)	1 (5.6)	7 (14.9)	-	-	-
£25,001–£35,000	3 (14.3)	4 (22.2)	7 (14.9)	-	-	-
£35,001–£45,000	4 (19)	1 (5.6)	5 (10.6)	-	-	-
£45,001–£55,000	2 (9.5)	4 (22.2)	9 (19.1)	-	-	-
£55,001–£65,000	2 (9.5)	3 (16.7)	3 (6.4)	-	-	-
£65,001 or more	5 (23.8)	2 (11.1)	13 (27.7)	-	-	-

[a]One missing response AS group, one missing response SMS group
[b]One missing response AS group, one missing response SMS group
[c]Two missing responses SMS group, one missing TD group
[d]One missing response AS group, two missing responses SMS & TD groups
Post hoc analysis of ability to walk unaided involved pairwise comparisons using the z-test of two proportions with a Bonferroni correction. The proportion of children with Angelman syndrome who were not able to walk unaided was significantly lower than the Smith-Magenis or Typically Developing groups. The Typically Developing also contained significantly more male participants than the syndrome groups.

2.3.2 Measures

2.3.2.1 Background questionnaires

Information on participant age, gender and family environmental factors, such as income and education, were gathered through a caregiver completed background questionnaire. Information on seizure experiences and physical health was also collected.

2.3.2.2 Actigraphy

All participating children were provided with a Philips Respironics Actiwatch 2, which has a sampling rate of 32Hz paired with 30-second epochs. Whilst the device captures light data it does not incorporate this into its scoring algorithm. Sleep onset was denoted using the clock times at the beginning of the first ten minutes scored as sleep. The last ten minutes scored as sleep were described as sleep offset. A medium sensitivity setting (40 counts per epoch) was used to detect Wake After Sleep Onset (WASO). Default Actiware settings were used for the calculations of additional sleep parameters, known to have the largest polysomnography concordance. Such settings when applied to school-aged children have moderate specificity to detect waking (.69) coupled with high sensitivity to detect sleep (.94) (Trickett et al., 2019). Data taken from the actigraphy software with these settings prior to the application of a cleaning protocol is referred to as 'autoscored'.

2.3.2.3 Sleep diaries

Caregivers were asked to complete a paper sleep diary for each child taking part in the study. These are provided in Appendices B, C (weekday and weekend for Angelman & Smith-Magenis groups) and D (Typically Developing children). The diaries collected the following variables: 'Time Got in to Bed', 'Time Lights Off', 'Event Marker Accuracy', 'Estimated Sleep Onset', 'Morning Wake Time' and 'Time Got Out of Bed'. For the Angelman and Smith-

Magenis groups, diaries also included questions regarding daytime behaviour though these data are not included in the present study analyses. Further, these syndrome groups had different versions of the diary to complete, dependent on whether it was a weekday or weekend. Here, the wording of the behavioural items was subtly changed to indicate either 'before/after school' or 'behaviour in the morning/afternoon'. Caregivers across all groups were asked to detail any sedentary periods for their child after 18:00, daytime naps and times during which the actiwatch was removed. The purpose of this was to support the cleaning of the actigraphy data.

2.3.2.4 Sleep parameters

Table 2.2 presents both the objective sleep parameters derived from the actigraphy data and their analogous sleep diary variables. Where a diary composite variable has been calculated the formula is provided.

2.3.2.5 Vineland Adaptive Behaviour Scales, second edition (VABS-II, Sparrow, Cicchetti & Balla, 2005)

The VABS-II assesses children's adaptive ability and functioning across the domains of communication, daily living skills, socialisation and motor skills. It also enables age equivalents and standardised scored to be computed alongside an overall adapted behaviour composite, reported in Table 2.1. The data derived from the assessment permit the computation of age equivalents and standard scores by domain. A cross domain overall adaptive behaviour composite score can also be calculated, and it is these data that are reported in Table 2.1. A score >86 denotes typical functioning relative to chronological age with a score of ≤ 70 representative of deficit. To acquire the data presented here, a semi-structured interview using

the parent version of the VABS-II was administered by a researcher with parents of children in the Angelman and Smith-Magenis participant groups.

2.3.3 Procedure

Parents provided consent for the children to participate. Children were asked to wear an actiwatch for seven continuous nights. Prior to the start of the study, a member of the research team visited the home of the Angelman and Smith-Magenis syndrome participants. At this visit video equipment was installed to record children's night behaviour and parents were given guidance on how to complete sleep diaries and press the event marker on the watches (video data played no role in the current study). The actiwatch and sleep diaries were either collected or posted back to the research team at the end of data collection. For consistency, all data were collected during school term time.

2.3.3.1 Actiwatch placement

The actiwatch was worn on the wrist by all typically developing children. For the syndrome groups, children were permitted to wear the watch on their wrist or ankle owing to behavioural and sensory difficulties.

2.3.3.2 Cleaning Protocol

The actigraphy data from all participants were subjected to a cleaning protocol (See Appendix E). Artefacts were removed and 'bedtime' i.e., the beginning of the intended rest interval was taken from a combination of the sleep diary, event marker and automatically calculated rest interval. Conversely, the autoscored rest interval was used to identify sleep offset as it was felt parental reports of morning final wake time may be inaccurate given that parents

may themselves be asleep and children may be sleeping in a separate room. In the event that an additional 20 minutes after the end of the autoscored period were coded as sleep by the software but these occurred before the wake-up time noted in the sleep diary, intervals were manually extended to capture the entire sleep period. Inter-rater reliability for 20% of the lights out time data in the Angelman and Smith-Magenis groups were excellent; Angelman intra-class coefficient: .97 (CI: 94-99) Smith-Magenis group intra-class coefficient .99 (CI:.98-1.0). The intra-class coefficient for the TD group was good: .61 (CI: .29-.81) (Trickett et al., 2019).

Table 2.2: Sleep parameter definitions across data types

	Autoscored actigraphy	Cleaned actigraphy	Diary
Time Got in to Bed	The start of the automatically calculated rest interval according to Actiwatch default settings (medium sensitivity, 40 counts per epoch	Clock time child was put to bed with lights out, thus entering a 'restful' state. This was determined using the event marker, sleep diary and automatically calculated rest interval to avoid sedentary activity being included in the automatically calculated rest interval.	Parental clock time response to 'Time got into bed'.
Sleep Onset Latency	Time between time got in to bed and first sleep period (the first ten minutes scored as sleep after time got in to bed, according to actigraphy)	Time between time got in to bed and first sleep period (the first ten minutes scored as sleep after time got in to bed, according to actigraphy)	Parental clock time response to 'Estimated time taken to fall asleep'
Get Up Time/Time Woken	Clock time of the end of the final period of sleep in the morning	Clock time of the end of the final period of sleep in the morning	Parental clock time response to 'time woken'
Total Time in Bed	Time between time got in to bed and Get Up Time	Time between Time got in to bed and Get Up Time	'time out of bed' – 'time got in to bed'
Total Sleep Time	Total amount of time scored as sleep between sleep onset and Get Up Time	Total amount of time scored as sleep between sleep onset and Get Up Time	'wake up time' – 'lights out time' – 'total waking time' – 'time taken to fall asleep'
Sleep Efficiency	Percentage of total time in bed spent asleep: Total Sleep Time/ Total Time in Bed x 100	Percentage of Total Time in Bed spent asleep: Total Sleep Time/ Total Time in Bed x 100	Percentage of total time in Bed spent asleep: Total Sleep Time/ Time in Bed x 100
Wake After Sleep Onset	Number of minutes scored as wake after first period of sleep, according to Actiwatch default settings (medium sensitivity, 40 counts per epoch)	Number of minutes scored as wake after first period of sleep, according to Actiwatch default settings (medium sensitivity, 40 counts per epoch)	Sum of all waking parental recorded waking duration(s)

2.3.4 Data analysis

For each participant, autoscored 'not cleaned' actigraphy data were obtained direct from Actiware and exported into an additional database. This was then recorded alongside the cleaned data in order that both cleaned and autoscored actigraphy data in the form of a parameter mean and night-by-night data co-existed within a single database. Analogous parental reported sleep diary parameter means were also added. Where a participant did not have all three types of data for a given night, that night was omitted from analysis.

Data were analysed to address each of the aims of the study. Outliers, defined as +/- 1.5 IQR from the mean were removed for each variable prior to analyses[6] (See Appendix F for outlier box plots), for primary analyses ran prior to outlier removal see Appendix G. Each sleep parameter was examined using a Two-way mixed ANOVA, with Group (Angelman, Smith-Magenis, Typically Developing) as a between-subjects variable and Data Type as a within subject variable (Autoscored actigraphy, Diary, Cleaned Actigraphy). In the event of significant main effects, post-hoc comparisons were undertaken. For the current purposes, the key tests of interest relate to the main effect of Data Type – indicative of differing estimates based on method of data collection, and the interaction between Data Type and Group, indicative that means of data collection impacted estimates for different groups differently. Here, the main effects of Group were not a central focus, as controlled syndrome-level sleep differences from these samples are reported elsewhere (Trickett et al., 2019; Trickett et al., 2020).

Given the small sample sizes and subsequent limitations in power for the interaction effect, coupled with the knowledge that the participant groups included have differing sleep profiles, an a priori decision was made to examine each group separately, regardless of the

[6] Number of outliers removed within each parameter: Time Got in to Bed, n =1; Time Woken, n = 2; Onset Latency, n = 7; Total Sleep Time, n = 2; WASO, n = 3; Total Time in Bed, n = 1, Sleep Efficiency, n = 2.

significance of the interaction. This allows for examination of the impact of assessment method across each individual group. Here, in the event of trends in the data, these were explored with post-hoc tests as a means for generating hypotheses for future research, rather than providing statistical confirmation of a difference between data types.

The comprehensive analysis approach undertaken necessitated making a large number of comparisons. This in turn increased the risk of type-1 error, through increasing the probability of identifying a spurious effect. Identifying the "family of tests" over which to control for such comparisons is not straightforward – as correcting across every test in the whole analysis would significantly risk type-II error. Here it was equally crucial not to conclude that syndrome groups are equivalently affected, when evidence runs counter to this. An appropriate approach balances these factors (Lindquist & Meija, 2015). Ultimately, a conservative Bonferroni correction was applied. Within each parameter, up to nine comparisons were made: Autoscored vs. Cleaned, Cleaned vs. Diary and Autoscored vs. Diary, for each of the three groups. Therefore, for significance testing, $p < 0.006$ (.05/9) was used. Given the conservative nature of this choice, where $p < .05$, these were labelled as *trends* worthy of future consideration in research.

2.4 Results

Table 2.3 presents descriptive data of each sleep variable across the three groups. Tables 2.4 – 2.9 provide data for all analyses across all groups. Figure 2.8 gives a visual summary of data across all parameters ordered by presence or absence of an interaction effect.

Table 2.3: Descriptive statistics of each sleep variable across participant groups.

	Angelman			**Smith-Magenis**			**Typically Developing**		
	Autoscored actigraphy	Diary	Clean actigraphy	Autoscored actigraphy	Diary	Clean actigraphy	Autoscored actigraphy	Diary	Clean actigraphy
Mean (SD)									
Time Got in to bed (hr:min)	19:39 (1:44)	19:37 (0:53)	20:18 (1:04)	19:41 (1:38)	19:39 (1:17)	20:11 (0:51)	20:30 (1:11)	20:16 (1:01)	20:30 (1:09)
Time Woken/get up time (hr:min)	06:15 (1:38)	06:56 (0:43)	06:50 (0:57)	05:01 (1:11)	05:46 (0:46)	05:17 (1:05)	07:07 (0:38)	07:06 (0:28)	07:04 (0:31)
WASO (hr:min)	0:59 (0:29)	0:23 (0:21)	1:24 (0:48)	1:10 (0:24)	0:24 (0:33)	1:25 (0:41)	0:49 (0:16)	0:00 (0:00)	0:49 (0:16)
Total Time in Bed (hr:min)	09:18 (1:58)	11:27 (1:07)	10:23 (1:17)	08:55 (1:40)	10:19 (1:17)	09:05 (1:16)	10:01 (0:55)	10:56 (0:56)	10:09 (0:58)
Onset Latency (hr:min)	0:15 (0:11)	0:25 (0:22)	0:25 (0:25)	0:03 (0:02)	0:10 (0:05)	0:07 (0:06)	0:11 (0:09)	0:24 (0:19)	0:23 (0:23)
Total Sleep Time (hr:min)	07:27 (1:49)	10:05 (1:15)	07:57 (1:23)	07:24 (1:30)	08:39 (0:55)	07:13 (1:03)	08:39 (0:53)	10:07 (0:56)	08:35 (0:44)
Sleep Efficiency (%)	81 (6.3)	88 (8.5)	78 (7.8)	83 (4.2)	86 (8.2)	80 (6.4)	86 (4)	91 (5)	84 (5)

2.4.1 Time Got in to Bed

For 'Time Got in to Bed', there was a trend for a main effect of Group, $F(2,82) = 4.456$, $p = .015$, partial $\eta^2 = .098$, see Figure 2.1.There was a trend for a main effect of Data Type, $F(2,164) = 5.32$, $p = 0.008$, partial $\eta^2 = .061$, post-hoc comparisons suggested a significant difference of Diary < Clean, a trend for Autoscored < Clean, and no difference between Diary and Autoscored actigraphy data. There was not a significant interaction between Data Type and Group, $F(4,164) = 1.67$, $p = .169$, partial $\eta^2 = .039$.

There was not clear evidence that data collection and cleaning processes had significantly impacted estimates of 'Time Got in to Bed' across groups; planned comparisons within each group were also consistent with this (see Table 2.6)

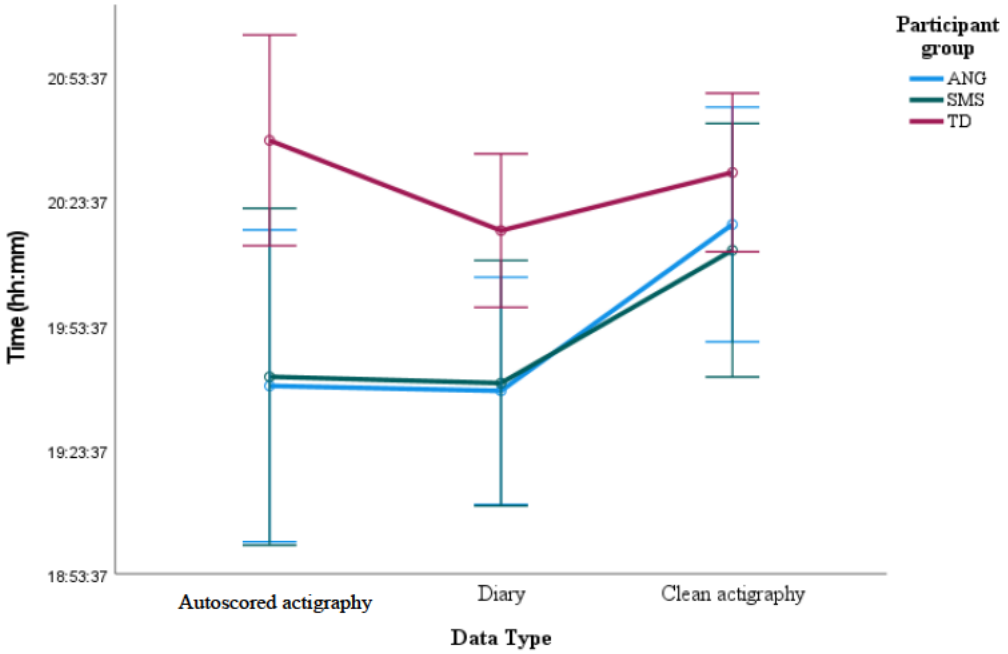

Figure 2.1: Time Got in to Bed by children with Angelman Syndrome, Smith Magenis syndrome and typically developing children, as measured by autoscored actigraphy data, cleaned actigraphy data and parent diary.

2.4.2 Time Woken

For 'Time Woken', there was a significant main effect of Group $F(2,81) = 39.53$, $p < .001$, partial $\eta^2 = .494$, Smith-Magenis < Angelman = Typically Developing[7], see Figure 2.2. There was also a significant main effect of Data Type, $F(2,162) = 11.56$, $p < .001$, partial $\eta^2 = .125$, Clean = Autoscored < Diary There was a significant interaction between Data Type and Group, $F(4, 162) = 4.57$, $p = .005$, partial $\eta^2 = .101$. The Smith-Magenis group showed a trend for an effect $F(2,34) = 4.6$, $p = .039$, post hoc comparisons showed a trend for Autoscored < Clean, Clean < Diary and no differences between Clean and Autoscored data. There were no significant differences for the Angelman and Typically Developing groups (see Tables 2.6 & 2.8).

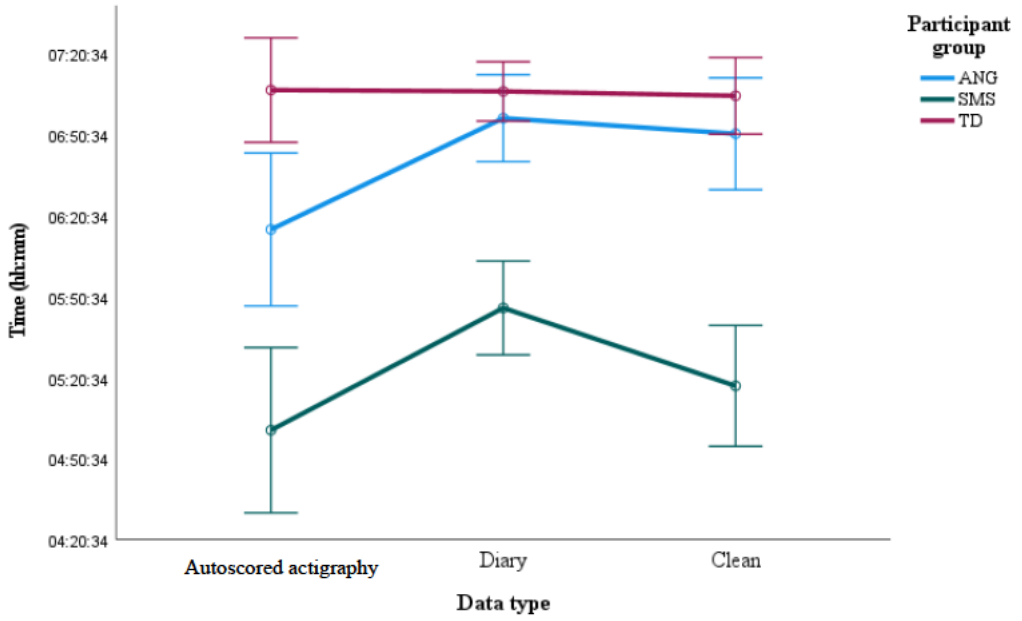

Figure 2.2: Time woken by children with Angelman Syndrome, Smith Magenis syndrome and typically developing children, as measured by autoscored actigraphy data, cleaned actigraphy data and parent diary.

[7] Throughout the results section, for post-hoc tests, significant differences, as defined in the methods section as $p < .006$, are indicated symbolically through the use of the less-than symbol (<). Trends in the data, $.006 > p > .05$, are reported in prose. Post-hoc comparisons that showed no difference, $p > .05$, are indicated through the equals symbol (=) or in prose, as appropriate.

2.4.3 Onset Latency

For 'Onset Latency', there was a trend for main effect of Group, $F(2,71) = 5.254$, $p = .007$, partial $\eta^2 = .129$, Smith-Magenis < Angelman = Typically Developing. There was a significant main effect for Data Type, $F(2,1142) = 9.73$, $p < .001$, partial $\eta^2 = .121$, Autoscored < Clean = Diary.

There was no significant interaction between Data Type and Syndrome Group, $F(4,142) = .715$, $p = .583$, partial $\eta^2 = .020$. A significant effect was found for the Typically Developing, $F(2,84) = 10.97$, $p < 0.001$, partial $\eta^2 = .207$, Autoscored < Clean = Diary , and Smith Magenis Groups, $F(2,24) = 7.92$, $p = .002$, partial $\eta^2 = .397$, Clean = Autoscored < Diary. There was a trend for an effect for the Angelman group, $F(2,34) = 3.64$, $p = 0.037$. Post hoc comparisons of data in the Angelman group showed a trend for Autoscored < Clean, a trend for Autoscored < Diary, and no differences between Diary and Clean actigraphy data. See Figure 2.3.

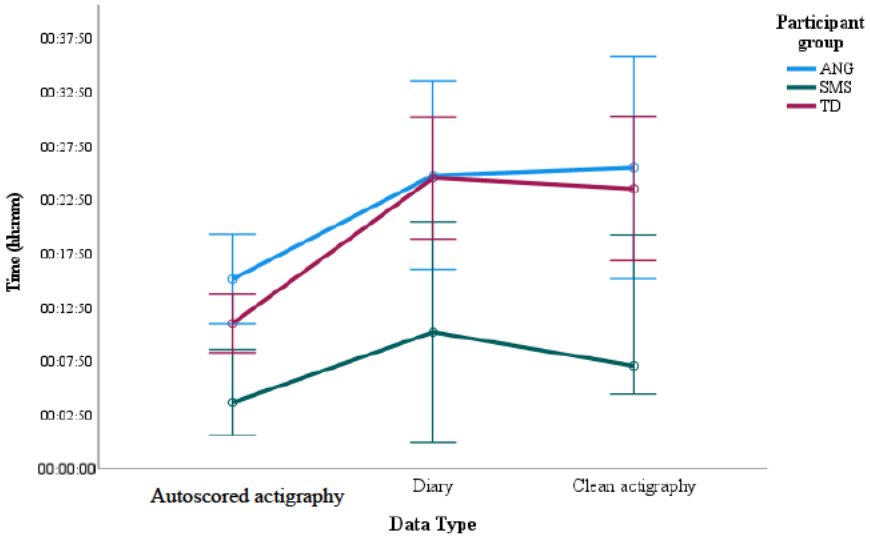

Figure 2.3. Onset Latency by children with Angelman Syndrome, Smith Magenis syndrome and typically developing children, as measured by autoscored actigraphy data, cleaned actigraphy data and parent diary.

2.4.4. Total Sleep Time

For 'Total Sleep Time', there was a significant main effect of Group, $F(2,81) = 14.87$, $p < 0.001$, partial $\eta^2 = .269$, Angelman = Smith-Magenis < Typically Developing. There was also a significant main effect of Data Type, $F(2,162) = 112.7$, $p < 0.001$, partial $\eta^2 = .582$, Clean = Autoscored < Diary.

There was a significant interaction between Group and Data Type, $F(4,162) = 4.67$, $p = .004$, partial $\eta^2 = .104$. The significant effect of Data Type was noted at the group-level within Angelman, $F(2,40) = 26.44$, $p < .001$ partial $\eta^2 = .569$, Smith-Magenis, $F(2,24) = 13.56$, $p < .001$ partial $\eta^2 = .444$ and Typically Developing groups, $F(2,88) = 199.64$, $p < .001$ partial $\eta^2 = .819$. All three groups following the same pattern on Clean = Autoscored < Diary according to pairwise comparisons. See Figure 2.4 for graphical representation.

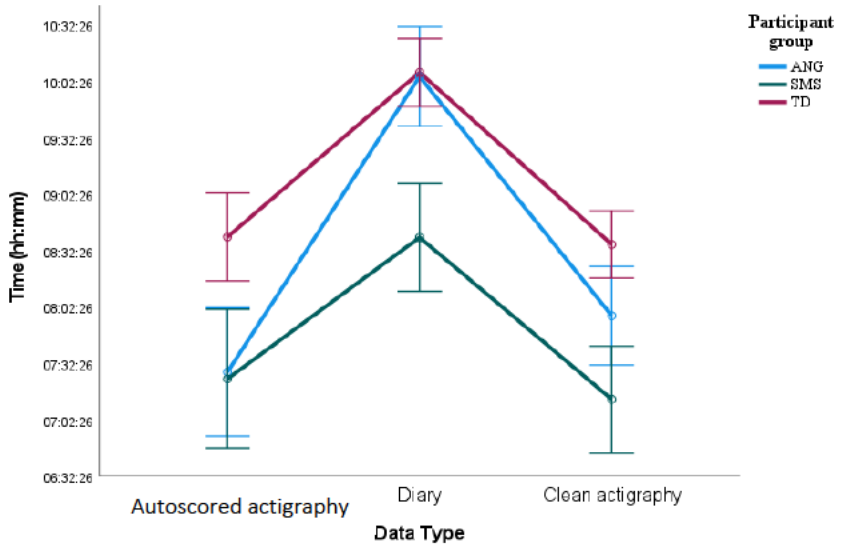

Figure 2.4. Total Sleep Time by children with Angelman Syndrome, Smith Magenis syndrome and typically developing children, as measured by autoscored actigraphy data, cleaned actigraphy data and parent diary.

2.4.5 Wake After Sleep Onset (WASO)

For 'WASO', there was a significant main effect of Group, $F(2,80) = 18.93$, $p < 0.001$, partial $\eta^2 = .321$, Typically Developing < Angelman = Smith-Magenis. There was also a statistically significant overall difference in 'WASO' across the Data Types $F(2,160) = 136.44$, $p < 0.001$, partial $\eta^2 = .630$, Autoscored < Clean < Diary.

There was a trend for an interaction, $F(4,160) = 2.79$, $p = .028$, partial $\eta^2 = .065$. There was a statistically significant effect of Data Type on 'WASO' for Angelman syndrome, $F(2,40) = 18.36$, $p < .001$, partial $\eta^2 = .479$, Diary < Clean = Autoscored; Smith-Magenis Syndrome, $F(2,34) = 26.35$, $p < .001$, partial $\eta^2 = .608$, Diary < Clean = Autoscored and the Typically Developing group, $F(2,86) = 379.52$, $p < .001$, partial $\eta^2 = .898$, Diary < Clean = Autoscored. Graphical representation is provided in Figure 2.5.

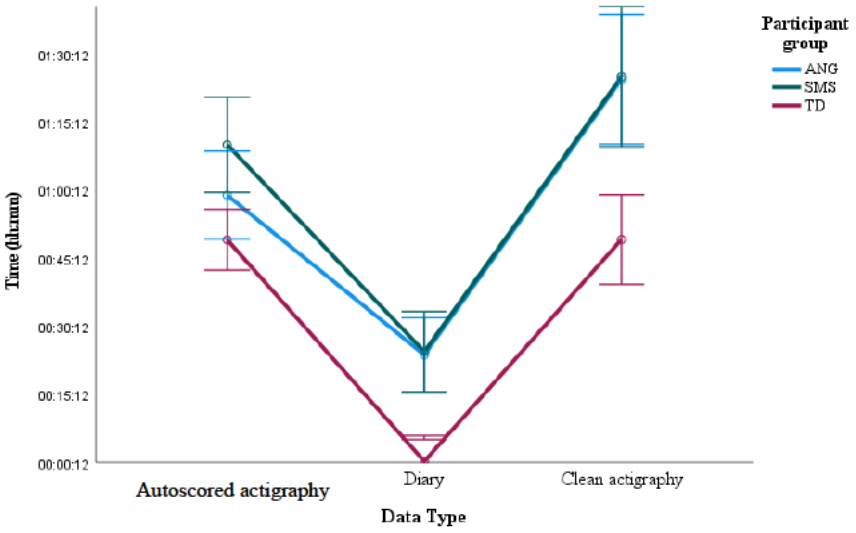

Figure 2.5. Wake After Sleep Onset (WASO) by children with Angelman Syndrome, Smith Magenis syndrome and typically developing children, as measured by autoscored actigraphy data, cleaned actigraphy data and parent diary.

2.4.6 Total Time in Bed

For 'Total Time in Bed', there was a significant main effect of Group, $F(2,81) = 6.07$, $p = 0.003$, partial $\eta^2 = .131$, Smith Magenis < Angelman = Typically developing. There was a significant main effect of Data Type, $F(2,164) = 40.62$, $p < 0.001$, partial $\eta^2 = .331$, Autoscored < Clean < Diary.

There was a significant interaction between Data Type and Group, $F(4,162) = 4.55$, $p = .005$, partial $\eta^2 = .101$. There was a statistically significant effect of data type on 'Total time in bed' for all participant groups: Angelman Syndrome; $F(2,40) = 15.22$, $p < .001$, partial $\eta^2 = .432$, Autoscored < Diary with a trend for difference between the Autoscored and Cleaned actigraphy data at $p = .024$.; Smith-Magenis Syndrome; $F(2,34) = 11.31$, $p = .001$, partial $\eta^2 = .4$, Clean = Autoscored < Diary; Typically Developing: $F(2,88) = 49.8$, $p < .001$, partial $\eta^2 = .531$, Clean = Autoscored < Diary.

Data are presented graphically in Figure 2.6.

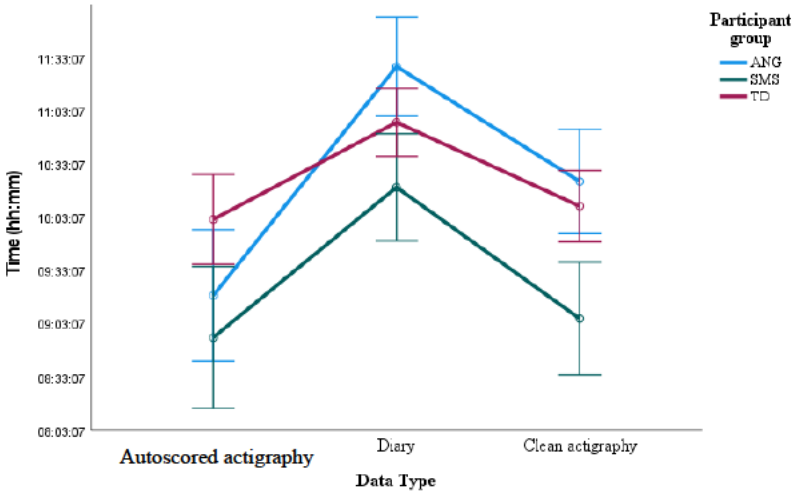

Figure 2.6: Total Time in Bed by children with Angelman Syndrome, Smith Magenis syndrome and typically developing children, as measured by autoscored actigraphy data, cleaned actigraphy data and parent diary.

2.4.7 Sleep Efficiency

For 'Sleep Efficiency', there was a significant main effect of Group, $F(2,79) = 14.44$, $p < .001$, partial $\eta^2 = .268$., Angelman = Smith-Magenis < Typically Developing. There was a significant main effect of Data Type $F(2,158) = 40.24$, $p = <.001$, partial $\eta^2 = .337$, Clean < Autoscored < Diary.

There was no significant interaction between Group and Data Type, $F(4,158) = .998$, $p = .390$, partial $\eta^2 = .025$. There was a statistically significant effect of Data Type on 'Sleep Efficiency' for Angelman Syndrome: $F(2,48) = 11.13$, $p = .002$, partial $\eta^2 = .369$, Clean < Diary = Autoscored and Typically Developing : $F(2,86) = 28.29$, $p < .001$, partial $\eta^2 = .471$, Clean < Autoscored < Diary groups. There was a trend for significance within Smith-Magenis Syndrome, $F(2,34) = 5$, $p = .031$, partial $\eta^2 = .227$, post hoc comparisons showed Clean < Autoscored, a trend for Clean < Diary and no differences between Diary and Autoscored Actigraphy.

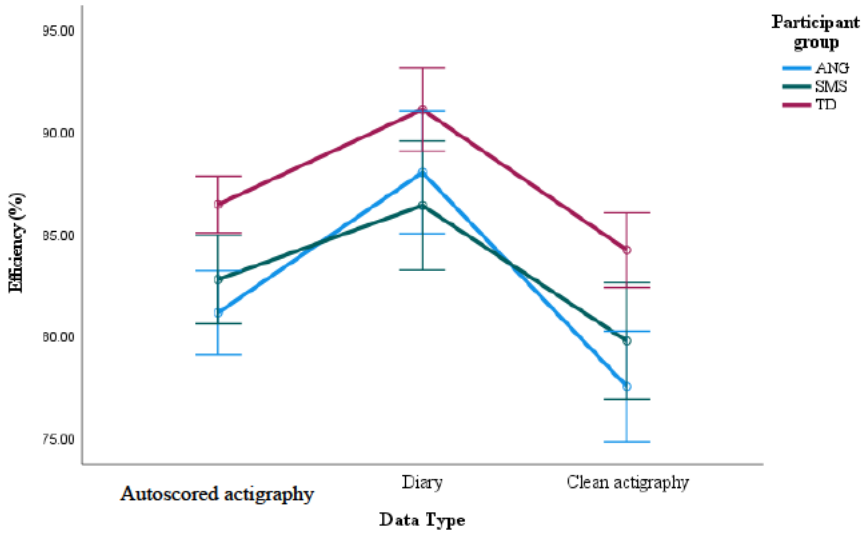

Figure 2.7: Sleep Efficiency by children with Angelman Syndrome, Smith Magenis syndrome and typically developing children, as measured by autoscored actigraphy data, cleaned actigraphy data and parent diary.

Table 2.4 Pairwise comparisons of overall sleep parameter differences between groups across data types

	Smith-Magenis **(SMS)** x Angelman **(AS)**			Typically developing **(TD)** x Angelman **(AS)**			Typically developing **(TD)** x Smith-Magenis **(SMS)**			**Post hoc**
	M	*SE*	*P*	*M*	*SE*	*p*	*M*	*SE*	*p*	
Time Got in to Bed	0:00	0:18	.969	0:36	0:15	.017	0:37	0:15	.021	SMS = AS TD = AS TD = SMS
Time Woken	-1:19	0:13	< .001	0:25	0:11	.027	1:44	0:11	< .001	SMS < AS* TD = AS TD > SMS*
Onset Latency	-0:14	0:04	.004	-0:02	0:03	.584	0:12	0:04	.004	SMS = AS* TD = AS TD > SMS*
Total Sleep Time	-0:44	0:17	.014	0:37	0:14	.012	1:21	0:15	< .001	SMS = AS TD = AS TD > SMS*
WASO	0:04	0:05	.488	-0:22	0:04	< .001	-0:26	0:05	< .001	SMS = AS TD < AS* TD < SMS*
Total Time in Bed	-0:56	0:19	.005	0:00	0:15	.958	0:55	0:16	.001	SMS < AS* TD = AS TD > SMS*
Efficiency %	.74	1.28	.563	5.00	1.06	< .001	4.26	1.1	< .001	SMS = AS TD > AS* TD > SMS*

Table 2.5 Pairwise comparisons for each sleep parameter of within subject variables across participant groups.

	Autoscored (**A**) x Cleaned actigraphy (**C**)			Diary **(D)** x Autoscored actigraphy **(A)**			Diary **(D)** x Cleaned actigraphy **(C)**			**Post hoc**
	M	*SE*	*p*	*M*	*SE*	*p*	*M*	*SE*	*p*	
Time got in to Bed	-0:20	0:09	.031	-0:08	0:10	.438	-0:28	0:07	<.001	A < C^{T} D = A D < C*
Time Woken	-0:16	0:06	.017	0:28	0:06	<.001	0:12	0:03	.001	A = C D > A***** D > C*
Onset Latency	-0:08	0:02	.001	0:09	0:02	< .001	0:01	0:02	.661	A < C* D > A* D = C
Total Sleep Time	-0:05	0:06	.411	1:46	0:10	< .001	1:41	0:07	< .001	A = C D > A* D > C*
WASO	-0:13	0:03	< .001	-0:43	0:03	< .001	-0:56	0:03	< .001	A < C* D < A* D < C*
Total Time in Bed	-0:27	0:09	.003	1:29	0:10	< .001	1:02	0:05	< .001	A < C***** D > A* D > A*
Efficiency %	2.94	.47	<.001	5.03	.1	<.001	7.98	1.1	< .001	A > A* D > A* D > C*

Table 2.6 Effects of Data Type on Sleep Parameters by group

	Angelman Syndrome				Smith-Magenis Syndrome				Typically developing			
	F	df	*P*	partial η^2	F	df	*p*	partial η^2	F	df	*p*	partial η^2
Time Got in to Bed	3.2	2, 40	.078	.138	1.53	2, 34	.234	.083	2.29	2, 90	.107	.048
Time Woken	3.46	2,40	.059	.148	4.6	2, 34	.039	.213	.29	2, 88	.713	.006
Onset Latency	3.635	2, 34	.037	.176	7.92	2, 24	.002*	.397	10.966	2, 84	< .001*	.207
Total Sleep Time	26.44	2, 40	< .001*	.569	13.56	2, 34	< .001*	.444	199.64	2, 88	< .001*	.819
WASO	18.36	2, 40	< .001*	.479	26.35	2, 34	< .001*	.608	379.52	2, 86	< .001*	.858
Total Time in Bed	15.22	2, 40	< .001*	.432	11.31	2, 34	.001*	.400	49.8	2, 88	< 001*	.531
Efficiency %	11.13	2, 48	.002*	.369	5	2, 34	.031	.227	38.29	2, 86	<.001*	.471

Table 2.7 Pairwise comparisons for each sleep parameter of within subject variables in Angelman Syndrome

	Autoscored **(A)** x Cleaned actigraphy **(C)**			Diary **(D)** x Autoscored actigraphy **(A)**			Diary **(D)** x Cleaned actigraphy **(C)**			**Post hoc**
	M	*SE*	*p*	*M*	*SE*	*p*	*M*	*SE*	*p*	
Time Got in to Bed	-	-	-	-	-	-	-	-	-	-
Time Woken	-	-	-	-	-	-	-	-	-	-
Onset Latency	- 0:10	0:04	.036	0:09	0:03	.020	-0.00	0:04	.876	A < C^{T} D > A^{T} D = C
Total Sleep Time	-0:29	0:15	.071	2:37	0:29	< .001	2:07	0:21	< .001	D > A* D > C* A = C
WASO	-0:25	0:10	.030	-0:35	0:09	.001	-1:00	0:09	< .001	A = C D < A* D < C*
Total Time in Bed	-1:04	0:26	.024	2:08	0:28	< .001	1:04	0:11	< .001	A = C D > A* D > C*
Efficiency %	3.6	1.08	.004	6.85	2.47	.012	10.45	2.81	.001	A > C* D = A D > C*

- No significant effect of Data Type on given parameter for this group

Table 2.8: Pairwise comparisons for each sleep parameter of within subject variables across in Smith-Magenis Syndrome

	Autoscored **(A)** x Cleaned actigraphy **(C)**			Diary **(D)** x Autoscored actigraphy **(A)**			Diary **(D)** x Cleaned actigraphy **(C)**			**Post hoc**
	M	*SE*	*p*	*M*	*SE*	*p*	*M*	*SE*	*p*	
Time Got in to Bed	-	-	-	-	-	-	-	-	-	-
Time Woken	- 0:16	0:19	.417	0:45	0:15	.010	0:28	0:07	.001	A = C D > A[T] D = C
Onset Latency	-0:03	0:01	.059	0:06	0:01	.002	0:03	0:01	.079	A = C D > A* D = C
Total Sleep Time	0:10	0:16	.515	1:15	0:22	.004	1:26	0:13	< .001	A = C D > A[*] D > C[*]
WASO	-0:14	0:08	.088	-0:45	0:08	< .001	-1:00	0:09	< .001	A = C D < A[*] D < C[*]
Total Time in Bed	-0:10	0:20	.617	1:24	0:24	.003	1:14	0:10	< .001	A = C D > A[*] D > C[*]
Efficiency %	3	.85	.003	3.61	2.39	.149	6.61	2.6	.021	A > C[*] D = A D > C[T]

- No significant effect of Data Type on given parameter for this group

Table 2.9 Pairwise comparisons for each sleep parameter of within subject variables in Typically Developing participants

	Autoscored **(R)** x Cleaned actigraphy **(C)**			Diary **(D)** x Autoscored actigraphy **(R)**			Diary **(D)** x Cleaned actigraphy **(C)**			**Post hoc**
	M	*SE*	*p*	*M*	*SE*	*p*	*M*	*SE*	*p*	
Time Got in to Bed	-	-	-	-	-	-	-	-	-	-
Time Woken	-	-	-	-	-	-	-	-	-	-
Onset Latency	-0:12	0:03	<.001	0:13	0:02	< .001	0:00	0:03	.770	A < C* D > A* D = C
Total Sleep Time	0:03	0:03	.290	1:27	06	< .001	1:31	0:05	< .001	A = C D > A* D > A*
WASO	0:00	0:00	.927	-0:48	0:02	< .001	-0:48	0:02	< .001	A = C D < A* D < C*
Total Time in Bed	-0.07	0:05	.152	0:64	0:07	< .001	0:47	0:05	< .001	A = C D < A* D < C*
Efficiency %	2.23	.54	< .001	4.66	87	< .001	6.86	.94	< .001	A > D* D > A* D > C*

- No significant effect of Data Type on given parameter for this group

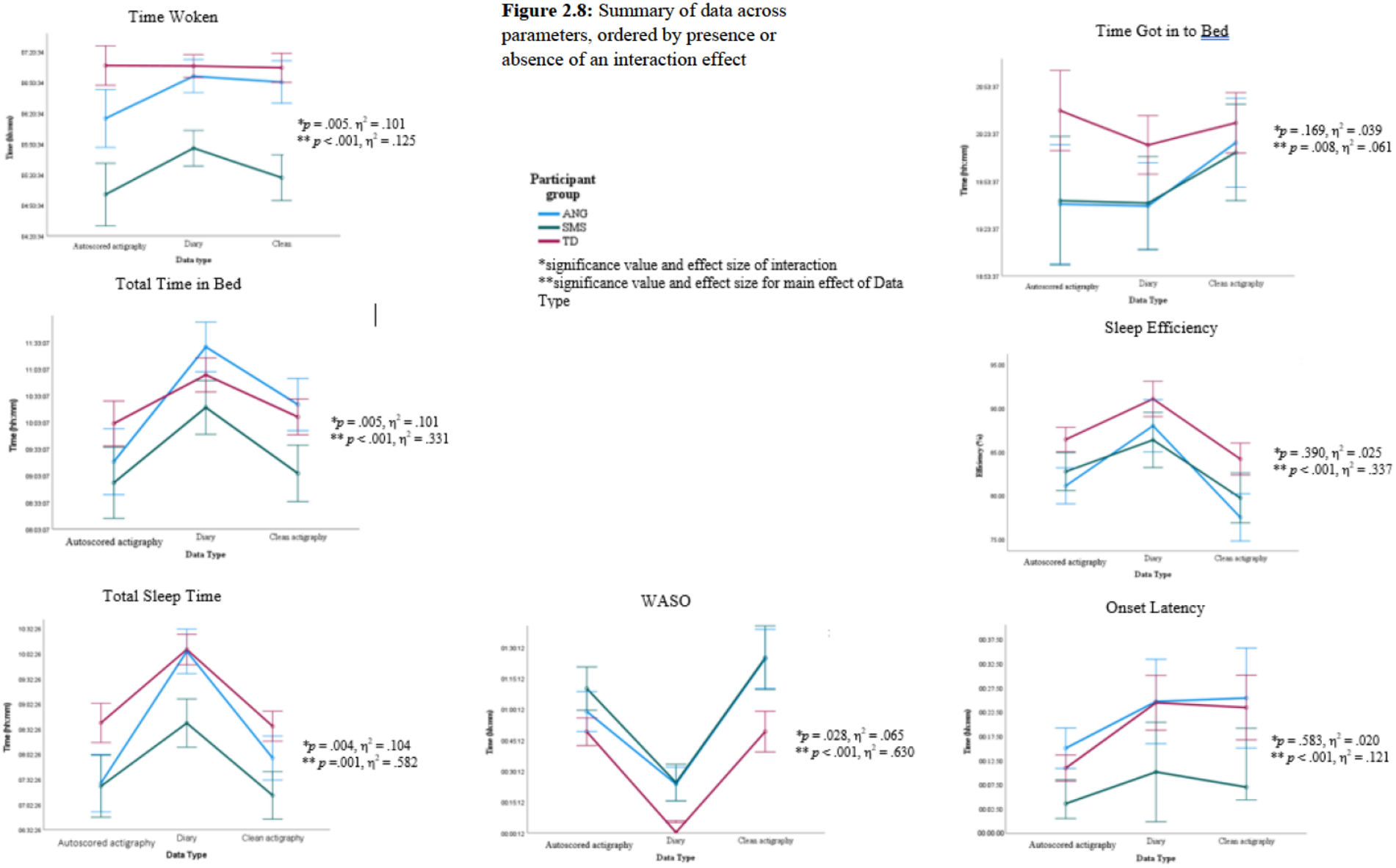

Figure 2.8: Summary of data across parameters, ordered by presence or absence of an interaction effect

2.5 Discussion

The present study examined whether different means of sleep data collection and management affected sleep parameters across neurogenetic syndromes and a Typically Developing cohort. In a secondary analysis, sleep, as measured through parent-completed diaries, was compared to both autoscored and cleaned actigraphy data. Diary and actigraphy measures are amongst the most commonly used measures of sleep in young people (Schoch et al., 2021; Short et al., 2017). In the field of rare genetic syndrome sleep research, methods by which actigraphy data are cleaned are rarely described (See Chapter One; see Agar, Oliver, & Richards, (2022) as an example of where cleaning is described) and analysis of how such procedures are affecting data have not been undertaken elsewhere.

Summary of findings

Objective 1.1 Did the cleaning protocol have an overall impact on the actigraphy data? If so, what was the nature of this?

For 'Onset Latency', 'WASO' and 'Total Time in Bed' there was a significant overall effect of the cleaning protocol. Autoscored actigraphy estimated children taking less time to fall asleep, waking less in the night and spending less total time in bed than cleaned actigraphy. Within these data, there was also a trend for difference in relation to 'Time Got in to Bed', suggesting a possible impact of cleaning. There was no evidence that the cleaning protocol affected the data for 'Time Woken' and 'Total Sleep Time' (see Table 2.10 for a summary of the findings).

To understand why these particular parameters were impacted, it may be that one aspect of the data cleaning protocol has a key impact across several parameters. The protocol instructs

the extension of the sleep interval to reflect parent-reported time into and out of bed. This is necessary, as autoscored actigraphy only commences sleep intervals after a period of sustained rest and can estimate the final morning wake time of the child as too early in the event of *periods* of wake early in the morning or late at night. Lengthening sleep intervals in this way can not only increase estimates of 'Total Time in Bed' but can also increase 'Sleep Latency' by increasing onset time before sleep. 'Wake After Sleep Onset' estimates can also be increased by lengthening the period over which night waking may be identified. Subsequently this can increase 'Sleep Efficiency', by increasing night waking without increasing sleep estimates. These findings in sum support recommendations for the use of cleaning protocols for actigraphy data and suggest a need for standardisation of reporting across the field (Ancoli-Israel et al., 2015; Follesø et al., 2021; Sadeh, 2011).

Table 2.10 Overall impact of cleaning protocol by parameter

	Time Got in to Bed	**Time Woken**	**Onset Latency**	**Total Sleep Time**	**WASO**	**Total Time in Bed**	**Efficiency**
Significant difference	-	-	✓ A < C	-	✓ A < C	✓ A < C	✓ A > C
Trend toward difference	✓ A < C	-	-	-	-	-	-
No difference	-	✓	-	✓	-	-	-

Wake After Sleep Onset (WASO), A (Autoscored actigraphy), C (Cleaned actigraphy)

Objective 1.2 & 1.3 Was there any differential impact of the cleaning protocol between the groups? What were the nature of these differences?

Viewed together, Tables 2.11 & 2.12 highlight whether the method of assessment had a differential impact on sleep parameter estimates between groups (Table 2.11) and, where related to the impact of the cleaning protocol (Table 2.12), the nature of these differences. A

significant interaction was observed for the parameter of 'Total Time in Bed'. A trend for an interaction was observed for the parameter of 'WASO', which followed a similar pattern to 'Total Time in Bed' in terms of individual sample differences. Whilst the interaction was not significant for both 'Onset Latency' and 'Efficiency', preventing the conclusion that the cleaning protocol impacted on these groups differentially, some between groups differences were observed which warrant further exploration in future research. The cleaning protocol did not appear to impact differentially on estimates of sleep parameters for 'Time Woken', 'Time Got in to Bed' or 'Total Sleep Time'.

Table 2.11 Summary of interaction between data type and participant group

	Time Got in to Bed	**Time Woken**	**Onset Latency**	**Total Sleep Time**	**WASO**	**Total Time in Bed**	**Efficiency**
Significant interaction	-	✓	-	✓	-	✓	-
Trend for interaction	-	-	-	-	✓	-	-
No significant interaction	✓	-	✓	-	-	-	✓

Table 2.12 Impact of cleaning protocol by group

	Time Got in to Bed	**Time Woken**	**Onset Latency**	**Total Sleep Time**	**WASO**	**Total Time in Bed**	**Efficiency**
Typically Developing	✘	✘	✓ A < C	✘	✘	✘	✓ A > C
Smith-Magenis	✘	✘	✘	✘	✘	✘	T A > C
Angelman	✘	✘	T A < C^{T}	✘	✓ A < C^{T}	T A < C^{T}	✓ A> C

✘ No evidence for impact of cleaning protocol within this group
T/^{T}, Trend (p = .05 - .006)

The above findings, taken from conservative estimates of significance, highlight that actigraphy cleaning may be having differential impacts on data from different groups. Whilst cleaning data is always recommended, for example, it may be that using autoscored actigraphy for 'WASO' and 'Total Time in Bed' provides an acceptable estimate for Typically Developing and Smith-Magenis groups, with cleaning the data having negligible impact. However, given the trends for difference between autoscored and cleaned actigraphy, cleaning the data potentially holds more importance for children with Angelman syndrome. As a hypothesis for why this may be, children with Angelman Syndrome appear to have reduced ability to mobilise independently and lower adaptive behaviour as seen in Table 2.1. Therefore, parents may be required to be more present during night and subsequently be more aware of waking. This would lead to parents citing more night waking in sleep diaries which, as per the cleaning protocol would then lead the sleep interval within actigraphy to be extended and capture more night waking within this.

As well as highlighting specific differences, these data highlight areas of possible difference that warrant further investigation. Such differences could reflect difference in the reliability of autoscored actigraphy data prior to cleaning, differences in the reliability of diary data for use in cleaning, or potentially the appropriateness of cleaning protocol-specific measures for different groups. Knowing where differences lie in how 'important' cleaning data is across groups would enable us to formulate best practice guidelines advocating for cleaning, citing instances where a difference between the data types is observed. In the future, syndrome-specific protocols may be considered. In clinical settings, clinicians are often working in contexts where optimum assessment data is not possible. For example, diaries may be partially completed, particularly by parents with their own additional needs. Such incomplete diaries effectively negate cleaning processes and clinicians therefore have to determine what sense can

be made of autoscored data. Moreover, many children are not being served by specialist sleep clinics.

Objective 2: To examine concordance between diary and actigraphy data

2.1 Were there any overall differences between diary and actigraphy estimates across the groups?

There was overall poor evidence for concordance between diary and actigraphy data, as seen in Table 2.13. Across five parameters (Time Woken, Total Sleep Time, WASO, Total Time in Bed & Efficiency), the data indicated a significant difference between diary estimates and both the autoscored and cleaned actigraphy. Here, parental report estimated children as waking later into the morning and spending more time in bed. Parents also estimated their children achieved more total sleep, with less night waking. Sleep was also estimated to be more efficient according to parent report. Of interest, for the parameter 'Onset Latency', parental estimates of how long their child took to fall asleep were greater than autoscored actigraphy but concorded with cleaned actigraphy estimates. This is likely to be due to the autoscored actigraphy algorithm using reduced movement to denote latency within Actiware software, whereas both diary and the cleaned actigraphy use parental reports of the time they intended for their children's sleep period to begin.

Table 2.13 Were there any overall differences between actigraphy and diary data across the groups?

	Time got in to Bed	**Time Woken**	**Onset Latency**	**Total Sleep Time**	**WASO**	**Total Time in Bed**	**Efficiency**
Significant difference	-	✓ D > A – C	✓ C = D > A	✓ D > A = C	✓ D < A <C	✓ D > C > A	✓ D > A > C
Difference trend	✓ A = D > C	-	-	-	-	-	-
No evidence for difference	-	-	-	-	-	-	-

Wake After Sleep Onset (WASO), Autoscored actigraphy (A), Cleaned actigraphy (C), Diary (D)

2.2 Were there any differences in concordance of diary with actigraphy estimates between the groups?
2.3 What were the nature of any differences identified in 2.2

Taken together, Tables 2.12 & 2.14 demonstrate that concordance, or lack thereof, between diary and actigraphy data remained broadly consistent across the groups with a much clearer picture of findings compared to the impact of the cleaning protocol.

On the parameter of 'Time Woken', there was a significant interaction. Here, good concordance between diary and actigraphy estimates were shown for both the Typically Developing and Angelman cohorts. However, for children with Smith-Magenis syndrome it appears that parental estimates of the time their child woke are later into the morning than cleaned actigraphy and potentially also autoscored actigraphy. Perhaps here children with Smith-Magenis syndrome, operating with an inverted circadian rhythm (De Leersnyder et al., 2001), were more prone to early waking, of which their parents remained unaware – this may make a particular case for use of actigraphy in this group (Trickett et al., 2020). For 'Total Sleep Time', whilst there was a significant interaction between the groups, each group showed a pattern of parental report estimating significantly greater 'Total Sleep Time' than actigraphy. However, the strength of the concordance varied with the greatest difference observed in the Typically Developing group when effect sizes were also considered. This may be due to parents underestimating the amount of wake experienced by their children, who can be thought of as more able to manage wake episodes independently than their peers with neurogenetic syndromes. The nature of concordance across the groups for parameters of 'WASO' and 'Total Time in Bed' was also static across groups with parents underestimating wake and overestimating the total time their children spent in bed compared to actigraphy. However here, *trends* for an interaction were reported, leaving us uncertain as to whether the magnitude of this concordance varied across the groups. No significant interaction between Data Type and Group

was reported for the parameters of 'Onset Latency' and 'Efficiency'. For 'Onset Latency' we can be confident that the diary concords with cleaned actigraphy but not with autoscored in both Typically Developing and Smith Magenis groups. Further research is required to confirm whether this is also the case for the Angelman group. Similarly, for 'Sleep Efficiency', Diary estimates were greater than actigraphy in both the Typically Developing and Angelman groups, uncertainty remains for children with Smith Magenis syndrome.

Table 2.14 Did the nature of concordance between diary and actigraphy data vary between the groups?

	Time Got in to Bed	**Time Woken**	**Onset Latency**	**Total Sleep Time**	**WASO**	**Total Time in Bed**	**Efficiency**
Typically Developing	✘	✘	✓ D > A	✓ D > A D > C	✓ D < A D < C	✓ D > A D > C	✓ D > A D > C
Smith-Magenis	✘	T D > A^{T} D > C	✓ D > A	✓ D > A D > C	✓ D < A D < C	✓ D > A D > C	T D > C^{T}
Angelman	✘	✘	T D > A^{T}	✓ D > A D > C	✓ D < A D < C	✓ D > A D > C	✓ D > C D > A^{T}

✓ Evidence of difference between diary and actigraphy data i.e., lack of concordance
✘ No evidence for differences between diary and actigraphy data. i.e., evidence for concordance
T/^{T}, Trend (p = .05 - .006)

The importance of considering how subjective and objective data relate to each other has been highlighted in Chapter One. This study has included the opportunity to look at concordance between parental reported diary data and different types of actigraphy data. In summary, there are several parameters for which diary and actigraphy data are different. Here, we have defined concordance as the concordance of absolute values of parameter estimates, rather than concordance of individual differences in parameter estimates (through correlations), as is often calculated. The important distinction being that estimates may correlate through systematically over- or under-estimating parameters. Though systematic non-concordance was identified, this does not necessarily appear to be different *across* the groups included here.

Given that diary data across groups were found to relate to objective actigraphy data in similar ways, strategies for understanding and adjusting data may be usefully adopted across groups.

Study critique

The present study can be merited for an initial exploration of something that has otherwise been neglected in the field of sleep research and neurogenetic syndromes, the impact of applying a cleaning protocol to actigraphy data. This is problematic as we know that in healthy adults, significant changes across several sleep parameters were reported following the application of a procedure to define rest intervals (Follesø et al., 2021) and here we have groups of children for whom we know sleep profiles are unique. We also know that in the neurogenetic syndrome literature there is inconsistency in how data cleaning is reported (see Chapter One) which has additional implications for replicability and extrapolation to clinical settings. Whilst actigraphy cleaning is commonplace, reporting of procedures is scarce and no other study has specifically drawn comparisons between autoscored and cleaned data. This study also recognised that the differing sleep profiles of genetic syndromes may mean that cleaning actigraphy data has a differential impact between groups. As with most studies using actigraphy, participants took part from their own homes meaning that the data collected was likely to be more representative of a child's typical sleeping pattern than if conducted in a sleep laboratory.

A potential limitation of this study is the matching of the actigraphy parameter of 'Time Got in to Bed' with diary reported 'Time Got in to Bed'. Diary reported 'Time Got in to Bed' was derived from parental reported clock times on sleep diaries which was a separate variable to 'Lights off time'. 'Lights off time' could be argued as being more comparable to actigraphy 'Time Got in to Bed' and this may have contributed to observed differences between the data types here. It is possible however that such an approach has been taken in the wider literature

and potentially reflects how different terms are often being used interchangeably within parameter labels and definitions, supporting the argument that detailed parameter definitions are an essential component of data reporting within the field of sleep research, as discussed chapter one. The collection of additional data regarding the placement location of the actiwatch would have been useful when considering data type comparisons. Van Kooten, Jacobse, Heymans, de Vries, Kaspers, & van Listenburg (2021) reported that estimates of 'Sleep Efficiency' were significantly higher when accelerometers were attached to the ankle in a meta-analysis of accelerometer outcomes in children. There were some differences in the format of the sleep diaries between the syndrome and typically developing groups. The syndrome diaries were longer and required additional data from parents for additional research questions asked of the original data set. They also asked parents whether they felt the event marker was pressed at the correct time which was not a feature of the diaries for typically developing children. Here it is possible that responses from parents of children with syndromes were more heavily influenced by recording-fatigue than their typically developing counterparts. The use of identical diaries could have controlled for this confound. It is noted that over half of children with Angelman syndrome (57.1%) and Smith-Magenis syndrome (66.6%) reported using medication to aid sleep. The sleep parameters obtained in both the SMS and AS groups replicate those observed in the wider literature (Trickett et al., 2019 & Trickett et al., 2020) and as such, the variability in the actigraphy parameters likely reflects naturally occurring variability within both of the syndromes. It is not clear whether this variability is attributable directly to the syndrome or to the higher rates of sleep medication used in the syndromes. However, as the primary research questions for this study were concerned with concordance of measurement, the inclusion of children on sleep medications did not present a threat to internal validity. An additional limitation to this study is the potential for other factors not assessed for here which

could influence the validity of parent reporting. Levels of parental stress and fatigue may impact on reporting differentially across groups. Additionally, parents of children who experience nocturnal seizures may be more vigilant to their child's activity at night and proximity between parent/child and the use of monitoring devices within the home may also contribute to variance in diary reporting. Future research should consider these factors and incorporate methods to control for or assess these variables as any development of syndrome specific protocols would need to allow for these factors. This should be done alongside an acknowledgment that diaries are typically assessing caregiver *perception* of sleep, which would provide additional interesting information to help explain differential impacts of cleaning actigraphy and varying concordance between methods.

Several analyses conducted identified marginal trends, rather than clear significant effects – in spite of relatively large effect sizes. Larger sample sizes would have enabled more conclusive outcomes in these areas. When considering mechanisms for sleep differences in Smith-Magenis syndrome, the notion of inverted circadian rhythms features heavily in the literature (e.g., De Leersnyder et al., 2001). Not knowing how this featured in this present sub-sample and its relation to the effect of cleaning is a limitation. Collecting additional data on

Future research and clinical implications

In line with findings from Follesø et al., (2021) and a further review from Schoch, Kurth, & Werner (2021), who advocated for improvements in the reporting of actigraphy data management, and in the context of the present study, the author here advocates for the reporting of actigraphy data cleaning to become commonplace. This would also enable further research to examine the impact of cleaning data in larger sample sizes across a broader range of neurogenetic syndromes. Dependent on the results, it may be that syndrome specific cleaning

protocols are required to account for the sensitivities of varying sleep profiles with these importantly including an acknowledgement of the additional factors which could affect parental reporting. Clinicians should expect that the application of a cleaning protocol will impact on findings of several sleep parameters and that this impact may be different depending on the syndrome profile of the child in front of them. However, the author would exercise caution in assuming that across other sleep parameters the profile of difference between Autoscored and Cleaned actigraphy is the same regardless of syndrome group. Clinicians should remain mindful for the propensity of different methods of sleep assessment to report different findings in the context of using a detailed assessment to inform intervention techniques. Actigraphy data which has been cleaned with adjunctive diary data is likely to give the best estimates of child sleep patterns. This study also provides further evidence that parameter estimates from diaries regularly diverge from objective measures (Short, Gradiasar, Lack, Wright, & Carskadon, 2012; Iwasaki et al., 2010; Mazza, Bastuji, & Rey, 2020). Interestingly, the pattern of this was broadly the same across groups. Clinicians may be able to have some confidence in which parameters are more or less reliable across syndrome groups.

Conclusion

The literature is clear on the importance of sleep for children with neurogenetic syndromes. It is vital that researchers and clinicians work together to develop the best ways of supporting these families. In order to design, implement and evaluate the most effective intervention strategies, robust assessment tools are required. The present study has contributed to this need by providing preliminary evidence as to the impact of an actigraphy data cleaning protocol and furthering our knowledge of how different assessment means relate to each other. It is hoped that this will both help to educate clinicians who perhaps often feel

lost or limited in what they can do to help and encourage others in the research field to continue with this work and contribute towards high quality sleep assessment.

CHAPTER THREE

PRESS RELEASES

Do different ways of measuring sleep in children with neurogenetic syndromes agree with each other?

Children with neurogenetic syndromes, genetic disorders which affect how the brain works, often do not sleep well. This can put their wellbeing, and that of the parents, at risk. It is vital that we know how to best support these families to experience better sleep. There are lots of different ways to measure sleep. Researchers at the University of Birmingham have been especially interested in whether data from tools such as actigraphy and polysomnography matches up with data from sleep diaries and questionnaires. An actiwatch is a small watch-like device worn on the wrist which uses movement and light to denote sleep. Polysomnography typically takes place in a lab setting and involves wearing electrodes and various other pieces of equipment overnight which can tell us about a person's sleep.

The team found existing research papers which have used both types of objective and subjective assessment when looking at the sleep of people with neurogenetic syndromes. Objective measurement usually involves using equipment and is based on factual data. Subjective measurement typically involves asking about how someone feels about something; their perception. There were only a small number of previous studies which had done this, which meant it was not possible to come to any firm conclusions. The team noticed that the ways in which tools such as actigraphy are used in clinical research were very varied and have called for better consistency and the production of guidelines which could be used by both researchers and clinicians alike.

Researchers also noticed that most of the existing studies did collect the data needed to look at agreement between the different subjective and objective sleep tools, they just had not analysed or presented the findings from these data. The team at the University of Birmingham have said “we could clearly see that the potential to look at this more closely was there, it just isn’t being done routinely”. Lead researcher Natalie Knight has recommended that in future all authors make their data freely available so that more research can be done in this area. “When we have a better understanding of how different ways of assessing sleep relate to each other, the quality of our research and the support we give to these families will improve”.

Helping children with neurogenetic syndromes get a good night's sleep

Improving the accuracy of sleep data will help children with neurogenetic syndromes get the right support, say researchers at the University of Birmingham.

A team in the University's School of Psychology has been investigating the best way to make sure data from activity sensors is as useful as it can be, so that the sleeping patterns of children with neurogenetic syndromes can be properly analysed, and then best support put in place. One part of this is about making sure the data are processed properly. Sometimes the activity sensor can make a mistake and think a child is awake when they are asleep, or vice versa. This is because the sensor broadly assumes that if the child is not moving, they are asleep and if there is movement then the child is awake. We all know this might not be the case! Researchers often use a sleep diary which parents are asked to complete to make some changes to what the sensor thinks has happened in terms of the child’s sleeping pattern. This is called ‘data cleaning’.

The researchers at the University of Birmingham were specifically interested in whether the data from the sensor was different depending on whether it had been 'cleaned'. Does cleaning make a difference? The research team were also interested in whether this difference was the same for all children or whether the impact of 'cleaning' changed depending on which neurogenetic syndrome the child has. We know that children with different syndromes have different sleeping patters. There was some evidence that this was indeed the case but much more research will be needed to confirm the findings. The researchers were also interested in whether the data from the sensor matched what parents reported about their child's sleep in diaries. The team found that in general, for all groups, there was a poor match.

Lead researcher Natalie Knight says: "A good night of sleep is important for us all. Parents of children with additional needs, particularly those with neurogenetic syndromes will know all too well of the fall outs from consistent sleep deprivation and it is therefore important that we continue to thoroughly research this area"

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Appendix A: Actigraphy sub criteria & ratings

	McCarthur et al., 1998	Zhadanova et al., 1999	De Leesnyder et al., 2001	Stores et al., 2004	Goldman et al., 2009	Goldman et al., 2012	Allen et al., 2013	Ashworth et al., 2013	Gibbs et al., 2013	Mahon et al., 2014	Edgin et al m 2015	Sniecinska-Cooper et al., 2015	Esbensen et al., 2018a " impacrt…"	Esbensen et al., 2018b " convergent…"	Gimenez et al., 2018	Merbler et al., 2018	Trickett et al., 2019(a)	Trickett et al. 2019
1.A minimum of five nights of data are included in analysis for all participants with explicit reporting of this. [1]									X	X				X			X	
2.Worn on wrist, ankle, or inside pocket sewn into a t-shirt	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X
3.Includes concurrent sleep diary with below parameters as a minimum a) Bedtime																	X	X

b) When my child wakes up for the day c) Any time my child wakes up after lights are out for the night d) removal of device e) sedentary periods f) movement due to bed sharing g) any reason for atypical night of sleep e.g. illness																		
4. A definition of each actigraphy variable has been provided.		X		X		X		X	X	X			X		X	X		
5.Watch placed on participant at least one hour prior to bedtime and left on after waking (to ensure sufficient baseline of activity counts)	X				X	X	X	X	X	X		X				X	X	X
6.Includes description of when the activity marker should be									X								X	X

used on the actiwatch including a clear definition of 'bedtime' (so as not to underestimate latency)																		
7.Manual scoring of actigraphy data (not autoscore function)					X	X				X								
8.Includes a description of how data were cleaned and artefacts dealt with e.g. diary data to remove artefact	X[1]								X	X						X	X	X
9.Rules for handing missing data have been well defined.																		
10.Scoring algorithm or wake threshold specificity should be based on study population and previously published validation studies							X						X	X				

11.If multiple personnel are involved with scoring then inter-rater reliability should be examined[2]	NA	NA	NA		NA	NA	NA	NA	NA	NA	X	NA	NA	NA	NA	X	X	X
12.In studies involving multiple groups, those scoring the data should be blinded to the group/treatment. In studies not involving multiple groups mark as N/A and do not include in % calculation.	NA	NA	NA		NA	NA	NA		NA				NA	NA	NA	NA		
Total %	30	20	0	8	30	40	30	27	50	54	16	18	30	30	20	45	63	63

[1]In studies citing group level data, a range should be reported with respect to number of nights analysis and the minimum here should be five.
[2]If only a single rater is used or there is no reference to number of raters used then this criterion should be marked as NA and do not include in % calculation
Main papers used: Meltzer et al., (2012) & Fawkes (2015)
Acebo (1999) used for no. of nights- signposted to by Meltzer and commonly cited.
Sadeh (2011) used for reliability criteria- also signposted to by Meltzer.

Appendix B: Syndrome sleep diary (weekday)

Please complete the diary as close as you can to the time specified below. The diaries need completing each day, information about behaviour relates before school after the child has got out of bed, and behaviour after school when the child returns home from school one. We would also like you to enter times of any naps, and times the actiwatch was taken off. We would like you to enter information about bedtime in the evening, as close to the actual times as possible, and aspects of children's sleep quality and wake up time in the morning. These diaries are ideally completed by the same person each day. If you have any questions, please call or email Jayne Trickett [redacted] or [redacted] For out of office queries, please call or text [redacted]

BEFORE SCHOOL **Please rate the severity of the behaviour observed and whether the behaviour observed is typical of the child**		
	SEVERITY 1= not at all severe 5= very severe	**TYPICALITY** 1= significantly less severe than typical 3=typical for the child 5 = significantly more severe than typical
Difficult behaviour Punching, pushing, kicking, pulling hair or grabbing other's clothing Disruption and destruction of property or the environment: e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal. Self-injurious behaviour e.g. heading banging, head punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing.	1 2 3 4 5	1 2 3 4 5
Overactivity and impulsivity Finding it difficult to wait Acting as if driven by a motor Wanting things immediately Finding it difficult to hold still	1 2 3 4 5	1 2 3 4 5
Irritability Is easily annoyed by others Often and easily loses his/her temper Stays angry for a long time Gets angry frequently Overall irritability causes him/her problems	1 2 3 4 5	1 2 3 4 5
Daytime sleepiness Yawning Rubbing eyes Dazed/daydreaming Resting head on desk/lying down Eyes closed	1 2 3 4 5	1 2 3 4 5

AFTER SCHOOL **Please rate the severity of the behaviour observed and whether the behaviour observed is typical of the child**		
	SEVERITY 1= not at all severe 5= very severe	**TYPICALITY** 1= significantly less severe than typical 3=typical for the child 5 = significantly more severe than typical
Difficult behaviour Punching, pushing, kicking, pulling hair or grabbing other's clothing Disruption and destruction of property or the environment: e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal. Self-injurious behaviour e.g. heading banging, head punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing.	1 2 3 4 5	1 2 3 4 5
Overactivity and impulsivity Finding it difficult to wait Acting as if driven by a motor Wanting things immediately Finding it difficult to hold still	1 2 3 4 5	1 2 3 4 5
Irritability Is easily annoyed by others Often and easily loses his/her temper Stays angry for a long time Gets angry frequently Overall irritability causes him/her problems	1 2 3 4 5	1 2 3 4 5
Daytime sleepiness Yawning Rubbing eyes Dazed/daydreaming Resting head on desk/lying down Eyes closed	1 2 3 4 5	1 2 3 4 5

To be completed throughout the day				Completed by (initials)
Time Actiwatch Removed		Time Actiwatch Replaced		
Time Actiwatch Removed		Time Actiwatch Replaced		
Time Actiwatch Removed		Time Actiwatch Replaced		

To be completed in the evening			
Nap 1 Start time: End time:	**Nap 2** Start time: End time:	**Nap 3** Start time: End time:	

Please list any sedentary activities after 6pm e.g. reading alone or with an adult, watching TV			
Type of activity (select one) ☐ Watching TV ☐ Reading alone or with an adult ☐ Other- please state	**Start time of activity**	**End time of activity**	
Type of activity (select one) ☐ Watching TV ☐ Reading alone or with an adult ☐ Other- please state	**Start time of activity**	**End time of activity**	
Type of activity (select one) ☐ Watching TV ☐ Reading alone or with an adult ☐ Other- please state	**Start time of activity**	**End time of activity**	

Time got into bed:	
Time lights turned off: 	
Child's behaviour at bedtime (Select one): ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Upset when caregiver leaves the room ☐ Become distressed – no obvious reason ☐ Destructive or self-injurious behaviour	
Response to child's behaviour at bedtime (Select one): ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about bedroom expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet	
To your knowledge, was the event marker pressed at the correct time? (Please circle)	

Yes	No	

To be completed in the morning		
Time woke up: 		
Time got out of bed:		
Estimated time taken to fall asleep:		
To your knowledge, was the event marker pressed at the correct time? (Please circle)		
Yes	**No**	
Child's behaviour when getting out of bed: ☐ No behaviours of concern ☐ Refuses to get out of bed		
Response to child's behaviour (select one): ☐ Not applicable- no behaviours of concern ☐ Ignore behaviour ☐ Verbally remind child about morning routine expectations ☐ Suggest removal of preferred activity/item if will not get up		
Please rate how typical your child's sleep quality was **1 = Significantly better than usual, 3 = Typical and 5 = Significantly poorer than usual**		
1 2 3 4 5		
Do you think your child slept well? (Please circle)		
Yes	**No**	

Please record any times your child woke up during the night	
Waking 1	**Waking 2**
Time of waking: **End of waking:** **Perceived reason for waking (select one):** ☐ Wet/needing toilet ☐ Hungry/thirsty ☐ Pain/discomfort ☐ Anxiety ☐ Unknown ☐ Other – please state: **Child's behaviour during waking (select one):** ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Become distressed ☐ Destructive or self-injurious behaviour **Response to child's behaviour (select one):** ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about night-time expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet ☐ Give child a drink/take to the toilet etc.. but minimising attention	**Time of waking:** **End of waking:** **Perceived reason for waking (select one):** ☐ Wet/needing toilet ☐ Hungry/thirsty ☐ Pain/discomfort ☐ Anxiety ☐ Unknown ☐ Other – please state: **Child's behaviour during waking (select one):** ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Become distressed ☐ Destructive or self-injurious behaviour **Response to child's behaviour (select one):** ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about night-time expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet ☐ Give child a drink/take to the toilet etc.. but minimising attention

Waking 3	Waking 4
Time of waking: **End of waking:** **Perceived reason for waking (select one):** ☐ Wet/needing toilet ☐ Hungry/thirsty ☐ Pain/discomfort ☐ Anxiety ☐ Unknown ☐ Other – please state: **Child's behaviour during waking (select one):** ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Become distressed ☐ Destructive or self-injurious behaviour **Response to child's behaviour (select one):** ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about night-time expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet ☐ Give child a drink/take to the toilet etc.. but minimising attention	**Time of waking:** **End of waking:** **Perceived reason for waking (select one):** ☐ Wet/needing toilet ☐ Hungry/thirsty ☐ Pain/discomfort ☐ Anxiety ☐ Unknown ☐ Other – please state: **Child's behaviour during waking (select one):** ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Become distressed ☐ Destructive or self-injurious behaviour **Response to child's behaviour (select one):** ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about night-time expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet ☐ Give child a drink/take to the toilet etc.. but minimising attention

Any other notes:

……

……

……

Appendix C: Syndrome sleep diary (weekend)

BEHAVIOUR IN THE MORNING **Please rate the severity of the behaviour observed and whether the behaviour observed is typical of the child**		
	SEVERITY 1= not at all severe 5= very severe	**TYPICALITY** 1= significantly less severe than typical 3=typical for the child 5 = significantly more severe than typical
Difficult behaviour Punching, pushing, kicking, pulling hair or grabbing other's clothing Disruption and destruction of property or the environment: e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal. Self-injurious behaviour e.g. heading banging, head punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing.	1 2 3 4 5	1 2 3 4 5
Overactivity and impulsivity Finding it difficult to wait Acting as if driven by a motor Wanting things immediately Finding it difficult to hold still	1 2 3 4 5	1 2 3 4 5
Irritability Is easily annoyed by others Often and easily loses his/her temper Stays angry for a long time Gets angry frequently Overall irritability causes him/her problems	1 2 3 4 5	1 2 3 4 5
Daytime sleepiness Yawning Rubbing eyes Dazed/daydreaming Resting head on desk/lying down Eyes closed	1 2 3 4 5	1 2 3 4 5

FLACC SCALE: Please observe child for 10 minutes in the morning then complete the following Tick one box on each row			
Face	☐ No particular expression or smile	☐ Occasional grimace or frown, withdrawn, uninterested	☐ Frequent to constant quivering chin, clenched jaw
Legs	☐ Normal position or relaxed	☐ Uneasy, restless, tense	☐ Kicking, or legs drawn up
Activity	☐ Lying quietly, normal position, moves easily	☐ Squirming, shifting, back and forth, tense	☐ Arched, rigid or jerking
Cry	☐ No cry (awake or asleep)	☐ Moans or whimpers, occasional complaint	☐ Crying steadily, screams or sobs, frequent complaints
Consolability	☐ Content, relaxed	☐ Reassured by occasional touching, hugging or being talked to, distractible	☐ Difficult to console or comfort

BEHAVIOUR IN THE MORNING **Please rate the severity of the behaviour observed and whether the behaviour observed is typical of the child**		
	SEVERITY 1= not at all severe 5= very severe	**TYPICALITY** 1= significantly less severe than typical 3=typical for the child 5 = significantly more severe than typical
Difficult behaviour Punching, pushing, kicking, pulling hair or grabbing other's clothing Disruption and destruction of property or the environment: e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal. Self-injurious behaviour e.g. heading banging, head punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing.	1 2 3 4 5	1 2 3 4 5
Overactivity and impulsivity Finding it difficult to wait Acting as if driven by a motor Wanting things immediately Finding it difficult to hold still	1 2 3 4 5	1 2 3 4 5
Irritability Is easily annoyed by others Often and easily loses his/her temper Stays angry for a long time Gets angry frequently Overall irritability causes him/her problems	1 2 3 4 5	1 2 3 4 5
Daytime sleepiness Yawning Rubbing eyes Dazed/daydreaming Resting head on desk/lying down Eyes closed	1 2 3 4 5	1 2 3 4 5

BEHAVIOUR IN THE AFTERNOON		
Please rate the severity of the behaviour observed and whether the behaviour observed is typical of the child		
	SEVERITY 1= not at all severe 5= very severe	**TYPICALITY** 1= significantly less severe than typical 3=typical for the child 5 = significantly more severe than typical
Difficult behaviour Punching, pushing, kicking, pulling hair or grabbing other's clothing Disruption and destruction of property or the environment: e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal. Self-injurious behaviour e.g. heading banging, head punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing.	1 2 3 4 5	1 2 3 4 5
Overactivity and impulsivity Finding it difficult to wait Acting as if driven by a motor Wanting things immediately Finding it difficult to hold still	1 2 3 4 5	1 2 3 4 5
Irritability Is easily annoyed by others Often and easily loses his/her temper Stays angry for a long time Gets angry frequently Overall irritability causes him/her problems	1 2 3 4 5	1 2 3 4 5
Daytime sleepiness Yawning Rubbing eyes Dazed/daydreaming Resting head on desk/lying down Eyes closed	1 2 3 4 5	1 2 3 4 5

To be completed throughout the day				Completed by (initials)
Time Actiwatch Removed		Time Actiwatch Replaced		
Time Actiwatch Removed		Time Actiwatch Replaced		
Time Actiwatch Removed		Time Actiwatch Replaced		
To be completed in the evening				
Nap 1 Start time: End time:	**Nap 2** Start time: End time:	**Nap 3** Start time: End time:		
Please list any sedentary activities after 6pm e.g. reading alone or with an adult, watching TV				

Type of activity (select one) ☐ Watching TV ☐ Reading alone or with an adult ☐ Other- please state	**Start time of activity**	**End time of activity**	
Type of activity (select one) ☐ Watching TV ☐ Reading alone or with an adult ☐ Other- please state	**Start time of activity**	**End time of activity**	
Type of activity (select one) ☐ Watching TV ☐ Reading alone or with an adult ☐ Other- please state	**Start time of activity**	**End time of activity**	
Time got into bed:			
Time lights turned off: 			
Child's behaviour at bedtime (Select one): ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Upset when caregiver leaves the room ☐ Become distressed – no obvious reason ☐ Destructive or self-injurious behaviour			
Response to child's behaviour at bedtime (Select one): ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about bedroom expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet			
To your knowledge, was the event marker pressed at the correct time? (Please circle)			
Yes	**No**		

To be completed in the morning		
Time woke up: 		
Time got out of bed:		
Estimated time taken to fall asleep:		
To your knowledge, was the event marker pressed at the correct time? (Please circle)		
Yes	**No**	
Child's behaviour when getting out of bed: ☐ No behaviours of concern ☐ Refuses to get out of bed		
Response to child's behaviour (select one): ☐ Not applicable- no behaviours of concern ☐ Ignore behaviour ☐ Verbally remind child about morning routine expectations ☐ Suggest removal of preferred activity/item if will not get up		
Please rate how typical your child's sleep quality was **1 = Significantly better than usual, 3 = Typical and 5 = Significantly poorer than usual**		
1 2 3 4 5		
Do you think your child slept well? (Please circle)		
Yes	**No**	

Please record any times your child woke up during the night	
Waking 1	**Waking 2**
Time of waking: **End of waking:** **Perceived reason for waking (select one):** ☐ Wet/needing toilet ☐ Hungry/thirsty ☐ Pain/discomfort ☐ Anxiety ☐ Unknown ☐ Other – please state: **Child's behaviour during waking (select one):** ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Become distressed ☐ Destructive or self-injurious behaviour **Response to child's behaviour (select one):** ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about night-time expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet ☐ Give child a drink/take to the toilet etc.. but minimising attention	**Time of waking:** **End of waking:** **Perceived reason for waking (select one):** ☐ Wet/needing toilet ☐ Hungry/thirsty ☐ Pain/discomfort ☐ Anxiety ☐ Unknown ☐ Other – please state: **Child's behaviour during waking (select one):** ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Become distressed ☐ Destructive or self-injurious behaviour **Response to child's behaviour (select one):** ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about night-time expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet ☐ Give child a drink/take to the toilet etc.. but minimising attention

Waking 3	Waking 4
Time of waking: **End of waking:** **Perceived reason for waking (select one):** ☐ Wet/needing toilet ☐ Hungry/thirsty ☐ Pain/discomfort ☐ Anxiety ☐ Unknown ☐ Other – please state: **Child's behaviour during waking (select one):** ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Become distressed ☐ Destructive or self-injurious behaviour **Response to child's behaviour (select one):** ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about night-time expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet ☐ Give child a drink/take to the toilet etc.. but minimising attention	**Time of waking:** **End of waking:** **Perceived reason for waking (select one):** ☐ Wet/needing toilet ☐ Hungry/thirsty ☐ Pain/discomfort ☐ Anxiety ☐ Unknown ☐ Other – please state: **Child's behaviour during waking (select one):** ☐ No behaviours of concern ☐ Will not stay in bed/wants to play ☐ Become distressed ☐ Destructive or self-injurious behaviour **Response to child's behaviour (select one):** ☐ Not applicable – No behaviours of concern ☐ Ignore ☐ Verbally reassure/cuddles etc. then leave the room ☐ Verbally remind child about night-time expectations ☐ Stay in bedroom until child falls asleep ☐ Let child watch TV/play on tablet ☐ Give child a drink/take to the toilet etc.. but minimising attention

Any other notes:

……

……

……

Appendix D: Typically developing sleep diary

To be completed throughout the day <insert date>.				Completed by (initials)
Time Actiwatch removed				
Time Actiwatch replaced				
Time Actiwatch removed				
Time Actiwatch replaced				
Time Actiwatch removed				
Time Actiwatch replaced				
To be completed in the evening				
Time and duration of any daytime naps	Nap 1	Nap 2	Nap 3	
Timings and durations of activities in the evening when child sedate and not moving (e.g. watching TV or reading)				
Time got into bed				
Time lights turned off 				
Child's behaviour at bedtime				
What did you do to handle the problem (if applicable)				
To be completed in the morning				
Estimated time taken to fall asleep				
Time woken up 				
Time got out of bed				
Behaviour during wakings				
What did you do to handle the problem? (If applicable)				
Please make a note of the perception of your child's sleep quality				
Time and duration of any wakings	Waking 1	Waking 2	Waking 3	
Any other notes				

Appendix E: Cleaning protocol for actigraphy data

UNIVERSITY OF BIRMINGHAM

Actigraphy Cleaning Protocol

Jayne Trickett, Mary Heald, Andrew Surtees, Emma Clarkson, Georgie Agar, Chris Oliver and Caroline Richards

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School of Psychology

University of Birmingham

Please use this reference when citing this work:

Trickett J., Heald, M., Surtees, A., Clarkson, E., Agar, G., Oliver, C., & Richards, C. (2017). *Actigraphy Cleaning Protocol*. University of Birmingham, Birmingham.

Data cleaning

Needed to complete cleaning:

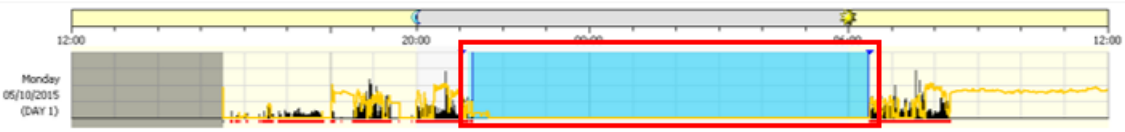
a) Open file on Philips Actiware
b) Child diary.

Step-1: Exclude any automatically-coded intervals which occur after the watch has been collected (E, Shift E, Ctrl E). This information can be gained from the sleep diary.

** Automatically-calculated sleep interval occurring on Saturday 12th has taken place after the watch has been collected. This interval has therefore been excluded*

Step-2: Exclude any nights during which the parent identifies a time when the watch was taken off.

- Open child diary to the relevant night, and confirm if parent reports any times that watch was taken off between lights out and wake-up time. If there are any such times check against actogram for consistency (i.e. no movement at this time). If consistent, exclude this night from data in actogram (E, Shift E, Ctrl E). If parent reports that the watch has been removed, but this is not evident on the actogram (i.e. evidence of movement during this time), keep the existing interval as it is and continue to step 3.



** Parent has recorded that the watch was removed on the night of Monday 6th. Inspection of the actogram suggests that there was no evidence of activity, and therefore appears to be consistent with parent report. The interval has therefore been excluded.*

** Parent has recorded that the watch was removed for part of the night of Thursday 10th. Inspection of the actogram suggests that there was activity throughout the interval, and this therefore appears to be inconsistent with parent report. The automatically-calculated interval has therefore been left.*

Step-3: Exclude any nights during which the watch appears to have been taken off, but this was not noted in parent diary.

- Visually inspect each night on actogram. If on any night, there is no recorded activity (**0 in activity column** of data list) for a period of 2 hours or more, exclude this whole night from actogram (E, Shift E, Ctrl E).

** Parent has not recorded that the watch was removed during the night of Monday 21st, but inspection of the actogram suggests that there were periods greater than 2hours without any evidence of activity. This would suggest that the watch was removed, and the automatically-calculated interval has therefore been excluded.*

Step-4: Clear any automatically-calculated sleep intervals from the day time and insert interval to night time

- Note any occasions on which the software has coded the sleep interval as in the day-time. Criteria for this is if the automatically-coded interval both starts and ends outside of period noted as sleep in parent diary. For any intervals on which this is the case, clear the sleep interval (Right click, clear interval).
- New interval should be inserted.
- To allocate start time of new interval: 1. Find first period of 20 minutes of sleep after lights out in diary (40 epochs coded as **0 in sleep/wake column** in data list). From there, go back to the last period of 10 minutes of activity (20 epochs coded as **1 in sleep/wake column**). Start time is first 0 after this.
- To allocate end time: 1. Find last period of 20 minutes of sleep before wake-up time in diary (40 epochs coded as **0 in sleep/wake column**). From there, go forward to the first period of 10 minutes of activity (20 epochs coded as **1 in sleep/wake column**). End time is first 0 before this.

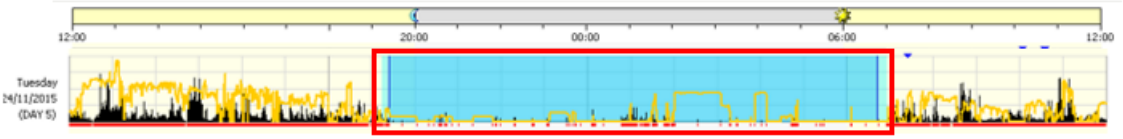
** Sleep interval has been automatically-calculated to fall between 9am and 7pm on Thursday 3rd. When consulting the parent diary, it can be seen that this interval falls outside of the time that the parent reported the child to be in bed, and so we can assume that the interval has been calculated incorrectly. As a result, we can clear the incorrect intervals, and insert new intervals.*

** New sleep intervals have been calculated using the data list, to identify times when the child is likely to have fallen asleep and awoken in the morning based on the data in the sleep/wake column. These data have been used to insert new intervals for Wednesday and Thursday nights.*

Step-5: Extend any intervals that have not captured entire night sleep.

- Locate any 20 minute periods coded as sleep in the actogram (40 epochs coded as 0 in sleep/wake column), that are **not** found within the automatically calculated sleep interval, **but are** between lights out and wake-up in sleep diary.
- If period is after the automatically calculated interval, extend interval from sleep period to last point before 10 minutes coded as awake (20 consecutive scores coded as 1 in sleep/wake column on datalist). To do this, clear the original interval and add a new one with the original start time and the new end time.
- If period is before the automatically calculated interval, extend interval from sleep period to first point after 10 minutes coded as awake (20 consecutive epochs coded as 1 in sleep/wake column on datalist). To do this, clear the original interval and add a new one with the original end time and the new start time.

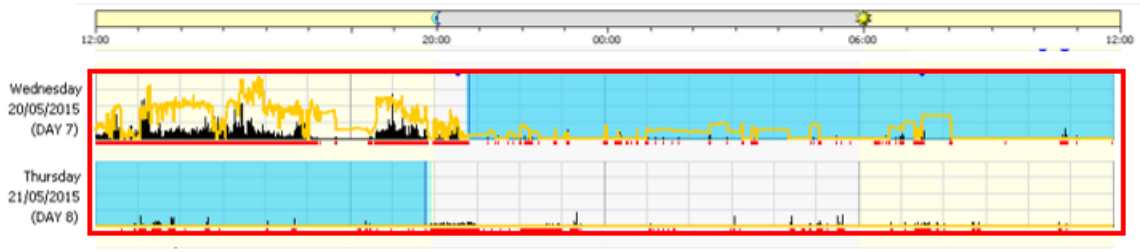
** The automatically-calculated sleep interval suggests that child is awake from 1 am on Wednesday 25th. However, inspection of the actogram suggests that there are several periods of non-activity after 1 am. Looking at the actogram more closely, it can be seen that some of these periods are greater than 20 mins, which implies that the child has returned to sleep and the automatically-calculated sleep interval has incorrectly estimated the child's final waking time as being too early. As a result, we can clear the incorrect interval, and insert a new interval.*



** A new sleep interval has been calculated using the data list, to identify the time at which the child is likely to have awoken in the morning based on the data in the sleep/wake column. The original time at which the sleep interval was automatically estimated to have begun has remained the same. The original start time, and new end time have therefore been used to insert a new interval.*

Step-6: Exclude any intervals that have twice the duration of the average Total Sleep Time

- Note any occasion where the software has created a sleep interval where the duration of Total Sleep Time and/or the sleep diary has stated that time between lights out and waking up time is twice that of the average TST. Exclude sleep interval.



**Parent has reported that child went to sleep at 20:45, woke up at 07:30 but did not get out of bed until 19:45. Total Sleep Time for this night is > twice as long as average Total Sleep Time across the whole week and therefore sleep interval has been excluded.*

Step-7: Exclude nights where parents reported that children had a sleepover with a friend

Step-8: Change any sleep intervals where it includes parent report sedentary activity.

- Check if the automatically-calculated sleep interval overlaps with the parent reported sedentary activity in the diary.
- If the sedentary activity in the sleep diary ends before the sleep interval in the actigraphy, do not change the sleep interval.
- If sleep interval starts during the period of sedentary activity, delete the sleep interval and create a new sleep interval. Extract the end of the sleep interval from the summary statistics and input the start of the sleep interval using the following guidance:
    - a) If the diary 'time lights turned off' and the event marker are congruent (+/- 15 minutes) use the time the event marker was pressed as the start of the newly created sleep interval.
    - b) If the diary 'time lights turned off' and event marker are incongruent (> +/- 15 minutes) use the time the event marker was pressed as the start of the newly created sleep interval **unless** the event marker was pressed during the sedentary activity (if this is the case, use the diary 'time lights turned off' as the start of the newly created sleep interval).
    - c) If the event marker was **not** pressed, use parent reported 'time lights turned off' as the start of the newly created sleep interval.
    - d) If the event marker was not pressed and the parent diary does not report 'time lights turned off' use the end of the period of sedentary activity in the sleep diary as the start of the newly created sleep interval.

** The automatically-calculated sleep interval suggests that parent has been in bed from 7:30pm on Thursday 4th. The parent diary reported sedentary activity between 7:30pm and 11:00pm. The diary and the event marker are incongruent, and the event marker was pressed during the sedentary activity. As a result, we clear this sleep interval and insert a new one using the parent reported 'time lights turned off'.*

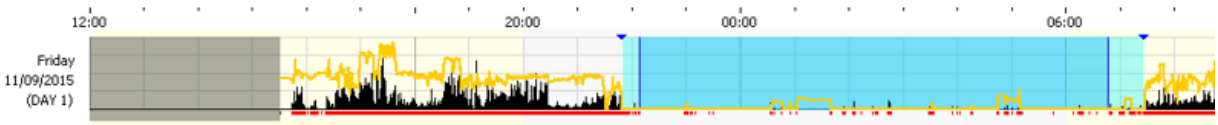
Step 9 – Changing the start of the rest interval

- Look over the whole week of the sleep diary. If on the majority of nights (e.g. 4/7) the following apply:
  - Event marker is missing
  - Event marker has been pressed multiple times within two hours of the automatic interval
  - Parent indicated that the event marker was pressed at the incorrect time

  Then use the sleep diary to adjust the start of the sleep intervals for each day. Use adjusted algorithms on page 10. For each day that the event marker is inaccurate (even if this is just 1/7) use the adjusted algorithm for that day specifically.

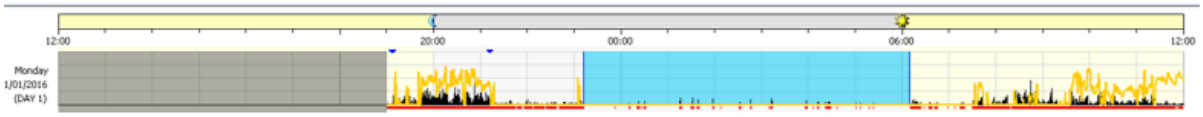
- Look at the event marker, sleep diary and the automatically calculated rest interval. If they are concordant (all three within +/-15 minutes of each other) then leave the automatically calculated rest interval.

**The sleep diary, event marker and automatically calculated interval all indicate that the lights were turned off at*



21:45, so the automatically calculated interval is left.

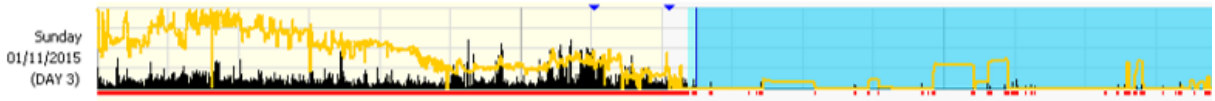
- If the event marker and sleep diary are concordant but discordant with the automatically calculated rest interval, delete this interval and replace it with a new interval. The new start time should be the time indicated by the event marker.



**The parent diary and event marker indicate that the lights were turned off at around 21:15. However, the automatically calculated rest interval begins at 23:13. Since they are discordant, the event marker is used to indicate when the child went to sleep and a new rest interval is added.*

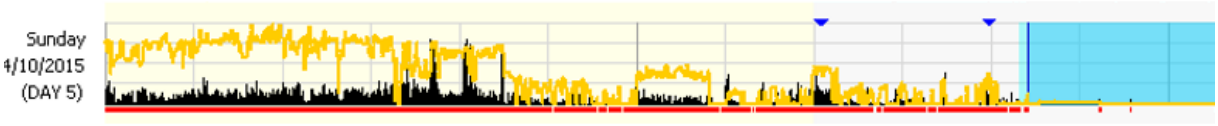
- If the event marker is discordant with the sleep diary but concordant with the automatically calculated rest interval, leave the automatically calculated rest interval.

**The event marker has been pressed at 20:06:30, but the parent reports in the sleep diary that they are not sure*



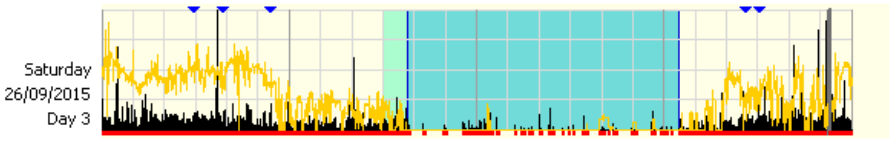
when it was pressed or when the lights were turned off. The automatically calculated rest interval begins within 15 minutes of the event marker being pressed, so no change is made to the start of the rest interval.

- If the sleep diary is discordant with the event marker but concordant with the automatically calculated rest interval, leave the automatically calculated rest interval.

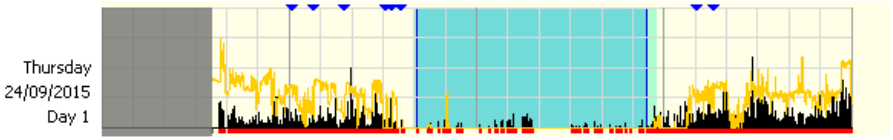


**The sleep diary indicates that the lights were turned off at 22:30, but the event marker has been pressed at 21:59. The automatically calculated interval suggests the child fell asleep at 22:24:30. Since this is within 15 minutes of the time indicated by the parent sleep diary, leave the automatically calculated interval.*

- If the sleep diary, event marker and automatically calculated rest interval are all discordant, leave the automatically calculated rest interval.



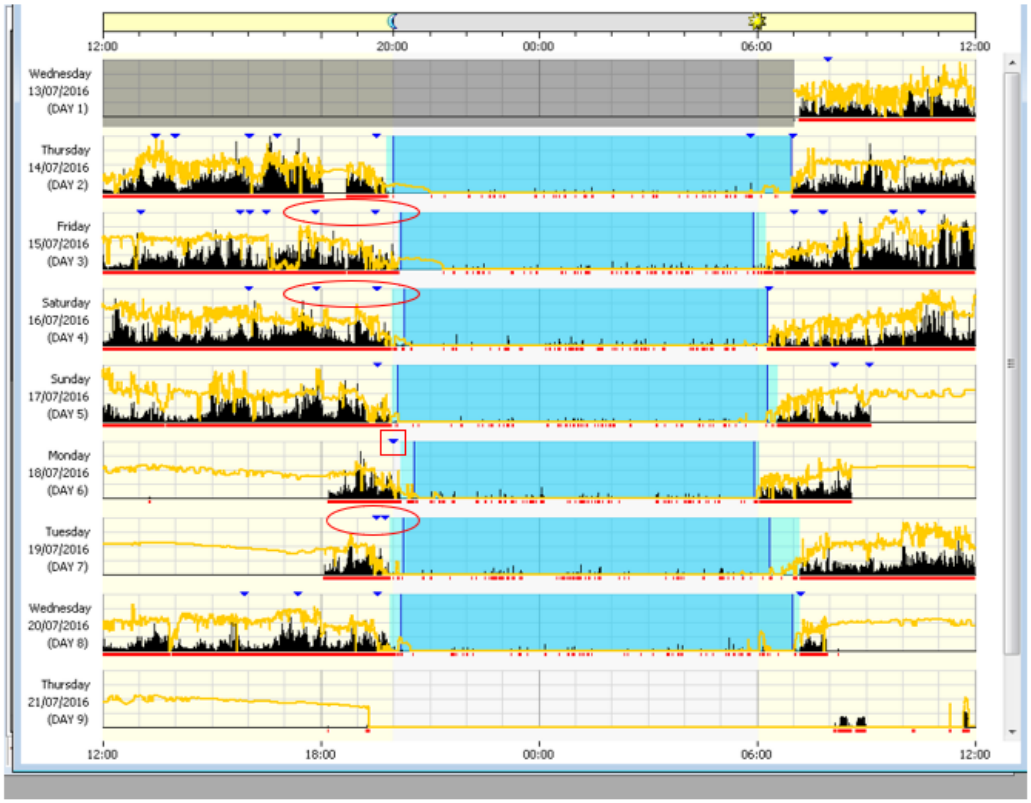
**Sleep diary indicated lights out at 20:15, this is discordant with light and activity levels by 45 mins. Sleep diary lights out time is earlier than automatic interval. No sedentary activity overlap with sleep period- used automatically calculated sleep interval.*



**Sleep diary indicated lights out at 22:30, this is discordant with lights and activity levels by 30 mins. Sleep diary lights out time is later than automatic interval. No sedentary activity overlap with sleep period- used automatically calculated sleep interval.*

ALTERNATIVE ALGORITHMS

- If the event marker has been identified as missing or inaccurate on a majority of nights, then it should be discounted.



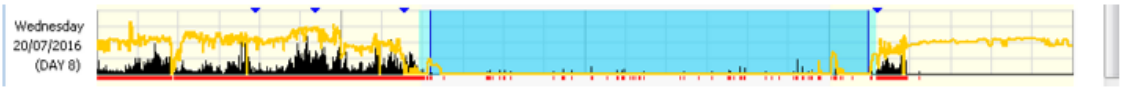
**On several nights (Friday, Saturday, Tuesday) the event marker has been pressed multiple times within two hours of the automatically calculated rest interval. Additionally, on Monday, the event marker has been pressed at 20:02, but the parent diary indicates it was pressed at 19:30. This means that the event marker is inaccurate for the majority of nights (4/7), and so should be discounted. This means that only alternative algorithms 1 and 2 should be used to clean the data.*

- If the event marker has been identified as inaccurate, but the sleep diary and automatically calculated rest interval are concordant, leave the automatically calculated rest interval.

**The event marker has been pressed several times. The sleep diary and automatically calculated interval indicate that the child went to sleep at around 19:45, so the automatically calculated interval is left.*

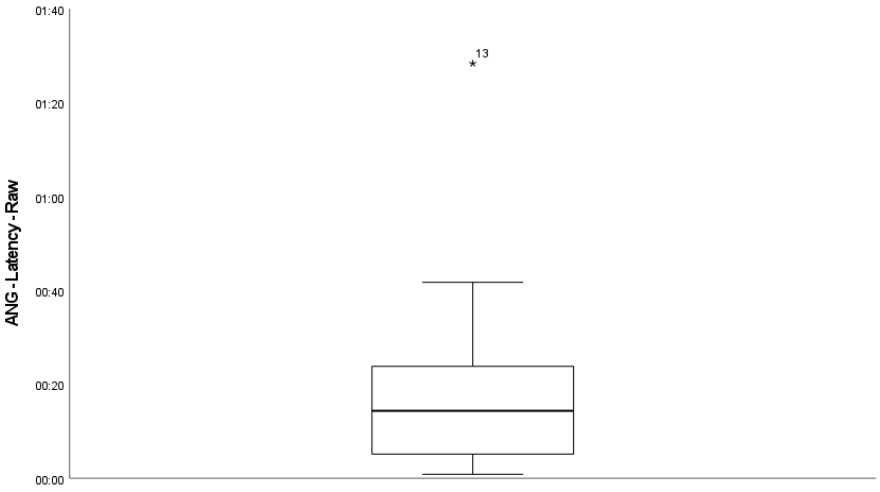
- If the event marker has been identified as inaccurate and the sleep diary is discordant with the automatically calculated interval, use the sleep diary to insert a new interval.

**The event marker has been pressed multiple times throughout this participant's sleep week, so the event marker is discounted. The sleep diary says that the lights were turned off at 19:35pm, but this is discordant with the automatically calculated sleep interval by 20 minutes. Therefore, the automatic interval is cleared and a new interval is inserted, which begins at 19:35pm.*

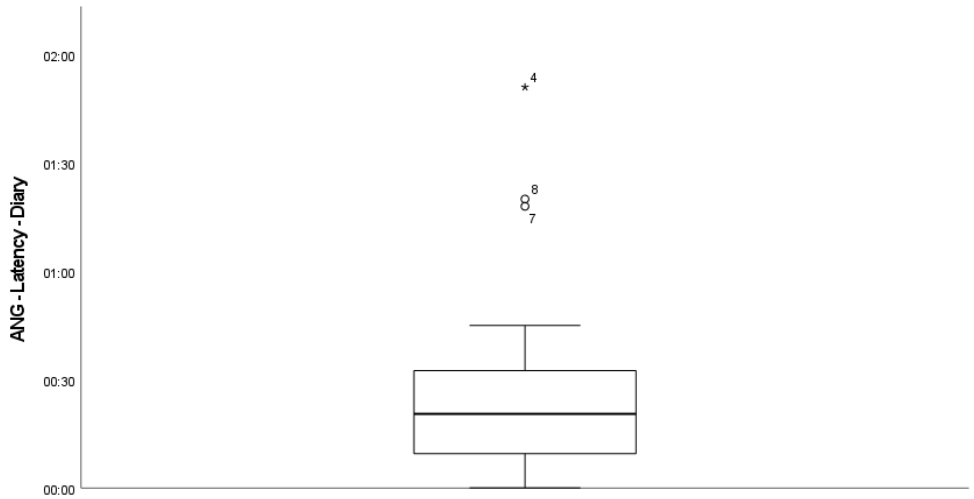


Appendix F: Box plots showing presence of far outliers

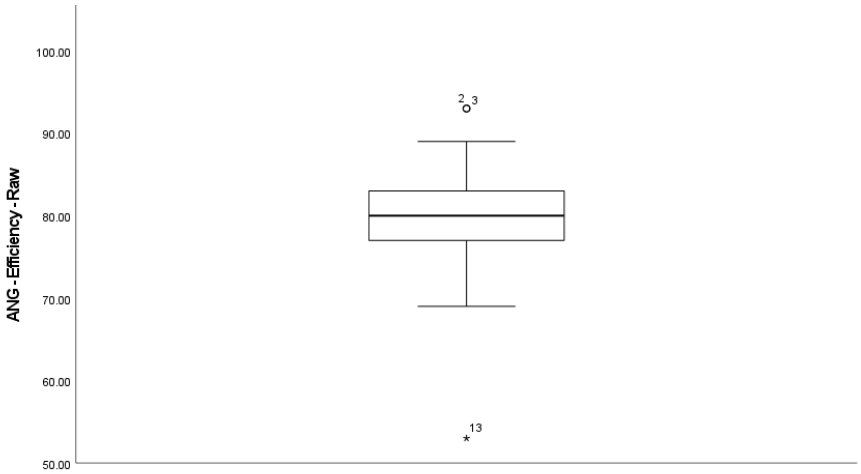
Angelman Syndrome – Onset Latency - Autoscored Actigraphy



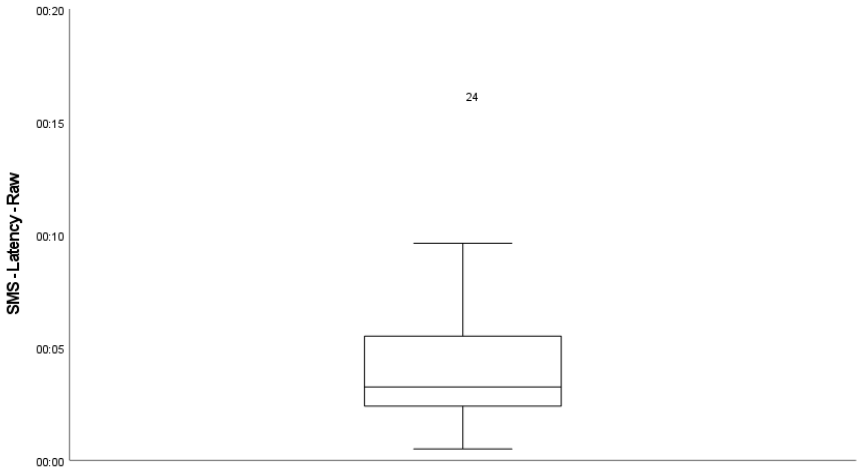
Angelman Syndrome – Latency – Diary



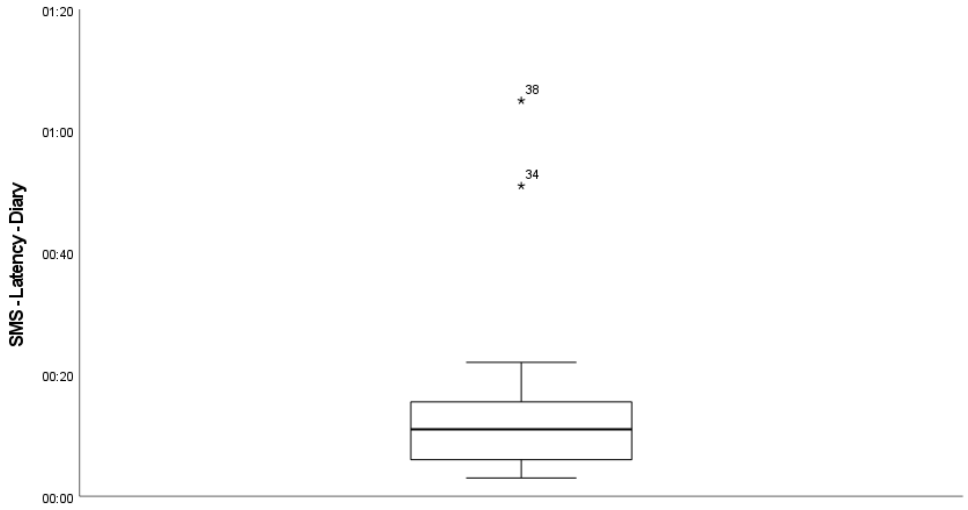
Angelman Syndrome – Efficiency – Autoscored Actigraphy



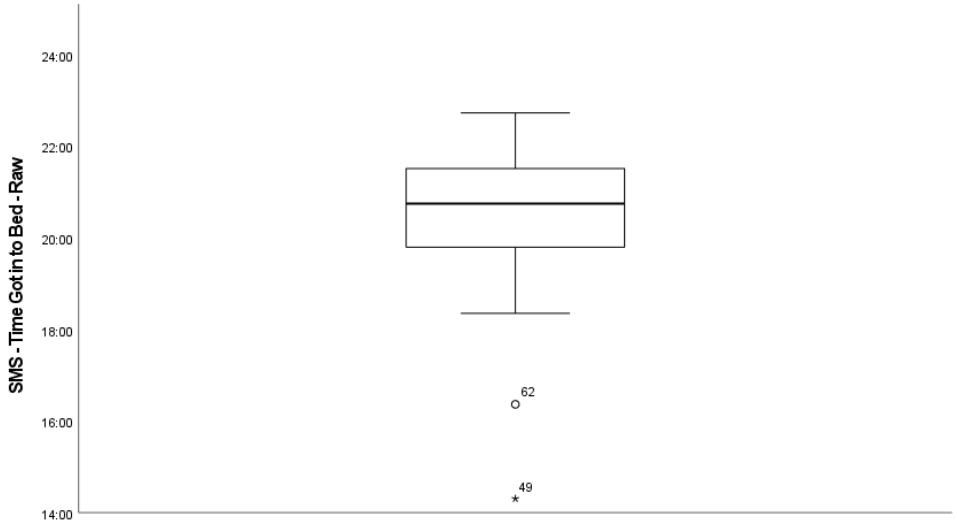
Smith-Magenis Syndrome- Latency – Autoscored Actigraphy



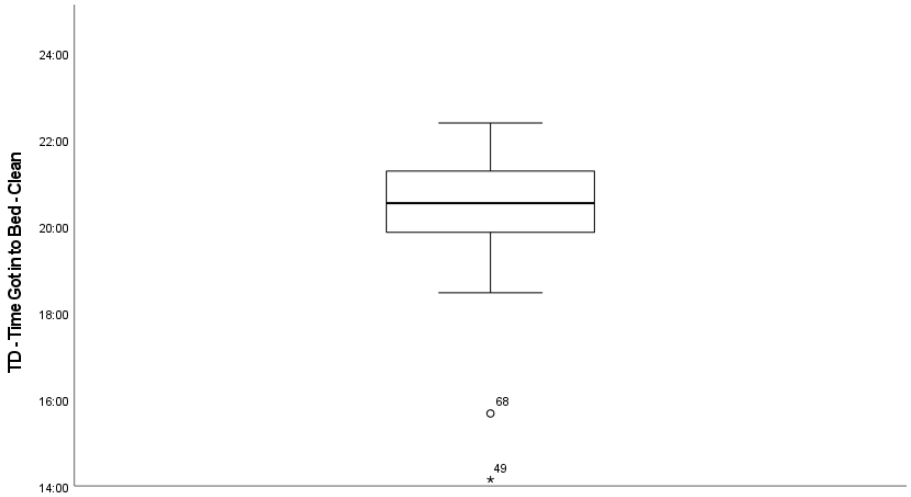
Smith-Magenis Syndrome – Latency – Diary



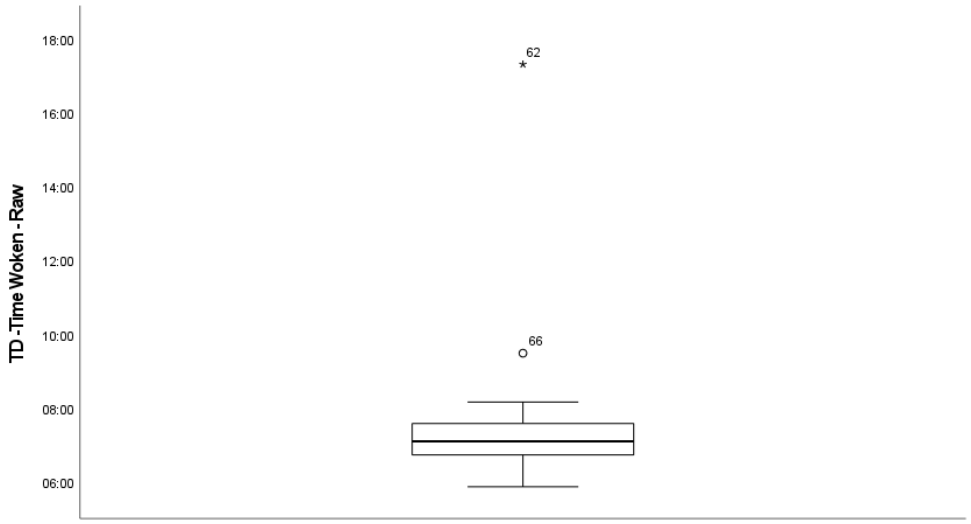
Smith-Magenis Syndrome – Time Got in to Bed – Autoscored Actigraphy



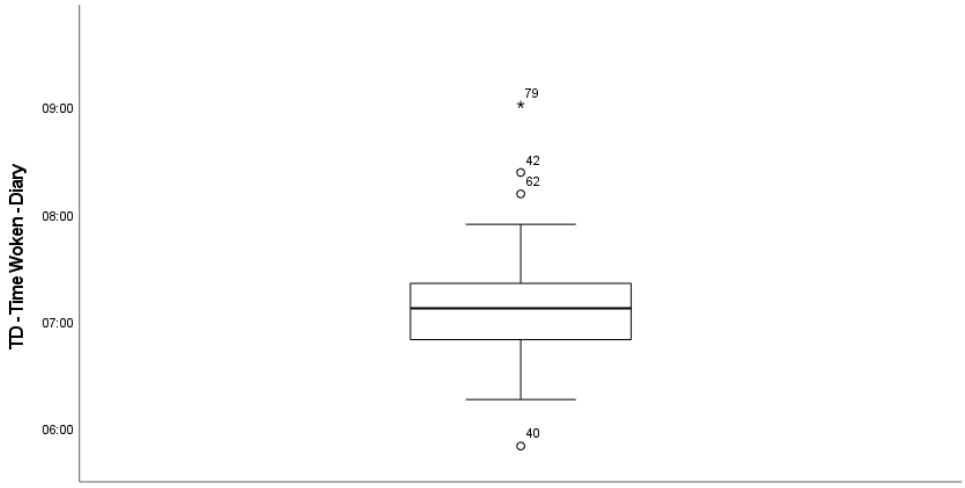
Typically Developing – Time Got in to Bed – Clean Actigraphy



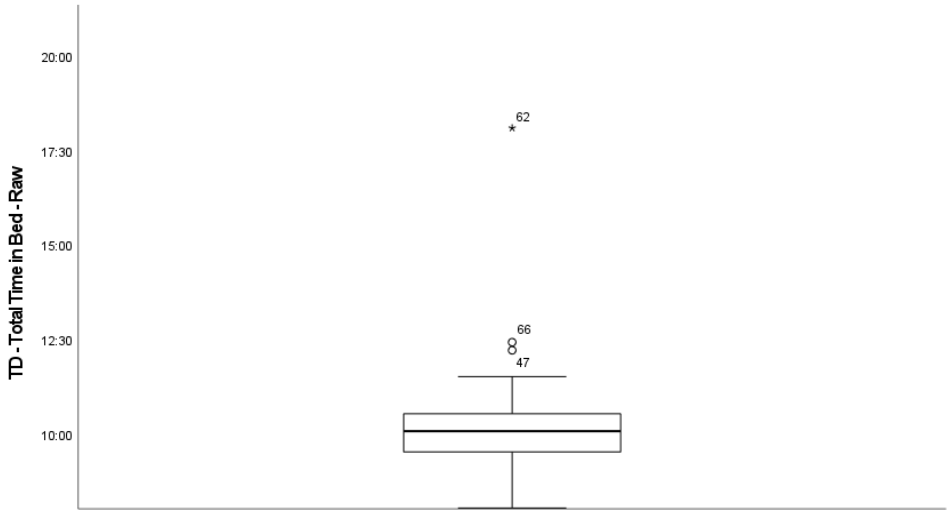
Typically Developing – Time Woken – Autoscored Actigraphy



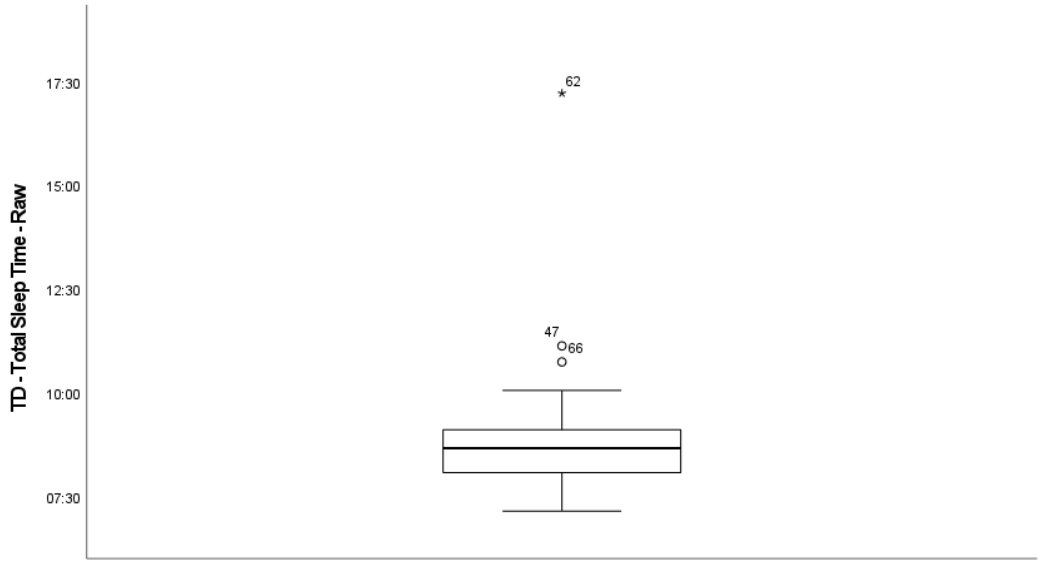
Typically Developing – Time Woken - Diary



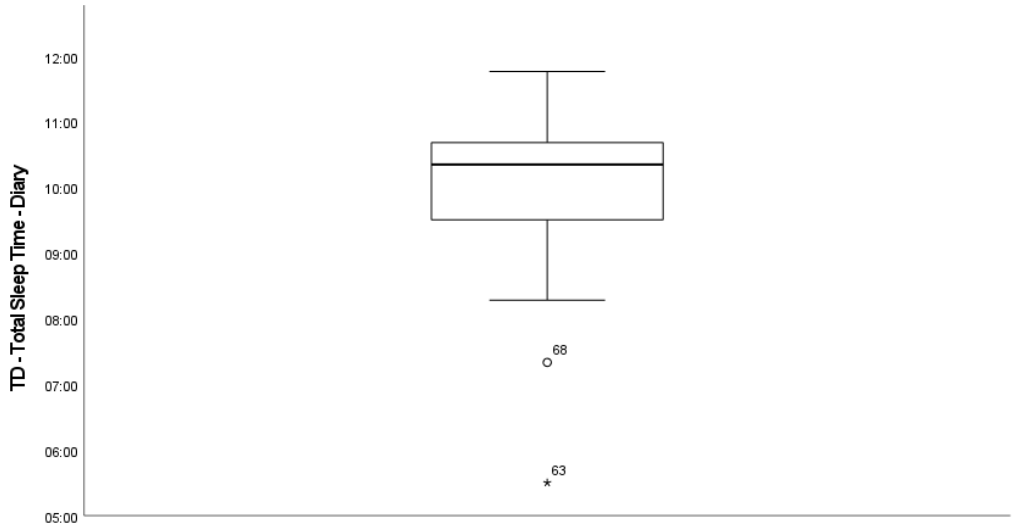
Typically Developing – Total Time in Bed – Autoscored Actigraphy



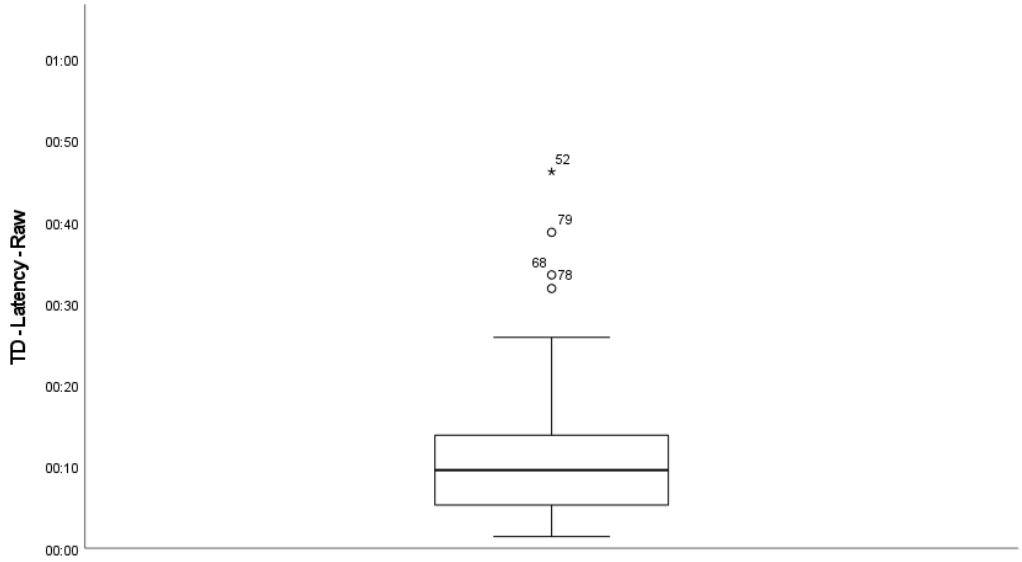
Typically Developing – Total Sleep Time – Autoscored Actigraphy



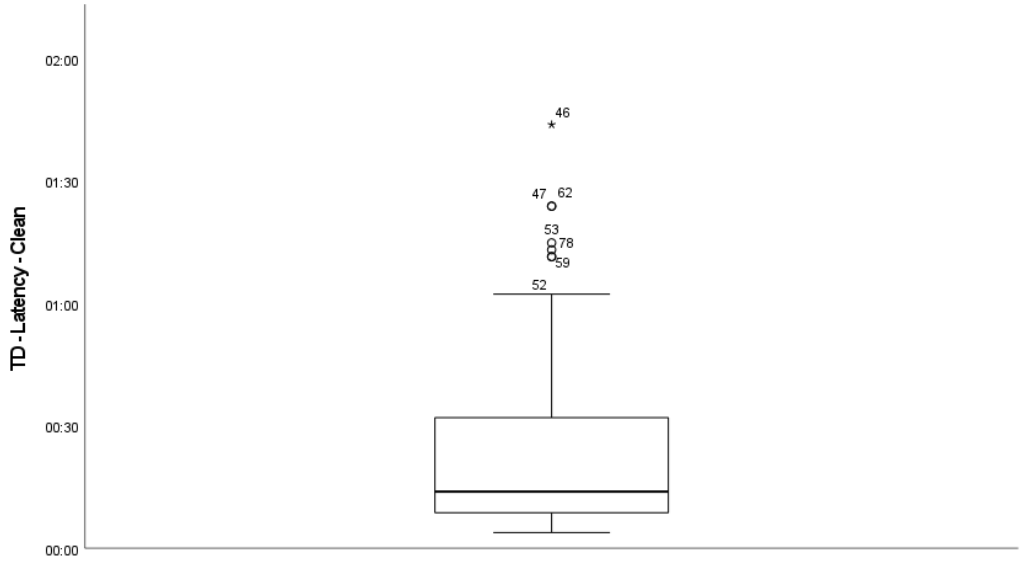
Typically Developing – Total Sleep Time – Diary



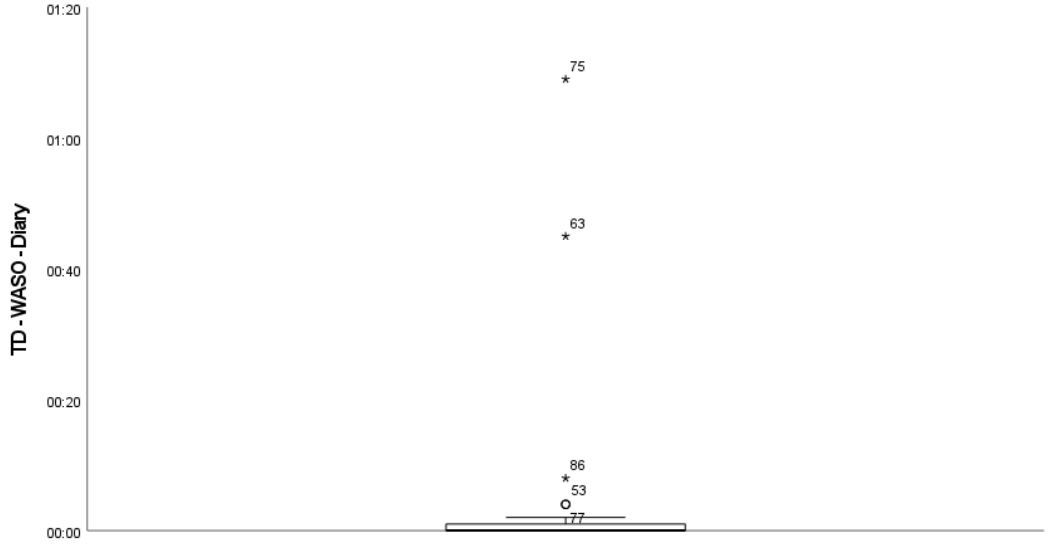
Typically Developing – Latency – Autoscored Actigraphy



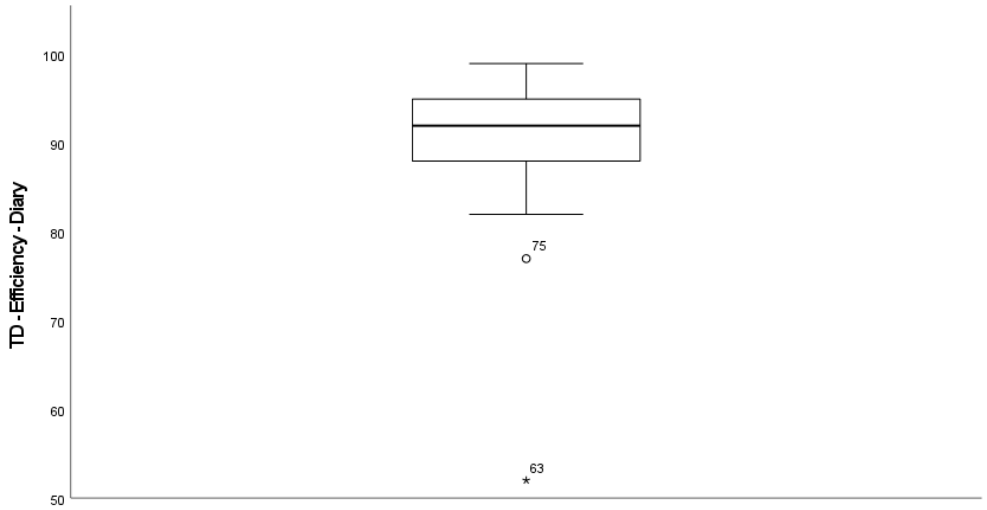
Typically Developing – Latency – Clean Actigraphy



Typically Developing – Wake After Sleep Onset - Diary



Typically Developing – Efficiency – Diary



Appendix G: Results for main effect of Group, main effect of Data Type and interaction of Data Type x Group prior to removal of far outliers.

Main effect of Group across parameters prior to outlier removal

	F	***p***	η^2
Time Got in to Bed	2.33	.104	0.53
Time Woken	32.21	.001	.437
Onset Latency	3.66	.030	.086
Total Sleep Time	13.08	.001	.240
WASO	17.79	.001	.616
Total Time in Bed	6.2	.003	.131
Sleep Efficiency	11.49	.000	.221

Main effect of Data Type across parameters prior to outlier removal

	F	***p***	η^2
Time Got in to Bed	4.6	0.014	.052
Time Woken	4.76	.024	.054
Onset Latency	10.88	.001	.122
Total Sleep Time	69.62	.001	.456
WASO	132.96	.001	.616
Total Time in Bed	40.62	.001	.331
Sleep Efficiency	33.66	.000	.294

Data type x Group interaction across parameters prior to outlier removal

	F	***p***	η^2
Time Got in to Bed	3.61	.176	.038
Time Woken	3.67	.020	.081
Onset Latency	.363	.835	.009
Total Sleep Time	4.07	.009	.089
WASO	3.01	.020	.068
Total Time in Bed	4.42	.008	.097
Sleep Efficiency	2.1	.120	.049