Objective Assessment of Sleep in Neurodevelopmental Disorders:

A Study of Children with Mucopolysaccharidosis Type III

A thesis submitted to the University of Manchester for the degree of Doctor of Clinical Psychology in the Faculty of Medical and Human Sciences

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List of Contents

Abstract ............................................................................................................................... 6
Declaration ............................................................................................................................ 7
Copyright Statement ........................................................................................................ 8
Acknowledgements ......................................................................................................... 9

Paper One: A Systematic Review of Objective Studies of Sleep in Neurodevelopmental Genetic Disorders

Abstract ........................................................................................................................... 11
Introduction ...................................................................................................................... 12
Method ............................................................................................................................. 15
  Search Strategy .............................................................................................................. 15
  Selection of Studies ..................................................................................................... 15
  Description of Studies ................................................................................................. 15
  Quality Assessment .................................................................................................... 16
Results ............................................................................................................................... 18
  Mucopolysaccharidoses ............................................................................................... 18
  Williams Syndrome .................................................................................................... 21
  Fragile X Syndrome ................................................................................................... 23
  Tuberous Sclerosis .................................................................................................... 24
  Angelman Syndrome .................................................................................................. 25
  Rett Syndrome .......................................................................................................... 27
Discussion ....................................................................................................................... 29
References ....................................................................................................................... 33
Paper Two: Actigraphic Assessment of Sleep in Children with Mucopolysaccharidosis Type III

Abstract........................................................................................................................................... 39
Introduction....................................................................................................................................... 40
Method.............................................................................................................................................. 44
  Participants....................................................................................................................................... 44
  Materials and Procedure.................................................................................................................. 46
  Analysis.......................................................................................................................................... 48
Results................................................................................................................................................ 49
  Children’s Sleep Habits Rating Scale.............................................................................................. 49
  Actigraphy....................................................................................................................................... 51
  Melatonin Analyses.......................................................................................................................... 53
Discussion......................................................................................................................................... 54
References.......................................................................................................................................... 63

Paper Three: Critical Appraisal

Introduction......................................................................................................................................... 69
Literature Review............................................................................................................................... 69
Empirical Paper................................................................................................................................ 70
  Recruitment and Sample Size.......................................................................................................... 70
  Consent and Capacity........................................................................................................................ 72
  Timing............................................................................................................................................. 73
  Children’s Sleep Habits Rating Scale............................................................................................... 74
  Actigraphy...................................................................................................................................... 74
  Medication....................................................................................................................................... 77
Analysis............................................................................................................................................. 78
Team Working.................................................................................................................................... 79
Meeting Families............................................................................................................................... 80
Salivary Sampling.............................................................................................................................. 82
Clinical Implications.......................................................................................................................... 83
Further Research............................................................................................................................... 85
Summary............................................................................................................................................ 86
References.......................................................................................................................................... 87
Appendices

Appendix A: Sleep Medicine Guide for Authors................................. 91
Appendix B: Quality Assessment of Studies........................................ 93
Appendix C: American Journal of Intellectual and Developmental Disabilities Guide for Authors................................................................. 98
Appendix D: Consent Forms................................................................. 100
  Consent Form for Parents of Children with MPS III.......................... 100
  Consent Form for Parents of Typically Developing Children............... 102
  Consent Form for Typically Developing Children Aged 14-15.............. 104
  Assent Form for Typically Developing Children Aged 6-13................ 105
Appendix E: NHS National Research Ethics Service Approval Letters........ 106
Appendix F: NHS Trust Research and Development Approval............... 113
Appendix G: Invitation Letter to Parents of Children with MPS III.......... 116
Appendix H: Participant Information Sheets........................................ 118
  Participant Information Sheet for Parents of Children with MPS III .... 118
  Participant Information Sheet for Parents of Typically Developing Children.. 123
  Participant Information Sheet for Typically Developing Children Aged 6-10.. 128
  Participant Information Sheet for Typically Developing Children Aged 11-15.. 132
Appendix I: Participant Demographic Sheets....................................... 136
  Demographics Sheets for Children with MPS III.............................. 136
  Demographics Sheets for Typically Developing Children................... 138
Appendix J: Children’s Sleep Habits Rating Scale.............................. 139
Appendix K: Scoring of the Children’s Sleep Habits Rating Scale.......... 141
Appendix L: Amendment to NRES to Recruit Across Britain................. 142
Appendix M: Amendments to NRES for Recruitment of Controls............. 144
Appendix N: Lone Working Procedure............................................... 149
Appendix O: Sleep Diary................................................................. 150
List of Tables

Paper One
Table 1: Quality Assessment Checklist ................................................................. 17
Table 2: Summary of Objective Sleep Investigations in Individuals with MPS .......... 20
Table 3: Summary of Objective Sleep Investigations in Individuals with Williams Syndrome ............................................................................................................... 21
Table 4: Summary of Objective Sleep Investigations in Individuals with Angelman Syndrome ............................................................................................................... 26

Paper Two
Table 1: MPS III Participant Information ................................................................... 46
Table 2: Comparison of MPS III and Control Group Data on the Children’s Sleep Habits Rating Scale ........................................................................................................... 50
Table 3: Sleep Parameters (per night) in MPS III Patients Averaged over the Recording Period .................................................................................................................... 51
Table 4: Comparison of Sleep Parameters of Children with MPS III and Controls ....... 53
Table 5: Median (IQR) Melatonin Concentrations across Groups, Time points and Days ................................................................................................................................. 54

List of Figures

Paper One
Figure 1: Flowchart of the process of study selection ................................................. 16

Word count: 19,216 (excluding references and appendices)
Abstract
This thesis, which focuses on sleep disturbance in people with neurodevelopmental disabilities, is divided into three sections. Paper one is a systematic review of the extant literature on objective studies of sleep in neurodevelopmental genetic disorders. Twenty papers met inclusion criteria and were subject to quality assessment, of which five were found to be high-quality, thirteen were medium-quality and two were low-quality. Studies were grouped by disorder and although there was some disparity across investigations, generally there was agreement about specific sleep difficulties in each disorder which seem to be part of the behavioural phenotypes. Overall a lack of total sleep, diminished REM sleep, and fragmented, less efficient sleep are prevalent across the disorders. Paper two is an empirical study which employed actigraphy to assess sleep in children with mucopolysaccharidosis type III (MPS III) and typically developing children. Parents completed a sleep diary, a sleep questionnaire and took saliva samples from their child. Actigraphic findings showed that MPS III patients had lengthened sleep onset latencies and greater daytime sleep than controls, but night-time sleep duration was within the normal range. In the MPS III group, some sleep problems correlated with age and progression of the disorder. Analysis of saliva samples revealed that children with MPS III had abnormal melatonin concentrations. Questionnaire responses demonstrated that children with MPS III had more sleep difficulties in all domains compared to controls. Implications for the management of sleep difficulties are discussed. Paper three is a critical appraisal of the research process which includes personal reflections on designing and conducting this research and a discussion of the principal issues which arose. Strengths and limitations of the research, ideas for further research and implications for clinical practice are considered.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.
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Acknowledgements

Firstly I would like to thank the children and parents who gave their time and effort to this project. I am grateful to the MPS Society UK who part-funded the project and provided help with advertising/recruitment.

I would like to thank Dr Dougal Julian Hare for his enthusiasm and guidance whilst supervising my research. I am grateful to Professor Ed Wraith and Dr Simon Jones whose advice and assistance was invaluable. I am also appreciative to others who have contributed to the project including Dr Brian Bigger, Dr Maria Canal and Kia Langford-Smith.

Finally, thank-you to my family and friends for their support over the years and a special mention to my parents for all their love, encouragement, and understanding.
Paper One

A Systematic Review of Objective Studies of Sleep in Neurodevelopmental Genetic Disorders

Keywords: Sleep, Actigraphy, Polysomnography, Neurodevelopmental, Developmental, Intellectual Disability, Systematic review

Prepared in accordance with author guidelines for submission to Sleep Medicine (Appendix A)

Word count: 6200
Abstract

Sleep difficulties have been reported in a range of neurodevelopmental disabilities which are manifested in the quantity and quality of sleep, as well as sleep architecture. Investigations have employed subjective methodologies (questionnaires, surveys, diaries) or objective measurement (actigraphy, polysomnography) to assess sleep. This systematic review examined the evidence on sleep in neurodevelopmental disabilities of genetic origin, which has been measured using objective devices. Twenty studies met inclusion criteria which involved individuals with mucopolysaccharidoses, Williams syndrome, fragile X syndrome, tuberous sclerosis, Angelman syndrome, or Rett syndrome. Papers were examined using a quality assessment checklist, which indicated that five studies were high-quality, thirteen were medium-quality and only two were poor-quality. Results are grouped and discussed by disorder, and commonalities across disorders are noted, including a greater prevalence of fragmented, less efficient sleep, reduced total sleep duration and lack of REM sleep, compared to neurotypical individuals. Limitations of the studies and shortcomings of the review as a whole are discussed.
Introduction

Neurodevelopmental disorders are associated with an irregularity of the growth or development of the neurological system and the brain. A disorder is considered neurodevelopmental when it originates before adulthood. The aetiology can be genetic, psychological trauma or neglect, an immune disorder, an infectious disease, a head injury, medication, or toxic/environmental causes. Symptoms can be pervasive and the full extent of cognitive impairments might only become clear as the child ages and developmental milestones are not achieved. Commonly, affected individuals experience difficulties with memory, learning and emotion. Some conditions are life-limiting, and diseases can be neurodegenerative in nature, such as Rett syndrome.

Sleep problems are frequently reported in people with intellectual disabilities, with prevalence estimates ranging from 13% to 86% [1]. Rates vary according to multiple factors including age, level of cognitive impairment, physical abnormalities, measures used, living environment, nature of sleep difficulty assessed and genetic disorder [2]. Typical sleep problems include irregular sleep patterns, shortened sleep duration, difficulties settling at night, frequent night waking and early morning wakening [3]. Daytime sleepiness and napping can also be an issue and might impact on night-time sleep.

Sleep difficulties can be caused by range of factors, many of which are more common in individuals with developmental disabilities. Sleep problems can be associated with seizure activity, breathing irregularities (e.g. obstructive sleep apnoea), involuntary limb movements, or an irregular sleep–wake cycle. Sleep disturbance can be also be part of the behavioural phenotype of a disorder. The duration and quality of sleep has persistent effects on cognition, behaviour and emotion [4]. Therefore for individuals with pre-existing intellectual impairments, disruptive sleep might further impede their cognitive abilities. Poor sleep has been found to be associated with daytime behavioural problems
Naturally, caregivers and other family members are also affected. Parents of children with developmental disorders and sleep difficulties have reported high levels of stress and irritability [7].

Sleep can be decomposed into distinct stages, each characterised by discrete neurological and physiological features. Typically a person takes around 90 minutes to enter rapid eye movement (REM) sleep and REM accounts for approximately 25% of total sleep time each night. There has been much deliberation over the functions of sleep [8-10]. A wealth of evidence has proposed that REM sleep is necessary for cognitive functioning, including memory, learning and information processing [11], although others have cast doubt on this [12]. It has long been postulated that non-REM serves a restorative function for physical health [13], such as muscle development and tissue repair.

Researchers have employed a variety of objective and non-objective methodologies to measure sleep. Questionnaires, surveys and diaries have been used, often completed by a parent/caregiver about their dependant’s sleep. Studies using these pen and paper measures can include large samples across a wide geographical area, which is useful for gathering data on sleep in rare disorders of which sufferers are geographically dispersed. There are a number of problems with their use, with specific difficulties relevant to the topic of this review. Reporter bias can be an issue, as caregivers have different views of what is, or is not, a problem, as well as the level of severity of a problem. Most questionnaire studies on sleep in individuals with neurodevelopmental disorders ask for the views of just one parent, often the mother, despite the fact that the other parent might have divergent views which are left unaccounted for. Social desirability can also be a problem, particularly if the research is conducted by a family’s regular clinician who is responsible for the patient’s care. There are several reports of strong correlations between parental questionnaire and objective measures of sleep, such as actigraphy and filmed
observational studies [14]. However despite the best efforts of caregivers at completing surveys or diaries, there are often omissions or errors. For instance, when sleep data was gathered concurrently by diary entries and actigraphy, it was apparent that parents had not been aware of a number of times when the child awoke at night [15].

Polysomnography (PSG) and actigraphy gather objective sleep data in a non-invasive way. PSG is considered to be the gold-standard of sleep assessment, and measures biophysiological functions including brain waves, limb movements, breathing, heart rhythm and eye movements. An actigraph, usually worn around the wrist, measures body movement and provides information on sleep quantity, quality and circadian rhythms. PSG provides richer data, and can be more accurate than actigraphy in measuring some sleep variables [16]. However individuals with intellectual disabilities, particularly those with a preference for routine and sensory sensitivities such as people with autism, might not tolerate being in an unfamiliar laboratory setting with electrodes and wires on their body. PSG is also more expensive compared to actigraphy. An actigraph can be used to gather data 24 hours a day, in a person’s natural environment, over days or even weeks.

There have been a number of reviews of sleep in individuals with developmental disabilities, both people with genetic developmental disorders or generic intellectual disabilities. However to date, there have been no systematic reviews on the topic of sleep in neurodevelopmental genetic disorders which has been measured by objective methodologies only. Therefore this article aims to address this gap. Identifying commonalities in sleep patterns across individuals with the same genetic disorder can enhance the understanding of the behavioural phenotype. Due to the wealth of research already available on sleep in autism [17-19], Asperger syndrome [20], Down syndrome [21], and Prader-Willi syndrome [22], these disorders will not be included in this review.
Method

Search Strategy

In December 2011, an electronic search was conducted on the following databases: Medline (1946-2011), Embase (1974-2011), PsycINFO (1950-2011), Scopus (1996-2011), PubMed (1950-2011), ISI Web of Knowledge (1945-2011) and Google Scholar (1950-2011). The following search terms (set as keywords or title words) were used: sleep AND mucopolysaccharid* OR sanfilippo OR hurler OR scheie OR hunter OR sly disease OR williams syndrome OR rett OR smith-magenis OR angelman OR fragile x OR tuberous sclerosis OR cornelia de lange OR cri du chat. Limits included English language, articles, peer reviewed journals and human studies.

Selection of Studies

All titles/abstracts were screened and compared against the inclusion criteria. Studies were required to include participants with a neurodevelopmental genetic disorder and to have used an objective methodology (PSG/actigraphy) to assess sleep. Studies had to report at least one outcome measure of sleep quantity, quality or architecture. Acceptable study designs included randomised controlled trials, case control studies and case series. Exclusion criteria consisted of studies that only involved patients with Down syndrome, autism, Asperger syndrome, Prader-Willi syndrome, generic intellectual disabilities, acquired brain injury or other neurological insults. Grey literature, reviews, case studies, qualitative studies and animal studies were also omitted. Articles which included a non-objective methodology only were rejected. Publications consisting of an abstract only, rather than the full text, were not included.

Description of Studies

Searches produced 2492 potential studies of interest. Following a process of screening titles/abstracts, reviewing the full-text of some articles and excluding irrelevant studies, 20
papers met the inclusion criteria and were included in this review (see Figure 1 for the selection process).

Figure 1. Flowchart of the process of study selection

**Quality Assessment**

Previous systematic reviews have employed scales or checklists to evaluate the strength of the evidence [23]. A quality assessment checklist (Table 1) was designed for the current review and each paper which met the inclusion criteria was examined. All studies were assigned a score for each item (either 0-2 or 0-1) and these were summed to reach a total score. A total score of 0-7 was designated as poor quality, 8-14 as medium quality and 15-22 as high quality. Of the 20 studies, 5 were high-quality, 13 were medium-quality and 2 were poor quality (a full breakdown of scores can be provided by the author on request;
Appendix B). The studies were grouped by disorder and the main results are outlined below.

Table 1

*Quality Assessment Checklist*

<table>
<thead>
<tr>
<th>Question</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do the researchers have verification of diagnosis?</td>
<td>No</td>
<td>Subjects recruited through 3rd party who had sight of diagnostic evidence/syndrome specific association</td>
<td>Researchers have sight of diagnostic evidence</td>
</tr>
<tr>
<td>2. Medication:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Is information on medication provided?</td>
<td>No</td>
<td>Some details provided</td>
<td>Full details provided</td>
</tr>
<tr>
<td>b) Are subjects taking their usual medication during the study?</td>
<td>Yes/no details provided</td>
<td>Medications which might affect sleep are stopped</td>
<td>All medications are stopped</td>
</tr>
<tr>
<td>3. Is information provided on previous treatment for sleep problems?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>4. Is information provided on co-morbid diagnoses?</td>
<td>No</td>
<td>Information provided but not controlled for</td>
<td>Information provided &amp; controlled for (e.g. excluded, matched)</td>
</tr>
<tr>
<td>5. How was the patient sample selected?</td>
<td>Only those with a disorder identified as having sleep problems</td>
<td>A convenience sample of patients with the disorder of interest</td>
<td>A selection of patients with the disorder of interest as part of ongoing clinical work</td>
</tr>
<tr>
<td>6. Is there a control group?</td>
<td>No</td>
<td>Yes but not matched appropriately</td>
<td>Yes &amp; appropriately matched</td>
</tr>
<tr>
<td>7. Are the hypotheses and aims clearly described?</td>
<td>No</td>
<td>Some details provided</td>
<td>Full description of aims and hypotheses</td>
</tr>
<tr>
<td>8. How was sleep assessed?</td>
<td>-</td>
<td>Actigraphy</td>
<td>PSG</td>
</tr>
<tr>
<td>Question</td>
<td>Score</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>a) Is there a power calculation?</td>
<td>No details provided</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>b) Is it powered (i.e. are there enough subjects to do the statistics?)</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>c) Has the data been inspected to ensure it meets the assumptions of the test?</td>
<td>No details provided</td>
<td>Yes (or can be assumed from the use of non-parametric statistics)</td>
<td>-</td>
</tr>
<tr>
<td>d) Are the statistics appropriate?</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>e) Are effect sizes given?</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>f) Are actual probability values reported (e.g. 0.024 rather than &lt;0.05), except where $p&lt;0.001$?</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
</tr>
</tbody>
</table>

**Results**

**Mucopolysaccharidoses**

The mucopolysaccharidoses (MPSs) are group of inherited metabolic disorders characterised by the deficiency of lysosomal enzymes to break down glycosaminoglycans (GAGs). The accumulation of GAGs causes progressive damage to cells, tissue and organs [24]. There are seven known types of MPS and additional subtypes of MPS III and MPS IV. A summary of the studies outlined below involving individuals with MPS is displayed in Table 2.

A selection of studies described below included patients with MPS of different types who showed signs of sleep disordered breathing. This might limit generalisation to the wider population of patients with MPS. PSG was performed in eleven children (median
age 5.2 years, range 0.8-17.8 years,) with MPS who displayed evidence of obstructive sleep apnoea, but were not on enzyme replacement therapy [25]. On average, patients displayed a diminished total sleep time of 382.5 minutes, normal sleep latency of 15.4 minutes, adequate sleep efficiency of 84%, 15 awakenings per night and REM onset latency of 99.5 minutes. In a separate medium quality study [26], PSG was undertaken in a group of 11 patients with MPS aged 2.9 to 29.6 years (median 18.6 years), who had history of sleep-respiratory problems. The mean total sleep time of 385.9 minutes was comparable to that reported by Nashed and colleagues [25]. Santamaria et al. [26] found no variation in the total sleep time of children and adults ($p = 0.1$). Unfortunately no other results on sleep architecture or quality are provided, as the study focused primarily on breathing-related constructs. Another PSG investigation included 24 patients with MPS aged 2 to 23.7 years (mean 10.8 years), who were selected on the basis of their diagnosis, rather than suggestive sleep or breathing difficulties [27]. On average patients took 101.4 minutes to enter REM sleep. Sleep was decomposed as follows: stage 1 (18.6 %), stage 2 (50.3%), slow-wave sleep (14.8%) and REM (15.3%). There were no differences between pre- and post-pubertal groups.

All of the studies described above used a heterogeneous group of patients with MPS, increasing variability within the group, thus limiting the scope to detect deviations from the norm. Although all MPS disorders have a lysosomal storage abnormality, there are variations in the manifestation of the disorders. For example some are life-limiting, (e.g. MPS I, MPS III), whereas others are expected to have a reasonably normal lifespan (e.g. a slowly progressive form of MPS IV). None of the studies described above included a control group to enable authors to determine how significantly patients’ sleep differed from normal.

Mariotti et al. [28], conducted a high quality study using 48-hour PSG with individuals with MPS IIIA only (mean 14.1 years, range 7-20 years). Compared to age- and sex-
matched controls, the six patients showed impoverished total night-time sleep (240.5 min vs. 458.3 min, \( p < 0.05 \)), but increased daytime sleep (88.8 min vs. 24.8 min, \( p < 0.05 \)). Stage III and IV sleep percentages were reduced in MPS III patients (10.18% vs. 24.63%, \( p < 0.01 \)), and REM sleep was lower (8.03% vs. 21.53%, \( p < 0.05 \)), compared to controls.

Sleep of the younger and older participants appeared distinct, with older individuals (aged 12-20 years) displaying extremely fragmented sleep of inconsistent duration which was dispersed over day and night. Sleep in the younger two patients mainly occurred at night, but was interrupted by several awakenings. This demonstrated how the nature of sleep problems can change as the disease progresses.

### Table 2

*Summary of Objective Sleep Investigations in Individuals with MPS*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size</th>
<th>% male/female</th>
<th>Quality score</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nashed et al. [25]</td>
<td>4 MPS IH</td>
<td>73/27</td>
<td>8/22</td>
<td>Total sleep = 382.5 min</td>
</tr>
<tr>
<td></td>
<td>2 MPS IHS</td>
<td></td>
<td>medium</td>
<td>Sleep latency = 15.4 min</td>
</tr>
<tr>
<td></td>
<td>3 MPS II</td>
<td></td>
<td></td>
<td>Sleep efficiency = 84%</td>
</tr>
<tr>
<td></td>
<td>2 MPS IV</td>
<td></td>
<td></td>
<td>No. of awakenings = 15</td>
</tr>
<tr>
<td>Santamaria et al. [26]</td>
<td>2 MPS IS</td>
<td>73/27</td>
<td>10/22</td>
<td>Total sleep = 385.9 min</td>
</tr>
<tr>
<td></td>
<td>3 MPS II</td>
<td></td>
<td>medium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 MPS IIIB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 MPS IVA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 MPS VI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al. [27]</td>
<td>3 MPS I</td>
<td>92/8</td>
<td>12/22</td>
<td>REM latency = 101.4 min</td>
</tr>
<tr>
<td></td>
<td>15 MPS II</td>
<td></td>
<td>medium</td>
<td>Stage 1 = 18.6%</td>
</tr>
<tr>
<td></td>
<td>1 MPS III</td>
<td></td>
<td></td>
<td>Stage 2 = 50.3%</td>
</tr>
<tr>
<td></td>
<td>1 MPS IV</td>
<td></td>
<td></td>
<td>Slow-wave = 14.8%</td>
</tr>
<tr>
<td></td>
<td>4 MPS VI</td>
<td></td>
<td></td>
<td>REM = 15.3%</td>
</tr>
<tr>
<td>Mariotti et al. [28]</td>
<td>6 MPS IIIA</td>
<td>33/67</td>
<td>15/22</td>
<td>Total night-time sleep ( p &lt; .05 )*</td>
</tr>
<tr>
<td></td>
<td>6 controls</td>
<td></td>
<td>high</td>
<td>Daytime sleep ( p &lt; .05 )*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Slow-wave ( p &lt; .01 )**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>REM ( p &lt; .05 )*</td>
</tr>
</tbody>
</table>

* \( p < .05 \), ** \( p < .01 \)

All the papers on sleep in MPS provided medium- or high-quality evidence. It was

---

1 Exact probabilities values are not reported when they cannot be obtained.
positive that all researchers had verification of patients’ diagnosis and information was provided on past treatments for sleep difficulties or airway obstruction. However, apart from Nashed et al.’s [25] paper, details about patients’ current medications were not available.

Williams Syndrome

Williams syndrome (WS) is caused by the deletion of genes on chromosome 7 (7q11.23) [29]. Clinical features include intellectual disabilities (IDs), congenital heart disease, growth delay, and connective tissue abnormalities. A summary of objective investigations of sleep in patients with WS is displayed in Table 3. Apart from the paper by Goldman and colleagues [30], all of the studies included an appropriately matched control group.

Table 3

Summary of Objective Sleep Investigations in Individuals with Williams Syndrome

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Sample size</th>
<th>% male/female</th>
<th>Quality score</th>
<th>Results</th>
</tr>
</thead>
</table>
| Mason et al. (2011) [31] | 35 WS 35 controls | 43/57 | 12/22 medium | Total sleep ns*  
Sleep efficiency p = .012*  
Slow-wave p = .011*  
REM ns  
Time awake p = .052 |
| Arens et al. (1998) [32] | 7 WS 10 controls | Not reported | 13/22 medium | Total sleep ns  
Sleep efficiency ns  
Stages 1-2 p <.001**  
Slow-wave p <.001**  
REM ns  
Time awake p <.05* |
| Goldman et al. (2009) [30] | 23 WS 0 controls | 52/48 | 6/22 medium | No control group for Comparison |
| Gombos et al. (2011) [33] | 9 WS 9 controls | Patients 33/67 Controls 22/78 | 14/22 medium | Total sleep p =.027*  
Sleep efficiency p = .023*  
Non-REM p =.0007**  
Slow-wave p = .008**  
REM p =.0007**  
Time awake p =.009** |

*ns = not significant (exact p value not available)  
*p < .05, **p < .01
A large, medium-quality, PSG assessment of children with WS (mean age 9.3, range 2-18 years), found reduced sleep efficiency (82.2% vs. 86.7%) in patients compared to typically-developing matched controls [31]. Slow-wave sleep, as a percentage of total sleep time, was higher in children with WS (29.4% vs. 24.8%). It cannot be determined from the paper if patients were currently taking any prescribed drugs.

Arens et al. [32], used PSG with children with WS with a possible movement arousal disorder (mean age 3.9 years, range 1.8-7 years) and healthy children (mean age 5.3 years, range 2-9 years). There were no details about any previous treatments for sleep difficulties. Two children currently took daily medications, one for hyperactivity and another for hypertension. WS participants showed increased duration in sleep stages 3 & 4 in comparison to healthy children (34% vs. 20% of total sleep), but less time in stages 1 and 2 (41% vs. 59% of total sleep). Although there were no differences in the number of awakenings between groups, children with WS spent more time awake during sleep periods (10% vs. 4%).

Two-night PSG with adolescents and young adults with WS (mean age 20.5 years, range 14-28 years) and age- and sex-matched healthy individuals, showed a range of differences between the groups [33]. Compared to controls, WS subjects had reduced sleep efficiency (80.2% vs. 94.4%), decreased total sleep (423.9 min vs. 530.2min), more time awake at night (68.6min vs. 16.4min), increased slow-wave sleep (24.8% vs. 14.4%), greater non-REM sleep (80.8% vs. 72.4%), and lowered REM sleep (19.2% vs. 27.6%). Apart from one participant who continued their concoction of medication during PSG, no subjects were taking any drugs.

In an uncontrolled, poor quality actigraphic study involving individuals with WS (mean age 25 years, range 17-35 years), subjects slept for 7.6 hours per night, achieved just 74.4% sleep efficiency, and were awake for 56.1 minutes at night [30]. Unlike the other investigations using WS patients described above, Goldman and colleagues provided no
details of how confirmation of WS diagnosis was obtained. There were also no details of any medications patients were taking.

Generally the investigations concurred that individuals with WS had reduced sleep efficiency, spent more time awake during the night and longer in slow-wave sleep than the norm. There was also some support for an atypical duration of stage 1-2 sleep.

**Fragile X Syndrome**

Fragile X syndrome is caused by changes in the FMR1 gene on the X chromosome. The disorder is associated with intellectual disabilities and language, social, emotional, behavioural, and attentional problems. Sixteen boys with fragile X syndrome aged 6 to 18 years (mean age 10.81 years) and 16 matched controls underwent PSG assessment in a high quality study [34] (quality score 15/22). Half of the fragile X group had controlled seizures and were taking either valproic acid or carbamazepine. Total sleep time (309.29 min vs. 404.17 min, \( p < 0.001 \)), sleep efficiency\(^2\), and percentage and number of REM periods (2.7% vs. 17.25% \( p < 0.001 \), 0.69 vs. 5.86, \( p < 0.001 \)) were all reduced in the fragile X group. Fragile X subjects had an increased number of awakenings\(^3\) (\( p = 0.01 \)) and percentage of stage 2 sleep (55.71% vs. 39.87%, \( p = 0.004 \)).

Two-night PSG recordings revealed that nine boys with fragile X syndrome (mean age 9.91 years) had decreased total sleep time (486.4 vs. 510.9 mins, \( p < 0.05 \)), reduced REM sleep (17.6 vs. 22.4%, \( p < 0.01 \)), elevated first REM latency (151.2 vs. 97.1 min, \( p < 0.01 \)) and increased slow-wave sleep (25.1% vs. 21.6%, \( p < 0.025 \)) compared to six controls [35] (medium quality score 11/22). The authors did not describe if, and how, the control group was matched to the patient group, but the mean age of the groups were similar.

A polysomnographic investigation included three groups of male subjects: 7 with fragile

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\(^2\) Sleep efficiency percentages are not provided. Using the mean total sleep time and time in bed, estimates for Fragile X and control participants are 85.5% and 91.9% respectively.

\(^3\) Figures for the number of awakenings are not reported.
X syndrome (mean age 9.92 years, range 8.25-12 years), 17 with Autism, and 6 healthy controls [36] (medium quality score 14/22). Compared to the participants with Autism, fragile X patients were found to have increased first REM latency (156.64 min vs. 91.38 min, \( p < 0.01 \)) and a greater percentage of stage 1 sleep (4.84% vs. 4.69%, \( p < 0.05 \)).

Fourteen males with fragile X (mean age 13.1 years, range 7-25 years) underwent overnight PSG, along with subjects with Down syndrome and a control group [37] (high quality score 15/22). Participants were excluded if there was evidence of obesity or sleep-disordered breathing. The results of this high quality study revealed that compared to controls, fragile X patients had decreased REM sleep percentage (17.7% vs. 22.6%, \( p < 0.05 \)), but higher stage 1 sleep percentage (6.7% vs. 3.5%, \( p < 0.01 \)).

In these high- or medium-quality studies, diagnosis of fragile X was confirmed by molecular genetic testing and karyotyping. Apart from the study by Tawfik and colleagues [34], drug prescriptions were not discussed. In summary, individuals with fragile X had reduced sleep overall, less REM sleep, lengthy onset to the first REM period, and spent longer in stage 1 sleep. There was also some evidence of an increase in stage 2 and slow-wave sleep.

**Tuberous Sclerosis**

In tuberous sclerosis (TS), mutations occur in either the TSC1 gene on chromosome 9, or the TSC2 gene on chromosome 16. Benign tumours affect multiple organs, including the brain, and sufferers often show intellectual disabilities, epilepsy, autism, attentional difficulties, heart problems and kidney problems.

In a high quality study (quality score 15/22), PSG was used with ten children with TS (mean age 11 years, range 2-17.1 years), whose diagnosis was confirmed by clinical and MRI examinations [38]. All children had partial epilepsy and were on antiepileptic medications. Compared to a group of matched controls, the TS group had diminished
total sleep (380.7 min vs. 505.3 min, \( p < 0.05 \)), decreased sleep efficiency (76.4\% vs. 91.1\%, \( p < 0.005 \)), and a greater number of nocturnal awakenings (13.5 vs. 1.5, \( p < 0.05 \)). TS children also showed increased wake after sleep onset (16.1\% vs. 2.1\%, \( p < 0.05 \)), and stage 1 sleep (14.2\% vs. 6.9\%, \( p < 0.05 \)), but depressed REM sleep (10.1\% vs. 20.8\%, \( p < 0.05 \), 3.2 vs. 4.85 REM periods, \( p < 0.05 \)). Disrupted sleep was related to seizure activity and the presence of large tumours in frontal and temporal regions.

**Angelman Syndrome**

The most frequent cause of Angelman syndrome is the deletion of chromosome 15q11-13 which is maternally-inherited [39]. Other causes include paternal disomy of chromosome 15, methylation or UBE3A imprinting mutations, or in a small percentage of cases the genetic actiology is unknown. The disorder is typified by speech impairment, intellectual disabilities, ataxia, epilepsy, and sleep problems. A summary of the studies described below can be found in Table 4. All authors verified the Angelman diagnosis by genetic analysis and by the presence of behavioural, physical and EEG features.

Actigraphic monitoring with thirteen children with Angelman syndrome (mean age 6.5 years, range 2-10 years), found that sleep duration was within the normal range, with an average of 554.7 minutes at night [40]. Three of the children who were prescribed drugs to aid sleep (melatonin or chloral hydrate), had their medications stopped two weeks before actigraphic recording.

In the two studies conducted by Miano and colleagues described below, antiepileptic medications were not altered, but hypnotic medications were ceased at least two weeks prior to the assessment. No details were available in the two papers about any past treatments to aid sleep difficulties. A high quality study obtained polysomnographic recordings in children with Angelman syndrome (mean age 7.2 years, range 3-16 years) with sleep disturbances, and two groups of age-matched subjects: a control group and a group
with IDs and epilepsy [41]. Participants were subdivided by age, with eight years of age used as the cut-off point. Compared to controls, subjects with Angelman syndrome aged below nine years, had reduced sleep efficiency (79.9% vs. 95.8%) and REM sleep (11.8% vs. 24.2%, 63.6mins vs. 129.2mins), but increased slow-wave sleep (34.7% vs. 23.5%). Sleep parameters in Angelman syndrome patients did not differ from the participants with IDs and epilepsy. Subjects with Angelman syndrome aged nine and above displayed less REM sleep than controls (85.3min vs. 123.2min). Compared to the group with IDs and epilepsy, Angelman syndrome patients aged above eight years showed more stage shifts per hour (5.9 vs. 8.8).

Table 4

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Sample size</th>
<th>% male/female</th>
<th>Quality score</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhdanova et al. (1999) [40]</td>
<td>13 Angelman</td>
<td>31/69</td>
<td>13/22 medium</td>
<td>Total sleep = 554.7 min</td>
</tr>
<tr>
<td>Miano et al. (2004) [41]</td>
<td>15 Angelman</td>
<td>47/53</td>
<td>15/22 high</td>
<td>Age &lt; 9: Sleep efficiency p=.004** REM (%) p=.017* REM (min) p=.036* Slow-wave p = .008*</td>
</tr>
<tr>
<td></td>
<td>24 controls</td>
<td>50/50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 ID &amp; epilepsy</td>
<td>ID &amp; epilepsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miano et al. (2005) [42]</td>
<td>10 Angelman</td>
<td>50/50</td>
<td>14/22 high</td>
<td>% wakefulness p=.03* Sleep efficiency p=.005** REM (%) p=.001** Awakenings/h p = .025*</td>
</tr>
<tr>
<td></td>
<td>15 ID alone</td>
<td>ID alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 ID &amp; epilepsy</td>
<td>ID &amp; epilepsy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Unable to determine proportion of males and females in the ID and epilepsy group due to an error in Miano et al.’s paper

b ns = not significant

* p < .05, ** p < .01
A medium-quality study recruited patients with Angelman syndrome (mean age 5.8 years, range 2-16 years) who were attending a sleep clinic. These participants underwent PSG, along with a group of subjects with IDs alone and a group with IDs plus epilepsy [42]. Patients with Angelman syndrome displayed a higher percentage of wakefulness after sleep onset than those with IDs alone (27.5% vs. 7.4%), therefore sleep efficiency was lower in these patients (61% vs. 85.7%). REM sleep percentage was depressed in those with Angelman syndrome when compared to those with IDs alone (10.4% vs. 22.2%). The rate of awakenings per hour was higher in subjects with Angelman syndrome compared to those with ID and epilepsy (3.2 vs. 1.5). Overall these investigations suggested that although total sleep did not seem to be reduced in patients with Angelman syndrome, sleep was less efficient with more awakenings and less REM sleep.

**Rett Syndrome**

Most cases of Rett syndrome are caused by a mutation on the MECP2 gene, located on the X chromosome, hence the majority of sufferers are female. Signs of the disorder include epilepsy, repetitive movements, curvature of the spine, autism, intellectual disabilities, as well as communication, mobility and breathing problems. Nine girls aged 4 to 17 years (mean 10.1 years) with Rett syndrome stage III or IV were monitored using actigraphy [15] (medium quality score 13/22). Anticonvulsant medications were unchanged during the study period. Several participants had unrelated illnesses during actigraphic monitoring, consequently those days were excluded from the analysis. Results showed lengthy sleep-onset latency (mean 42.1 min), poor sleep efficiency (68%), and a shortened, fragmented total sleep time (7.5 hours, 14.9 awakenings per night). The authors stated that there were no associations between severity of sleep disorder and age or stage of the disorder, but the relevant statistical analyses were not provided.
Polysomnograms of eleven girls aged 2 to 15 years with Rett syndrome were compared to those of age-matched controls [43] (medium quality score 12/22). It is not clear which, if any, drugs were currently prescribed. All patients with Rett syndrome were found to exhibit less REM sleep than controls ($p < 0.01$, under 5s: 14.2% vs. 22.8%, over 5s: 12.4% vs. 21.7%). There was an increase in stage 2 sleep percentage (50.8% vs. 37.7%, $p < 0.01$) and a decrease in sleep onset latency (4.4 vs. 24.6 min, $p < 0.01$) in patients under five years of age, when compared to healthy subjects of the same age. In participants over five years, the percentage of total sleep time was lower in Rett syndrome patients than controls (79.8% vs. 91.8%, $p < 0.01$).

Thirty females with Rett syndrome aged 1 to 32 years (median age 7 years), were subject to overnight PSG [44] (medium quality score 14/22). Medications which were deemed liable to affect results (diazepam, chloral hydrate) were ceased 12 hours before the recording commenced. All other prescribed medications (e.g. anticonvulsant agents, antibiotics) were not altered. Most of the patients were in stage III of the condition, several in stage IV and one individual in stage II. Girls who experienced simple snoring (without sleep apnoea) formed a control group. Although the authors attempted to match the groups by age, the matching did not appear to be very precise as the eldest control participant was just 17 years old. No significant differences were found between the groups for sleep quantity, quality or architecture. However the authors did not examine the results by age or stage of the disease, therefore any differences might have gone undetected.

PSG was conducted in eight patients with Rett syndrome in a poor quality longitudinal study [45] (quality score 6/22). No details were provided about patients’ medications and there was no control group in the study. A total of 12 polysomnograms were compared, six of these were recorded in Rett syndrome patients under five years old and six were undertaken in patients above five years. A student’s t-test was used although the groups
were not independent. Some of the same subjects underwent PSG when they were under five years and again when they were over five years, but the repeated nature of these recordings was not accounted for. There were no significant differences in the percentage of slow-wave sleep or REM sleep between age groups, and other sleep parameters were not reported.

The studies of patients with Rett syndrome have shown contrasting results, due in part to the methodological and analytical issues outlined above. In all the studies, the researchers had confirmation of Rett syndrome diagnosis. Overall it appeared that individuals with Rett syndrome showed reduced total sleep, took longer to settle at night, awoke several times and had less efficient sleep than healthy individuals.

**Discussion**

This review has highlighted the range of sleep difficulties in individuals with neurodevelopmental disorders of genetic origin. Generally, compared to neurotypical controls of the same age, sleep was more fragmented and of poorer quality in those with intellectual disabilities. Total sleep time, as well as duration of REM sleep, was often diminished across the syndromes reviewed.

Most of the reviewed studies were medium or high quality, with only two poor quality papers. The authors of all papers, apart from one, either had sight of evidence to verify their participants’ diagnosis, or were clinicians actually involved in providing diagnoses. Many of the studies included a control group who was appropriately matched to the patient group, usually by age and/or gender. Several studies described their subjects’ medications and some drugs were stopped that could have affected sleep. However, a number of papers failed to provide details on whether patients were taking any medications or not. The majority of investigations selected patients based on their diagnosis, rather than the presence of sleep disturbances, therefore the results can be generalised more widely to
individuals with the disorder. Other papers restricted their sample to patients with the disorder who displayed sleep difficulties (although for treatment trials, e.g. [40], this would be expected). For those studies which involved subjects with sleep problems, it would be expected that details would be provided about any previous treatments, medical or behaviour, which had been attempted to improve sleep, however few papers gave any relevant details. Finally a number of authors considered co-morbidity and some made attempts to control for this, by exclusion or matching.

The majority of the studies reviewed employed PSG rather than actigraphy. PSG is considered to be the gold-standard of sleep measurement, thus the results of the PSG investigations should be highly accurate. Although actigraphy cannot provide information on sleep architecture and sometimes it can be less precise than PSG, actigraphic assessment is generally accepted as a reliable and valid methodology, and actigraphic findings usually concur with PSG results.

This review only accepted papers which had been published in peer reviewed journals, which was considered to indicate studies of a high standard. “Grey literature”, reviews, unpublished dissertations and book chapters which were discovered during database searches were excluded, with the loss of potentially significant information. The same issue applied to the exclusion of papers which employed subjective methodologies, qualitative studies and papers which were not available in English, but this was deemed necessary to refine the focus of the review to a manageable level. Qualitative studies seemed to focus more heavily on the experience of parents and the impact of living with a family member with a sleep problem, rather than the nature of sleep difficulties. This would have distracted from the aim of the review. It is possible that publication bias might have been a factor, as significant results are more likely to be published than projects with non-significant findings (for a discussion see [46]).
Sleep varies with age [47] and in people with developmental disabilities, particularly those which are neurodegenerative, these changes can be dramatic. Some studies included a sample with a large age range, which can result in differences between patients and controls being missed. However, a small sample size, lack of randomised control trials and the use of non-parametric statistics feature in many of the studies. Whilst these could be viewed as limitations, they are to some extent inevitable given the rarity of some of the disorders studied. Furthermore the additional demand of taking part in research can be too burdensome for some families, thereby depleting sample size.

Although there are similarities in the nature of sleep problems across syndromes, commonalities are greater within each syndrome. Sleep difficulties appear to be intrinsic to certain disorders and can be part of the behavioural phenotype. Furthermore in conditions which are progressive and characterised by distinct stages, such as MPS III and Rett syndrome, it can be useful to examine and classify particular sleep problems at each stage. Knowledge of specific sleep difficulties (e.g. early morning wakening, settling difficulties) can help caregivers of diagnosed patients, and in some cases the individuals themselves, prepare and adjust for the difficulties ahead. It can also ensure that behavioural, drug and medical interventions are targeted at improving the particular sleep difficulties. With good-quality evidence on the quantity and quality of sleep in patients who are not taking medications which could alter their sleep-wake cycle (e.g. melatonin), a baseline can be established to which interventions can be evaluated.

When drawing conclusions about sleep in each neurodevelopmental disorder discussed, it should be acknowledged that there was not a wealth of papers on some disorders, for example there was only one study which met the inclusion criteria with tuberous sclerosis patients. Also some studies on the same disorder reported contrasting results. Further actigraphic or PSG investigations would be helpful to clarify and validate findings. As all
studies used objective rather than subjective measurements of sleep, authors generally reported the same outcome measures, apart from a small number of papers which explored mainly breathing related constructs. Accordingly even where there were just several studies on one disorder, identical sleep parameters could be examined precisely and easily across studies. With questionnaire studies, many different scales have been employed, which limits the scope to compare results and delays development of the evidence base.

There is a need for further research using objective methodologies in other genetic disorders. For example, no PSG or actigraphic studies of sleep in individuals with Cornelia de Lange or cri du chat met the inclusion criteria for this review at the time of writing. Although questionnaire-based and diary studies can provide valuable information, more comprehensive and accurate data can be gained from objective devices.

In conclusion, sleep of people with neurodevelopmental genetic disorders is atypical from their healthy counterparts. Defining the sleep phenotype of each disorder will aid families and can inform the development of appropriate interventions.
References


Paper Two

Actigraphic Assessment of Sleep in Children with Mucopolysaccharidosis Type III

Prepared in accordance with author guidelines for submission to American Journal of Intellectual and Developmental Disabilities (Appendix C)

Word count: 7122
Abstract

Sleep disturbances are common in mucopolysaccharidosis Type III (MPS III), yet there is a lack of objective evidence detailing sleep quantity and quality. Eight children with MPS III and eight age-matched typically developing children wore an actigraph for 7-10 days/ nights. Saliva samples were collected at three time-points on separate days, to permit analysis of endogenous melatonin levels. Parents completed a sleep questionnaire and a daily sleep diary. Actigraphic data revealed that children with MPS III had significantly longer sleep onset latencies and greater daytime sleep compared to controls, but night-time sleep duration did not differ between groups. In the MPS III group, sleep efficiency declined and sleep onset latency increased with age. Questionnaire responses showed that MPS III patients had significantly more sleep difficulties in all domains compared to controls. In controls melatonin concentrations could be differentiated by time points but there were no reliable patterns in the MPS III patients suggesting an alteration in the circadian system in MPS III. Implications for clinical practice and treatment of sleep problems are discussed.
Actigraphic Assessment of Sleep in Children with Mucopolysaccharidosis Type III

Mucopolysaccharidosis type III (MPS III), or Sanfilippo syndrome, is one of a group of seven inherited metabolic disorders in which there is an absence or defect of lysosomal enzymes to break down glycosaminoglycans (GAGs). The accumulation of GAGs leads to worsening damage to cells, tissues and organs (Muenzer, 2004). Prevalence estimates vary across countries, but in the UK it is estimated that 1 in every 89,000 babies are born with the disorder (Society for Mucopolysaccharide Diseases (MPS Society), UK). There are three phases of the condition (Cleary & Wraith, 1993). Developmental delay typifies the first stage which occurs between one and four years old. In the second phase, between the ages of 3/4 years to 10 years, behavioural disturbances become more prominent, including sleep difficulties, aggressive or destructive behaviours, hyperactivity and difficulties with attention. In the third or end phase, which begins around 10 years, children slow down, lose skills (e.g. language), display seizures, and develop problems with mobility and swallowing. The end phase has been likened to a dementia. The four types of MPS III classified as A, B, C or D, correspond to variations in enzyme deficiency, with types A and B being the most common, and type D being the most rare. There appears to be little clinical difference between subtypes (Cleary & Wraith, 1993), although it has been suggested that in some populations type A has a more severe course (Van De Kamp, Niermeijer, Von Figura, & Giesberts, 1981), and type C might manifest as a more attenuated disorder with slower progression (Ruijter et al., 2008).

Sleep difficulties are commonly found in MPS III, particularly settling problems, nighttime waking and early morning waking (Valstar, Ruijter, van Diggelen, Poorthuis, & Wijburg, 2008). There are a limited number of investigations which have examined sleep in MPS III patients and these are outlined below. Both pharmacological interventions and behavioural approaches have been used to treat sleep problems, and although there has
been improvement in some cases, treatment has been often been unsuccessful as described in the studies below.

One hundred and forty one questionnaires were completed by parents of affected individuals aged from birth to 40 years, of which 91.5% reported sleep disturbances (Fraser, Gason, Wraith, & Delatycki, 2005). The average age of onset of sleep problems was 3.8 years. Parents reported an association between sleep disturbance at night and daytime sleepiness or aggressive behaviours. Typically parents saw no relationship between seizure activity and sleep. Pharmacological treatment had been tried in the majority of cases of sleep disturbance, with melatonin and sedating antihistamines being the most commonly used. None of the medications were unanimously judged to be effective, but melatonin was viewed as the most helpful. Of the families who had tried behavioural modifications, over half found them successful to some degree.

Questionnaire responses (n = 96) revealed that 86% of caregivers of children with MPS III described the child as exhibiting sleep problems (Bax & Colville, 1995). During interviews with some of the parents, it became clear that a considerable number of children were staying up all night (45%), wandering around the house at night (38%), and laughing and singing at night (15%).

A sleep questionnaire was sent to 80 families who had between one and three children with MPS III (Colville, Watters, Yule, & Bax, 1996). Seventy-eight per cent of children, aged 4 to 25 years, were described as displaying sleep disturbances. Particular difficulties including waking during the night (59%), settling difficulties (56%), occasionally staying awake all night (45%), crying out (38%), wandering around the home (38%) and getting in parents’ bed (30%). Less common problems included chewing bedclothes (25%), talking whilst asleep (23%) and body rocking (18%). These problems had an impact on the whole family, hindering the sleep of parents and siblings. Children with MPS III type B showed
higher rates of early morning waking and night waking than children with type A. Behavioural intervention with five families resulted in meaningful improvements in four cases.

In a parental questionnaire study investigating behaviours in children and adults with MPS III, 12 out of 19 children exhibited sleep difficulties, of which 58% were described as severe (Cross, 2012). Four out of five adults with MPS III showed sleep problems, one of which was deemed severe.

Clinicians who have cared for patients with MPS III were surveyed (Fraser, Wraith, & Delatycki, 2002) and the majority of respondents reported that at least 80-95% of their patients experienced difficulties with sleep. The most frequently reported problems were disruptive behaviour at night (e.g. singing), difficulty getting to sleep, night-time waking and early morning wakening. Less widespread occurrences were dangerous behaviours, such as running outside, and daytime sleepiness. It is likely that the clinicians’ opinions were based on parental report rather than directly observed behaviours. The effectiveness of medications was variable and melatonin was judged to be the most useful by some physicians. Most of the clinicians who had used behavioural interventions found them to be moderately successful. No association between sleep disturbance and seizure activity was found, but the majority of clinicians reported a relationship between disturbances at night and daytime behaviour problems. Although the majority reported that daytime behaviours were worse when sleep difficulties were more severe, some found that behaviour actually improved when sleep was disturbed.

The studies described above used subjective measures of sleep, but objective measurement has been accomplished by the use of polysomnography (PSG). PSG was undertaken in six individuals with MPS IIIA, aged 7 to 20 years (mean 14.1 years; Mariotti et al., 2003). Compared to age- and sex-matched controls, MPS III patients displayed less
nocturnal sleep (240.5 min vs. 458.3 min), but greater daytime sleep (88.8 min vs. 24.8 min). REM sleep was decreased in MPS III subjects (8.03% vs. 21.53%), as was slow wave sleep (10.18% vs. 24.63%). The youngest two patients (aged 7 & 9 years) slept mainly at night, but they awoke several times. The older participants (aged 12 years and over) showed very fragmented sleep of variable duration, which was distributed over night and day.

In addition to PSG, objective monitoring of sleep has utilised actigraphy, where a device is worn, usually on the wrist, which detects body movement to distinguish between wakefulness and sleep. Actigraphy has been found to be more precise than a sleep diary (Tikotzky & Sadeh, 2001) and it correlates highly with PSG (Jean-Louis, Kripke, Mason, Elliott, & Youngstedt, 2001). PSG is superior in some respects as it provides highly accurate information and reveals sleep architecture (Ancoli-Israel et al., 2003). Actigraphy is a less expensive option and can be used to gather information over a longer time frame. As actigraphy infers sleep and wakefulness from movement, occasionally errors might be made. The strongest evidence for the validity of actigraphy is with normal, healthy adults, but it can be less accurate in differentiating between sleep and wake when sleep is fragmented (Ancoli-Israel et al., 2003). Sleep time might be overestimated and wakefulness underestimated (Pollak, Tryon, Nagaraja, & Dzwonczyk, 2001). However, actigraphy is particularly useful in gaining naturalistic sleep data in individuals who might not tolerate PSG, for example young children or individuals with intellectual disabilities or sensory sensitivities.

The biologically determined 24-hour sleep-wake cycle dictates when healthy children sleep, as melatonin secretion increases at night to encourage sleep and is inhibited by light during daytime. It has been suggested that there is an abnormality of the circadian rhythm of melatonin concentration in some developmental disorders of genetic origin. For
example an inversion of the circadian rhythm of melatonin has been demonstrated in Smith-Magenis syndrome, with onset of melatonin secretion at 6am, peak time at 12pm and offset at 8pm (De Leersnyder, Clastrat, Munnich, & Verloes, 2006; De Leersnyder et al., 2001). Due to the presence of irregularly distributed sleep, which appears to be dispersed over day and night in individuals with MPS III, it has been suggested that there is an abnormality of the circadian rhythm of melatonin in this disorder. In order to assess this, twelve patients with MPS III and nine controls, aged between six and fourteen years, provided urine samples at six separate time points over a 24-hour period (Guerrero, Pozo, Diaz-Rodriguez, Martinez-Cruz, & Vela-Campos, 2006). Analyses showed that MPS III patients had lower levels of melatonin at night, and higher levels during the day, compared to the control group. These findings supported the assertion that there is an abnormal sleep-wake cycle in MPS III.

The aim of the present study was to collect objective information about the sleep of children with MPS III. It is hypothesised that MPS III patients will experience settling difficulties as demonstrated by elevated sleep onset latency. Night-time sleep duration is expected to be depleted. It is anticipated that these children will have poorer quality sleep and will be awake for longer periods at night, compared to their healthy peers. It is predicted that daytime sleep will be increased in the patient group compared to controls. Salivary analysis is expected to show a disruption in the circadian rhythm of melatonin concentration of the patient group. Subjective questionnaire responses from parents of children with MPS III are predicted to confirm sleep disturbances in their child.

Method

Participants

Eight children with MPS III (5 males, 3 females; mean age 9 years 3 months, SD 4.86, age range 2 – 15 years) were enrolled through their physician at the Department of Genetic
Medicine, St Mary’s Hospital, Manchester, or through the MPS Society UK. Children were selected based on their diagnosis rather than the presence of sleep disturbance, and diagnosis was confirmed by analysis of urine GAGs and specific enzyme analysis. All children had been diagnosed with MPS III subtype A or B. Patients who were involved in a drug study, had a bone marrow transplant, a serious disease affecting another organ, or were near the end of life as advised by their doctor were excluded from this study. Demographic details are displayed in Table 1. Two MPS III participants had epilepsy, and another had displayed one seizure, but was not taking any anti-epileptic drugs. Parents of one child with epilepsy noted that a lack of sleep at night triggered seizures. The younger patients were not taking any medications, whereas the older patients were prescribed drugs for sleep (e.g. melatonin, chloral hydrate, zopiclone), epilepsy (e.g. sodium valproate), and other symptoms, such as pain. Only one patient was currently prescribed melatonin, but as exogenous melatonin impacts circadian rhythms (Samel et al., 1991), it was ceased two weeks prior to data collection. This ensured that no lingering effects of melatonin masked the circadian behaviour, or the physiologic levels of melatonin in saliva samples. No other medications were altered.

A group of age-matched typically developing controls (4 males, 4 females; mean age 8 years 7 months, SD 4.85, age range 3 – 15 years) were selected who did not have a developmental disability, psychiatric disorder, neurological disorder/brain injury or sleep disorder. None of the controls were taking medication.

Informed consent (Appendix D) was obtained from a parent of each child. Typically developing children aged 6 to 13 years also gave their assent, and those aged 14 to 15 years consented to participate. The study was approved by a local NHS National Research Ethics Service (Appendix E), NHS Research and Development (Appendix F), and the University of Manchester Research subcommittee. All children received a £10 gift voucher for taking part.
Table 1

*MPS III Participant Information*

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Ethnicity</th>
<th>MPS III subtype</th>
<th>Current intervention (effectiveness(^a))</th>
<th>Previous treatment for sleep problems (effectiveness(^a))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2</td>
<td>Pakistani</td>
<td>B</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>White Polish</td>
<td>A</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>White British</td>
<td>B</td>
<td>None</td>
<td>Behavioural advice (parents already used the techniques)</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>Pakistani</td>
<td>B</td>
<td>Melatonin(^b) (good for settling), Loperamide</td>
<td>Herbal medicine (not effective after the first week)</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>Pakistani</td>
<td>B</td>
<td>Walking (seems to help) Risperidone (not very helpful)</td>
<td>None</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>White British</td>
<td>A</td>
<td>Gonapeptyl</td>
<td>None</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>White British</td>
<td>A</td>
<td>Chloral hydrate, Zopiclone (both effective in the short-term, not long-term), Levetiracetam, Ibuprofen, Hyoscine</td>
<td>Melatonin (effective in the short-term, not long-term) Behavioural modification (not effective)</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>White British</td>
<td>A</td>
<td>Zopiclone, Clonazepam, Midazolam, Sodium Valproate, Senokot, Movicol, Omeprazole, Glycopyrrolate, Morphine, Paracetamol</td>
<td>Melatonin (no effect) Temazepam (effective initially but became tearful &amp; distressed)</td>
</tr>
</tbody>
</table>

\(^a\)Effectiveness of treatment as judged by parents.
\(^b\)Melatonin was withdrawn for the study

**Materials and Procedure**

A letter outlining the project (Appendix G) was sent to all families with a child with MPS III who were under the care of the Department of Genetic Medicine or known to the MPS Society UK. Children of colleagues at the University of Manchester or a local NHS
Trust formed the control group. Participant information sheets (Appendix H) were provided to families who expressed an interest in taking part. A researcher met with each family at the Department of Genetic Medicine, the University of Manchester or at the family home. Parents were asked to provide their child’s demographic details (Appendix I). Parents completed the Children’s Sleep Habits Rating Scale (E. Shapiro, personal communication, September 6, 2010; Appendix J) with the researcher present. This checklist was utilised as it was adapted from the Children’s Sleep Habits Questionnaire (Owens, Spirito, & McGuinn, 2000), for clinical and research use in assessing sleep problems in patients with MPS III. The checklist required parents to indicate how often each sleep behaviour occurred in the past week (or another recent week if the past week had been atypical). Items were rated on a three-point scale: ‘usually’ for behaviours occurring five to seven times per week, ‘sometimes’ for those happening two to four times per week, and ‘rarely/never’ for behaviours shown up to once per week. Nine subscales were derived consisting of related items.

All children wore an actigraph (Respironics Actiwatch 2/Cambridge Neurotechnology AW4) on their non-dominant wrist for seven to ten days and nights, whilst carrying out their usual activities. A 15 second sampling interval was employed. Previous research found that a minimum of five nights data are needed to provide meaningful actigraphic recordings of a child’s sleep, and actigraphic monitoring should cover at least seven nights to compensate for factors such as illness, technical problems and non-compliance (Acebo et al., 1999). Recording for a minimum of a week meant that data could be gathered over school days and over the weekend, as well as allowing for potential loss of data. The sleep parameters of interest were sleep onset latency (time between ‘lights out’ and sleep onset), total night-time sleep duration, sleep efficiency (percentage of time asleep between time of ‘lights out’ and ‘get up’), wake after sleep onset (WASO, total number of minutes awake between sleep onset and time of final waking), time in bed (minutes), and total daytime
sleep duration (total number of minutes asleep between time of final waking and bed time). To avoid confounding effects of large seasonal variation in circadian rhythms, data was gathered within a six-month period and during school term time to ensure comparability across subjects. In a daily diary (Appendix O) caregivers noted times the child got into bed at night, lights were turned out and the child attempted to sleep i.e. bedtime, the child got out of bed for the final time, lights were turned on and any night-time events.

To allow examination of endogenous melatonin levels, parents took saliva samples from their child at three time points (between 6-8h, 10-12h, & 22-24h), on the first and last day of actigraphic recording. Samples were collected using a suction catheter (de Lee suction catheter; Argyle, Sherwood Medical, Tullamore, Ireland) and were frozen at -20°C until analysis. Night collection was performed under dim light conditions. Samples were collected in accordance with procedures outlined by the enzyme-linked immunosorbent assays (ELISA) kit manufacturer (www.IBL-International.com), to allow testing using Non-Extraction Melatonin Saliva ELISA (IBL, Hamburg, Germany).

Analysis

Actigraphic data were transferred to Actiware version 5.5 software (Respirronics). Rest intervals were set based on diary information and review of the actogram (where activity and light intensity decreased). Actigraphic, questionnaire and melatonin data were entered onto SPSS version 19 for analysis. Two-tailed nonparametric statistics (Mann-Whitney U, Wilcoxon signed-rank, Friedman, Spearman’s rank correlation coefficient) were employed. One night’s actigraphic data had to be excluded from the analysis for several participants due to illness or non-compliance, but a minimum of seven nights’ data were available for all subjects. An alpha level of 0.05 was used for all statistical tests.
Results

Children’s Sleep Habits Rating Scale

The average age of onset of sleep problems for MPS III subjects was 2 years (SD 2.33, range birth-7 years). Sleep problems reported by parents included difficulties settling, waking up during the night, early morning wakening, and sleeping too little. Most children (62.5%) needed a parent in the room when trying to sleep. Half of the children fell asleep within twenty minutes on some nights, but 37.5% rarely or never did. Most parents believed their child slept too little on at least two nights each week, but on other nights they seemed to sleep the right amount. The majority of children woke up once (62.5%), or multiple times (87.5%) at night. Most children (75%) displayed disruptive behaviour at night (e.g. screaming, singing, laughing), and 25% of children displayed dangerous behaviours (e.g. running outside, playing with appliances). All children were restless and moved a lot at night, and 50% of children slept during the day. The most common parasomnias were being restless at night, wetting the bed and being alarmed by a scary dream.

Each item was assigned a score between 1 and 3 and some items were reverse-scored to ensure that a higher score represented poorer sleep (see Appendix K for scoring information). Items were grouped into nine subscales and results are displayed in Table 2.

The MPS III group had significantly more disturbed sleep in all areas including Bedtime Resistance, $U = 62.0$, $z = -3.26$, $p = 0.001$, $r = 0.82$, Sleep Onset Delay $U = 57.5$, $z = -2.92$, $p = 0.006$, $r = 0.73$, Sleep Duration, $U = 60.0$, $z = -3.30$, $p = 0.001$, $r = 0.83$, Sleep Anxiety, $U = 56.0$, $z = -2.90$, $p = 0.007$, $r = 0.72$, Night Wakings, $U = 55.0$, $z = -2.51$, $p = 0.016$, $r = 0.63$, Night behaviours, $U = 56.0$, $z = -2.93$, $p = 0.007$, $r = 0.73$, Parasomnias, $U = 63.0$, $z = -3.34$, $p = 0.000$, $r = 0.84$, Sleep Disordered Breathing, $U = 56.0$, $z = -2.91$, $p = 0.007$, $r = 0.73$, and Daytime Sleepiness, $U = 51.0$, $z = -2.03$, $p = 0.045$, $r = 0.51$. All of
<table>
<thead>
<tr>
<th>Subscale</th>
<th>Maximum score</th>
<th>MPS III</th>
<th>Controls</th>
<th>p</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Bedtime resistance</td>
<td>18</td>
<td>9.50 (2.07)</td>
<td>6.25 (0.46)</td>
<td>0.001**</td>
<td>62.0</td>
</tr>
<tr>
<td>Sleep onset delay</td>
<td>3</td>
<td>2.25 (0.71)</td>
<td>1.13 (0.35)</td>
<td>0.006**</td>
<td>57.5</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>9</td>
<td>6.13 (1.64)</td>
<td>3.00 (0)</td>
<td>0.001**</td>
<td>60.0</td>
</tr>
<tr>
<td>Sleep anxiety</td>
<td>12</td>
<td>6.38 (2.67)</td>
<td>4.00 (0)</td>
<td>0.007**</td>
<td>56.0</td>
</tr>
<tr>
<td>Night wakings</td>
<td>9</td>
<td>5.88 (1.46)</td>
<td>3.88 (0.99)</td>
<td>0.016*</td>
<td>55.0</td>
</tr>
<tr>
<td>Night behaviours</td>
<td>6</td>
<td>3.25 (1.28)</td>
<td>2.00 (0)</td>
<td>0.007**</td>
<td>56.0</td>
</tr>
<tr>
<td>Parasomnias</td>
<td>18</td>
<td>9.75 (1.67)</td>
<td>6.38 (0.74)</td>
<td>0.000**</td>
<td>63.0</td>
</tr>
<tr>
<td>Sleep disordered breathing</td>
<td>9</td>
<td>4.75 (1.83)</td>
<td>3.00 (0.00)</td>
<td>0.007**</td>
<td>56.0</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>27</td>
<td>16.0 (4.12)</td>
<td>12.25 (2.05)</td>
<td>0.045*</td>
<td>51.0</td>
</tr>
</tbody>
</table>

* p < .05, ** p < .01
the above Pearson correlation coefficients, $r$, are above 0.5 indicating large effect sizes (Cohen, 1988).

**Actigraphy**

For each participant, actigraphic data for one weekend plus weeknights were present. As suggested by Acebo et al. (1999), actigraphic data for each participant were averaged over the recording period prior to analysis. Actigraphic data for each MPS III patient can be seen in Table 3.

Table 3

*Sleep Parameters (per night) in MPS III Patients Averaged over the Recording Period*

<table>
<thead>
<tr>
<th>Sleep variable</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in bed (min)</td>
<td>570.9</td>
<td>589.5</td>
<td>593.8</td>
<td>579.1</td>
<td>528.8</td>
<td>558.2</td>
<td>659.4</td>
<td>397.4</td>
</tr>
<tr>
<td>Night-time sleep (min)</td>
<td>507.2</td>
<td>504.5</td>
<td>396.6</td>
<td>497.3</td>
<td>464.9</td>
<td>484.0</td>
<td>532.8</td>
<td>190.2</td>
</tr>
<tr>
<td>Daytime sleep (min)</td>
<td>46.5</td>
<td>0</td>
<td>1.2</td>
<td>0</td>
<td>40.6</td>
<td>0</td>
<td>16.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Sleep onset latency (min)</td>
<td>38.6</td>
<td>6.3</td>
<td>24.8</td>
<td>30.4</td>
<td>32.2</td>
<td>39.1</td>
<td>70.9</td>
<td>183.3</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>81.0</td>
<td>79.6</td>
<td>59.3</td>
<td>79.2</td>
<td>73.7</td>
<td>77.5</td>
<td>70.5</td>
<td>28.6</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>63.7</td>
<td>85.0</td>
<td>197.2</td>
<td>81.8</td>
<td>63.9</td>
<td>74.2</td>
<td>126.6</td>
<td>207.2</td>
</tr>
</tbody>
</table>

WASO, wake after sleep onset

Night-time sleep is diminished in some patients, particularly P8 who only slept for an average of 190 minutes per night, however most children slept a normal amount at night. Five out of eight children slept during the day on occasions during actigraphic monitoring, but most children did not nap every day. Sleep onset latency was markedly high in the majority of children. One of the youngest children settled very quickly, within approximately 6 minutes, but the eldest two children had distinctly long sleep onset
latencies of approximately 1 hour 10 minutes and 3 hours respectively. The remaining five children took between 25 minutes and 40 minutes to enter a sleep state. As can be seen from the bedtimes, some children took a long time to fall asleep despite going to bed to sleep at a late hour. Sleep efficiency was diminished in some children, with the eldest child sleeping only 28% of the time in bed and the five year old sleeping just 59% of the time in bed. WASO was elevated in all children, notably the oldest two subjects, and it ranged from 64 minutes to 207 minutes per night across participants.

Actigraphic data from the MPS III group is compared to the typically developing control group in Table 4. Sleep onset latency was significantly longer in children with MPS III (Mdn = 35.42, IQR = 36.79), compared to the control group (Mdn = 14.88, IQR = 7.59), U = 56.0, \( z = -2.52, p = 0.01, r = 0.63 \) (large effect). There were no differences in night-time sleep duration between the MPS III group (Mdn = 490.62, IQR = 92.89), and control group (Mdn = 496.15, IQR = 61.42), U = 32.0, \( z = 0.00, p = 1.0, r = 0.0 \). WASO was higher in the MPS III group (Mdn = 83.43, IQR = 113.06), but it was not significantly different to the control group (Mdn = 60.36, IQR = 94.70), U = 43.0, \( z = -1.16, p = 0.279, r = 0.29 \) (medium effect). Although sleep efficiency was lower in the patient group (Mdn = 75.63, IQR = 17.38), compared to healthy controls (Mdn = 82.76, IQR = 15.13), it did not reach statistical significance, U = 17.5, \( z = -1.52, p = 1.4, r = 0.38 \) (medium-large effect). Time in bed did not differ significantly between patients (Mdn = 574.99, IQR = 56.59) and controls (Mdn = 531.57, IQR = 55.58), U = 44.0, \( z = -1.26, p = 0.23, r = 0.32 \) (medium effect). Daytime sleep duration was significantly longer in MPS III participants (Mdn = 3.57, IQR = 34.59) than controls (Mdn = 0, IQR = 0), U = 48.5, \( z = -1.99, p = 0.046, r = 0.5 \) (large effect).

In the MPS III group there was a strong positive correlation between age and sleep onset latency, \( r = 0.755, n = 8, p = 0.031 \), and a strong negative correlation between age
and sleep efficiency, $r = -0.719$, $n = 8$, $p = 0.045$. Age was not significantly correlated with any other variables.

Table 4

*Comparison of Sleep Parameters of Children with MPS III and Controls*

<table>
<thead>
<tr>
<th>Sleep parameter</th>
<th>MPS III</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 8$</td>
<td>$n = 8$</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>$p$</td>
</tr>
<tr>
<td>Time in bed (min)</td>
<td>559.6 (75.4)</td>
<td>544.9 (53.7)</td>
</tr>
<tr>
<td>Night-time sleep (min)</td>
<td>447.2 (111.5)</td>
<td>479.0 (32.9)</td>
</tr>
<tr>
<td>Daytime sleep (min)</td>
<td>13.8 (19.2)</td>
<td>1.7 (4.9)</td>
</tr>
<tr>
<td>Sleep onset latency (min)</td>
<td>53.2 (55.6)</td>
<td>14.2 (5.1)</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>68.7 (17.7)</td>
<td>80.8 (8.0)</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>112.5 (58.9)</td>
<td>75.1 (51.1)</td>
</tr>
</tbody>
</table>

WASO, wake after sleep onset

* $p < .05$, ** $p < .01$

**Melatonin Analyses**

Preliminary analyses indicated that the data were reliable as standard deviations were less than 20% of the mean. One outlier was removed. Some saliva samples were missing or incomplete and were excluded (pairwise), but 88.5% of saliva samples were useable. Table 5 shows melatonin levels by day and time of collection for both groups. To determine whether melatonin concentrations were influenced by day of collection (first day vs. last day), Wilcoxon signed-rank tests were conducted on patient and control group data, which revealed no significant effects of day ($p > 0.05$). The Friedman test indicated that there was a statistically significant difference in melatonin concentrations for the control group across time points (Time 1: 6-8h, Time 2: 10h-12h, Time 3: 22-24h) on the first day, $\chi^2 (2) = 10.33$, $p = 0.002$, and last day, $\chi^2 (2) = 9.33$, $p = 0.006$. Post hoc Wilcoxon tests
with Bonferroni correction showed a significant difference between Time 2 and Time 3 on both days ($p = 0.016, r = 0.61$), but the difference between Time 1 and Time 3 was just above significance using Bonferroni adjustments ($p = 0.031, r = 0.59$). There were no reliable differences across time points for the MPS III group on the first day $\chi^2 (2) = 0.50, p = 0.931$, or last day $\chi^2 (2) = 2.80, p = 0.367$. Visual inspection of the data suggested that the MPS III group had higher melatonin concentrations at 6-8h and lower levels at 22-24h, compared to controls, however Mann-Whitney tests found no significant differences between groups.

Table 5

*Median (IQR) Melatonin Concentrations across Groups, Time points and Days*

<table>
<thead>
<tr>
<th>Group</th>
<th>First day</th>
<th>Last day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-8h</td>
<td>10-12h</td>
</tr>
<tr>
<td>MPS III</td>
<td>14.0 (18.3)</td>
<td>6.6 (11.6)</td>
</tr>
<tr>
<td>Controls</td>
<td>4.3 (10.8)</td>
<td>11.1 (29.3)</td>
</tr>
</tbody>
</table>

**Discussion**

Objective monitoring of sleep revealed that children with MPS III took longer to fall asleep and slept more during the day, compared to age-matched typically developing children. These results confirmed the initial hypotheses. There were trends towards diminished sleep efficiency and increased nocturnal wakefulness in the patient group. Night-time sleep duration was not depleted in the patient group which did not confirm the hypothesis. As predicted, responses on the Children’s Sleep Habits Rating Scale revealed that parents of children with MPS III saw their child displaying greater sleep disturbance in
all domains, compared to parents of healthy children. In the patient group, increased age was associated with greater sleep onset latency and lower sleep efficiency.

The MPS III group took an average of 53 minutes to fall asleep at night, which is much higher than the control group average of 14 minutes. A healthy child would be expected to fall asleep within 20 minutes (Galland, Taylor, Elder, & Herbison, 2012) or 30 minutes (Paavonen, Fjallberg, Steenari, & Aronen, 2002). The prolonged sleep onset latency of MPS III patients suggests that they experience difficulty initiating sleep, even when going to bed late during the evening. The sleep latency results from actigraphy concurred with parental responses on the Children’s Sleep Habits Rating Scale, which showed that most children with MPS III frequently struggled to fall asleep within 20 minutes, and some children were rarely or never able to achieve this.

On average the MPS III participants slept during the day for approximately 14 minutes. The eldest two children both had daytime naps on some days during recording, which would not typically be expected in 14 or 15 year old adolescents. Apart from the two year old who would be expected to have naps during the day, children in the middle phase of the disorder (aged 4 and 5) did not sleep during the day (or rarely had a brief nap). This confirmed a previous PSG study which showed greater daytime sleep in individuals with MPS III compared to controls, which tended to increase with age (Mariotti et al., 2003). Children who experience daytime sleepiness show poorer academic performance (Dewald, Meijer, Oort, Kerkhof, & Bogels, 2010), behavioural problems, depression, and reduced quality of life (Stores, Montgomery, & Wiggs, 2006), which highlights the importance of addressing this problem.

With increasing age and progression of this neurodegenerative disorder, sleep difficulties worsened. As children with MPS III got older, they took longer to fall asleep and they achieved less efficient sleep. Healthy children would be expected to sleep for at least 80% of the time in bed (El-Sheikh, Buckhalt, Keller, & Granger, 2008; Scholle et al.,
2011), which corresponded with the average sleep efficiency of 80.8% for the control group in the present study. The mean for the MPS III group was only 68.7% which is well-below normal. However sleep efficiency for some of the children was only just below normal and only two participants had poor or very poor sleep efficiency, of 59.3% and 28.6% respectively. The length of time that MPS III children were awake at night was considerably high, with an average of almost two hours per night and WASO was particularly high in the eldest two children. The average for the control group also seemed high at just over an hour, which concurred with some previous actigraphic studies (El-Sheikh et al., 2008; Werner, Molinari, Guyer, & Jenni, 2008). Even though most MPS III patients were achieving a sufficient quantity of sleep, the quality of their sleep was not high, as it was interrupted by awakenings.

In a previous study with patients with MPS III, night-time sleep was reduced when compared to healthy controls (Mariotti et al., 2003). In the current study, the average night-time sleep of the MPS III group was lower than that of typically developing controls, but it was not significantly different. Some patients’ sleep varied from one night to the next, and when sleep was averaged over the recording period, it seemed that children with MPS III were achieving a sufficient quantity of sleep. All of the subjects in Mariotti and colleagues’ (2003) study had been diagnosed with subtype A, whereas the children in the current study were either subtype A or B, which could account for differences across the studies. Another possible explanation for the disparity could be the difference in age of the subjects across the two studies. Half of the subjects in Mariotti and colleagues’ study were 17 years and above, whereas all of the patients in the current study were under 16 years. The eldest child in the present study had the lowest night-time sleep duration. In accordance, the eldest subjects in Mariotti et al.’s investigation slept the least amount at night. It is possible that night-time sleep duration reduces as children progress further into the end stage of the disorder.
The finding that children with MPS III spent at least as long in bed at night as their healthy counterparts is noteworthy. Despite the fact that these children often resist going to bed at night, take a long time to settle and wake up during the night for long periods, parents were able to ensure their child was in bed for enough time to get sufficient sleep. Despite the sleep-wake cycle in MPS III being abnormal, these parents successfully imposed a night-time routine with their child.

It has been demonstrated that actigraphy correlates with PSG (Jean-Louis et al., 2001), but as actigraphy infers sleep and wakefulness from movement, it is possible that misinterpretations might occur. Both groups were assessed with identical actigraphs, which should balance any miscalculations across groups. However some investigations have suggested that actigraphy is less proficient at distinguishing sleep-wake when sleep is fragmented (Ancoli-Israel et al., 2003).

Results from the Children’s Sleep Habits Rating Scale showed that in comparison to healthy children, parents of children with MPS III saw their child as having more difficulties with bedtime resistance, falling asleep, sleep duration, sleep anxiety, night waking, night behaviours, parasomnias (restless at night, wetting the bed, being alarmed by a scary dream), sleep disordered breathing and daytime sleepiness. The average age of onset of sleep difficulties was 2 years old, but some patients had sleep problems since birth. The prolonged settling time might be partly explained by bedtime resistance and sleep anxiety, such as difficulties getting the child to go to bed at a regular time, the child struggling to fall asleep without a parent in the room or being scared of sleeping alone. Sleep disordered breathing, mainly snoring and snorting/gasping was observed by parents, and one patient stopped breathing at night sometimes. This confirmed previous research involving heterogeneous groups of patients with mucopolysaccharidoses, which have demonstrated a high prevalence of breathing difficulties at night (Lin et al., 2010; Santamaria et al., 2007), and as a result, some children with MPS III have had an
adenoidectomy, tonsillectomy or adenotonsillectomy (Valstar et al., 2008). Parents of children with MPS III noted that their child woke up more at night and engaged in disruptive/dangerous behaviours whilst awake at night, which concurred with the actigraphy finding showing the extended time the children were awake at night. A greater number of parasomnias, or abnormal events which occurred during sleep in the patient group might account for some of the awakenings.

Salivary melatonin analyses showed that melatonin levels could be differentiated at specific time points over day and night in typically developing children. However in children with MPS III, no reliable differences across time were found, demonstrating a possible abnormality of the circadian rhythm of melatonin concentration. Melatonin levels were lower at night and higher early morning in children with MPS III, compared with healthy children. However these differences were not significant, partly due to the small sample size, which was depleted further by missing or insufficient samples. Disruption in the circadian rhythm of melatonin in MPS III, which has been demonstrated by previous research (Guerrero et al., 2006), could account for sleep disturbances exhibited by patients. Lower levels of the hormone at night correspond with difficulties falling asleep, and higher levels of melatonin in the morning could explain the increase in daytime napping. Exogenous melatonin was ceased two weeks before actigraphic monitoring to ensure that it did not affect natural circadian rhythms, and consequently sleep, during actigraphic recording. Some patients took other hypnotic medications (choral hydrate, zopiclone) to aid sleep, so it is possible that without these drugs, sleep would have been reduced and disrupted to a greater degree. Also daytime sleep might have been increased due to hangover effects of the medication. However research has demonstrated that hypnotic drugs have little or no effect on sleep disorders with an irregular sleep-wake cycle (Guilleminault, McCann, Querasalva, & Cetel, 1993). All parents described their child’s sleep medication as being of little or no obvious benefit to their sleep, so it is possible it had modest or no
impact. Concordantly the eldest child who was prescribed hypnotic drugs had the poorest sleep of the entire group.

As is the case with most research involving people with rare disorders, the sample size was small, limiting the statistical power to detect between-group differences. With a larger sample, it is likely that WASO and sleep efficiency might have reached statistical significance. A small sample also limited opportunities to detect any disparities between subtypes or stages of the disorder. Half of the children were diagnosed with subtype B and the other children had subtype A. The youngest child, aged 2, was in the first phase, the children aged 4 to 5 years were in the middle phase, children aged 10/11 years were in the middle to end phase, and the eldest two children were in end phase of the disorder. Generally sleep difficulties, particularly sleep onset latency and sleep efficiency, worsened as the children aged and the disease progressed. The eldest two children had subtype A, which has been reported to be a more severe form of MPS III (Van De Kamp et al., 1981), thus subtype, in addition to age/stage could be an important factor influencing sleep.

Much of the previous research investigating sleep in MPS III has used a questionnaire methodology. Actigraphic monitoring over seven to ten days allowed objective sleep information to be gathered in the child’s natural environment, and permitted data collection over weekdays and a weekend to capture more variability. Data from school nights and weekends were not analysed separately as there was no reason to suggest that children with MPS III would be affected any differently by weekends than typically developing controls. Polysomnography is more intrusive and usually undertaken in a laboratory, which might not capture a person’s typical sleep. As all data was gathered in a six-month period, and avoided school holidays, it minimised confounding variables and allowed a more robust between-group comparison. There were two occasions where actigraphs did not record any data and families were asked to repeat the recording. To
verify an actigraph is functioning correctly, in future, each device should be programmed to begin recording just before providing it to a family.

Actigraphy is more informative and accurate than diary entries, and should be used in clinical practice with MPS III patients. Parents, particularly those of the youngest children, were initially unsure if their child would tolerate wearing a watch. However parents reported few problems and there were only a small number of occasions where a child removed a watch for a short time. It would be helpful to use actigraphy in clinic to obtain a baseline of a patient’s sleep and to detect particular sleep difficulties (e.g. settling problems), to enable interventions to be targeted most appropriately. Recording can be repeated following intervention to assess its effectiveness. It might also be reassuring for parents of younger children to see that although their child might find it hard to fall asleep and be awake for long periods at night, they are probably getting a sufficient quantity of sleep. Caregivers of children with intellectual disabilities, including parents of children with MPS III, experience clinical levels of anxiety and depression (Aspil, 2012). By improving a child’s sleep using medical or behavioural interventions, other family members are likely to have more restful sleep and have improved wellbeing.

Given the abnormality of melatonin concentrations in MPS III, exogenous melatonin is likely to be the most effective pharmacological intervention, as substantiated by previous research (Fraser et al., 2002). The strongest evidence for the efficacy of melatonin is for reducing sleep onset latency, but there is less support for its effect on nocturnal waking (Phillips & Appleton, 2004). Rather than the usual fast release form, it has been demonstrated that sustained-release melatonin can improve sleep maintenance in children with neurodevelopmental disorders (Jan et al., 2000). However treatment of this type could increase daytime sleepiness, which should be avoided in patients who already display tiredness during the day. Melatonin should be used with caution as there are some concerns about its use with children and its long-term effects are unknown (Stores, 2003).
There is also some evidence to suggest an increase in seizures in children with neurodevelopmental disorders with epilepsy (Sheldon, 1998).

Successful outcomes have been demonstrated when behavioural interventions have been used to help parents manage sleep problems in children with severe developmental disabilities (e.g. Montgomery, Stores, & Wiggs, 2004; Quine & Wade, 1991). Advice on behavioural modification should be provided to caregivers as soon as possible after a diagnosis of MPS III has been given, and should focus on the problems highlighted in this paper, specifically bedtime resistance, sleep onset difficulties, sleep anxiety, night time waking, disruptive/dangerous behaviours at night, daytime sleep and tiredness. Good “sleep hygiene” in combination with various Zeitgebers or synchronising factors from the environment (e.g. physical exercise, eating/drinking patterns), and high intensity light, could help to synchronise the sleep-wake rhythm to a more regular pattern and therefore improve the quality of life for patients and carers. In addition, clinicians should enquire about sleep disordered breathing and refer a child for PSG for assessment if it is suspected. Future research should focus more on the efficacy and side effects of sleep interventions in MPS III.

Further investigations are needed to validate the findings of this study. With more time and resources, a larger sample including adults as well as children, would substantiate these results and provide greater clarity of sleep at different stages of the disorder. Some parents of children with MPS III reported that occasionally their child would not sleep at all for one night and this unpredictability makes it difficult to plan their daily lives. Recording over a longer time period of several weeks, would allow more variability across nights to be captured. Rather than averaging data across nights, a time series analysis would be helpful to identify patterns and allow periods of sleeplessness to be predicted. A longitudinal study following a group of MPS III patients through the progression of the disorder could
document more precisely how sleep patterns change with age and might reveal any variations in the progression of different subtypes.

A number of promising treatments for MPS III which target the central nervous system are currently being studied, including enzyme replacement therapy, hematopoietic stem cell transplantation, gene therapy, and substrate reduction therapy (de Ruijter, Valstar, & Wijburg, 2011). Until a clinically efficacious treatment for MPS III has been developed, it remains for clinicians to target behavioural manifestations of the condition, including sleep disturbance.
References


Paper Three

Critical Appraisal

Word count: 5894
Introduction

The following critical appraisal contains observations and personal reflections on the course of designing and completing this research. The strengths and limitations of the project will be discussed, including design, ethical, methodological, and analytical issues. Thoughts will be provided on the team-working environment in which this project was completed, alongside other Trainee Clinical Psychologists who conducted studies with the same patient group. The impact of meeting families with a child with a life-limiting condition will be considered. Finally, implications for clinical practice and ideas for future research will be suggested.

Literature Review

As MPS III is such a rare disorder, there is a scarcity of research with affected patients, and only one study has measured sleep. Therefore a review focusing exclusively on sleep in MPS III was not feasible. Other possibilities were considered, including sleep in neurodegenerative disorders, of which dementia is the most widely researched. As it has been established that MPS III is a genetic disorder affecting the intellectual development of a child, it was decided that it would be most relevant and informative to focus on sleep in neurodevelopmental disorders of genetic origin.

Preliminary searches on academic databases revealed a wealth of research on sleep in some disorders, namely Autism, Asperger syndrome, Prader-Willi syndrome and Down syndrome, including recent reviews, e.g. Glickman, (2010). It was considered redundant to write another review of sleep in these disorders, so it was decided that these diagnoses would be excluded from the review. Locating relevant papers for the review was a time-consuming and arduous process, as despite setting limits for searches (e.g. English Language, peer reviewed journals, human studies), typically an abundance of results were generated and titles/abstracts had to be screened to identify appropriate studies. Too many
papers fitted the inclusion criteria, so a decision was made to narrow the focus even further to only include studies which had employed objective methodology (actigraphy or polysomnography (PSG)) to measure sleep. As a result the review was more closely linked to the content of the empirical paper in which actigraphy was a central component.

It was decided that articles should be inspected to determine the quality. Existing quality assessment scales were examined (West et al., 2002), and although some of the items were appropriate to the current review, no scale was available which included all necessary criteria and was devoid of irrelevant items. Consequently a new checklist was created. It was positive that most of the papers reviewed were medium- or high-quality, and only two papers were poor-quality. The designation of the label low-, medium-, or high-quality was largely arbitrary, as it was based on a total score out of 22. Assessing the psychometric properties of the scale was beyond the scope of this work, but the scale appeared to have face validity. Examining papers on a range of neurodevelopmental disorders meant that commonalities in sleep disturbances across disorders, as well as similarities across studies on each disorder, could be established.

**Empirical Paper**

Recruitment and Sample Size

From the outset, it was anticipated that many families would be keen to participate given the uptake for a previous project involving family members of MPS III patients (B. Bigger, personal communication, September 10, 2010), the support of the MPS Society UK and the involvement of one of three principal clinics for MPS III patients in England. Following feedback from the University research subcommittee, it was considered not feasible for researchers to travel across England to visit families; therefore recruitment was restricted to the North West and Yorkshire areas only. It was decided that adults with MPS III would not be included, as under the Mental Capacity Act (2005), it would not be
acceptable to simply gain parental consent. Lengthy procedures outlined in the act would need to be adhered to in order to assess capacity, which was beyond the scope of the study. 

It transpired that uptake was not as high as expected. Since few families came forward during the initial months of recruitment, a decision was made to submit an amendment to the National Research Ethics Service (NRES) to gain approval for recruitment across Britain (Appendix L). However, time, financial and logistical constraints limited how many families could be seen. Some families with children with MPS III decided not to participate for a variety of reasons, some unknown, but others reasons cited were that the study was not going to directly benefit their child, parents were unwilling to withdraw melatonin, or their child was currently ill or in hospital. Parents were provided with the contact details of an independent nurse, who was available to discuss the decision of whether or not to stop melatonin to enable participation in the study, and/or to provide support during any period of withdrawal. This resource was scarcely used, perhaps because parents who were worried about stopping melatonin, discounted taking part outright.

Unlike some previous studies which investigated sleep in children with neurodevelopmental disorders, this study did not select participants based on the presence of sleep difficulties, but by their diagnosis. This meant that results could be generalised more widely to children with MPS III. As the project relied on caregivers to make contact with the researcher, it is possible than parents of children who showed few sleep problems saw the research as irrelevant to them, so did not volunteer to participate. However not all families who took part, believed their child had significant sleep difficulties. One mother reported that her child, who was not taking any medications to aid sleep, slept well most nights. From discussions with parents, it was apparent that the project included a range of children, rather than only those with more severe sleep difficulties. However those with the most severe sleep problems might not have wanted to stop melatonin or had the emotional resources to participate.
The small sample size, along with the use of nonparametric statistics, limited the statistical power to detect group differences and increased the possibility of type two statistical errors. As a result of the small numbers, it was not possible to conduct inferential statistics on subtype (A vs. B) or stage of disorder (middle vs. end), but patterns in the data could be described. At the time of writing, it is estimated that there are just 68 children with a diagnosis of MPS III aged below 16 in the UK (MPS Society UK, personal communication, 8 June 2012). Consequently the present study involved a significant proportion of the population. The sample also included both genders, which increased the generalisability of the results.

Initially it was decided that a control group would be formed of children of University staff or students. However, only one person made contact after viewing the advert on the university volunteering webpage. Amendments (Appendix M) were submitted to NRES to widen the pool of potential participants to include typically developing controls outside of the university, and to increase the range of methods that could be used to advertise the study (e.g. word of mouth). This action was successful and a sufficient number of age-matched controls were recruited.

**Consent and Capacity**

Guidelines stated that research with children should proceed only after gaining consent of a parent or guardian, and/or a child, subject to the competence of the child (Medical Research Council, 2004). All parents were provided with a written information sheet, in addition to discussing the project with the researcher. As all children were under 16 years old, parents were involved in the decision to participate and parental consent was sought for all participants. Information sheets were provided to typically developing children which were adapted for different age groups (one information sheet for children aged 6-10, another for those aged 11-15). As suggested by the Royal College of Paediatrics and Child
Health (2000), the assent of typically developing children aged 6 to 13 was sought in line with good practice. As research evidence has shown that children are generally not competent to make a decision until at least age 11, and do not have the required voluntariness until aged 11 to 14 (NRES, National Patient Safety Agency, 2009), a decision was made to seek consent of typically developing children aged 14 to 15. Due to the neurodegenerative nature of MPS III, by the age of 14, children are generally in the late stage of the disorder, which means that their cognitive and communication abilities are diminishing. The researcher carefully considered every aspect of the project which involved children who did not have the capacity to decide whether to participate or not. There was minimal risk to children from participation and the research had the potential to yield benefit for the individual patients, as well as informing future developments for MPS III. Every effort was made to explain the study procedure to each child in an appropriate way considering their age and developmental level. Parents were asked to explain the research to their child with MPS III, using the communication method they deemed most appropriate to the child’s cognitive ability and preferred way of communicating. The researcher was conscious that some of the patients lacked verbal communication skills to express a refusal to participate. Parents were advised that if their child became upset or showed any sign of distress, this should be accepted as a sign of refusal.

Timing

The study protocol was designed to ensure all data was collected within a six-month period and not during school holidays, which minimised confounding variables. This condensed the window for data collection, which inevitably decreased the sample size to some extent. As the process of designing the study and completing the Integrated Research Application System (IRAS) form took longer than expected, there was only one period of data collection rather than two comparable phases over two years. All participants who expressed an interest in participating were able to do so, however two
phases of data collection would have meant that more participants could have been recruited.

**Children’s Sleep Habits Rating Scale**

The Children’s Sleep Habits Rating Scale (E. Shapiro, personal communication, September 6, 2010), had been adapted from the Children’s Sleep Habits Questionnaire (CSHQ; Owens, Spirito, & McGuinn, 2000), for use with the MPS III population. The CSHQ was initially developed for use with children aged four to ten years and its reliability and validity have been established (Owens et al., 2000). Since its development it has been shown to be an effective screening tool with pre-school children aged 2 to 5.5 years (Goodlin-Jones, Sitnick, Tang, Liu, & Anders, 2008) and it has been used with a wide age range of children up to 18 years old (Goldman et al., 2011). The scale used in the current study included most of the same subscales as the CSHQ. However it also contained an additional subscale for night behaviours, an extra item on the daytime sleepiness subscale (sleeps during the day other than planned nap) and one fewer item (awakens screaming, sweating) on the parasomnias subscale. The psychometric properties of these three subscales have not yet been established. Scores on the remaining six subscales, which are identical to those on the CSHQ, can be compared with other research which has used the CSHQ. Although the CSHQ has been used with adolescents, the relevance of some items to older children could be questioned, for example ‘wets the bed’.

**Actigraphy**

Two different types of actigraphs were used in the study, which could potentially cause disparities in the data. This situation occurred as there were insufficient numbers of the original actigraphs to complete the study in the designated time period. It was not possible to order the same model, as a different company, Philips Respironics, had acquired the activwatch range, resulting in the discontinuation of the Cambridge Neurotechnology AW4
Actiwatch. Cambridge Neurotechnology recommended the Philips Respironics actigraph, which was essentially a comparable actigraph produced under a different name. It was decided that to minimise any possible incongruities, actigraph type was balanced across groups, and when data were inspected no such disparities across actigraph type were apparent. All data were analysed on one program (Actiware) as recommended by Philips Respironics, as discrepancies might have arisen if two different software packages were used.

No seizures were observed by parents during actigraphic monitoring. Although it should be acknowledged that seizures might have occurred without parental knowledge. Activity should be visible on the actogram during a seizure but without a note in the diary, it would be unclear what has taken place.

Over the study, occasional technical problems arose with the actigraphs. There were two instances when, for no apparent reason, the actigraph failed to collect any data, which was very frustrating for the researcher. One of these occurrences happened with a child with MPS III and the other with a control participant. The researcher explained the situation to the families and both were very understanding and agreed that their child would wear the watch again. The researcher was conscious of the importance of obtaining the sleep data from the child with MPS III or the sample size would have compressed further, however she was mindful not to pressurise the parents to repeat the data collection. As it transpired, parents were keen to know their child’s individualised results, so volunteered to repeat the actigraphic monitoring. In a future actigraphic study, it would be wise to set the device to begin recording just before being delivered to a family. Hence the actigraph could be checked to ensure recording has commenced.

The parents of one child with MPS III, who had agreed to take part, met with the researcher and were provided with the equipment to start data collection the following day. Unfortunately a few days later, the child’s mother telephoned to explain that following the
meeting, the child had taken ill and was taken to hospital due to an infection. A few weeks later, when the infection had cleared and the treatment had been completed, his parents met with the researcher again as they still wanted to participate. However after the child had been wearing the actigraph for several days, his parents telephoned to explain that the device had been lost at school and it was never recovered. His parents noted that they had also forgotten to inform his teachers that the device would be damaged if submerged in water, so it had been left on his wrist during his swimming lesson at school. After discussion with his parents, it was decided that actigraphic monitoring would not be attempted for a third time, as the family had additional demands on their time and energy.

Instead of actigraphy, other studies have gathered objective sleep data by polysomnography (PSG), but use of this method was not an option for the current project. Actigraphy seemed to be an appropriate methodology for the study for a number of reasons. The researcher wanted to examine participants’ naturalistic sleep which would have been compromised in a laboratory environment. Polysomnography, which is typically conducted over one or two nights, would have limited the scope to identify patterns over time and any variability across nights. It should be acknowledged that this project focused on averaged sleep data, rather than data from individual nights, in line with many previous actigraphic investigations. Given more time, the researcher would have liked to have examined sleep night-by-night for each child, to see if sleep disturbance could be predicted. Actigraphic monitoring allowed daytime sleep to be inspected, which might have been missed with PSG as it usually takes place over night-time only. However actigraphy is generally considered to be less accurate than PSG (Ancoli-Israel et al., 2003) and does not provide information on sleep stages which seem to be disrupted in individuals with developmental disorders. REM sleep is reduced, while non-REM sleep is often increased (Harvey & Kennedy, 2002; Hoban, 2000). Overall the correlation between actigraphy and polysomnography has been shown to be high (Jean-Louis, Kripke, Mason, Elliott, &
Youngstedt, 2001), and use of this methodology enabled aims of the current project to be met.

**Medication**

When designing the project, the decision to stop melatonin was taken after much consideration and deliberation with the medical experts involved in the study, in conjunction with the advice of a research associate with experience in investigating circadian rhythmicity. Only one participant was prescribed melatonin and it was used intermittently when needed, rather than as a daily dose. It can take a maximum of two weeks for exogenous melatonin to leave the system (M. Canal, personal communication, 14 September 2010), for that reason melatonin was stopped 14 days before actigraphic monitoring, in accordance with previous studies (e.g. Zhdanova, Wurtman, & Wagstaff, 1999). This ensured that no lingering effects of exogenous melatonin concealed natural circadian rhythms, or altered the concentration of melatonin in saliva samples. Children who continued to take their usual hypnotic drugs to aid sleep might have appeared to have better sleep than they would have shown naturally. Parents were reluctant to stop their child's sleep medications, even though all parents said that these drugs were not very effective. The researcher was conscious of the stress that parents were under caring for a child with additional needs, therefore did not pressure families to stop the sleep medications.

One family had a child with MPS III who was given daily melatonin and his parents were keen for him to participate in the study. Parents were fully informed about the study and understood that melatonin would need to be withdrawn for the study period. Melatonin was stopped, but after a few days his sleep became very disrupted. This child was in the end stage of the disease, thus had additional health needs. A joint decision was made between the researcher and his parents, for melatonin to be reinstated and for him to
withdraw from the study. After the medication was recommenced, his sleep returned to usual.

Analysis

The majority of previous research which has explored sleep in developmental disorders either included a patient group only and examined group means on a range of sleep variables (e.g. Nashed et al., 2009), or included a patient and control group and compared means (or ranked data in non-parametric tests) between groups (e.g. Mason et al., 2011). To compare two or more groups, between-subjects analyses have typically been employed including independent samples t-tests, ANOVA, or non-parametric equivalents. However actigraphic data provides an opportunity to conduct a detailed examination of sleep over time. As the quantity and quality of sleep can vary across nights in MPS III, a time-series analysis could have been used to ascertain any patterns over time. The sleep of healthy, neurotypical individuals is biologically determined to correspond to a 24-hour cycle, thus does not typically vary considerably between individuals. Therefore the value of repeatedly collecting new sleep data using healthy controls could be questioned. It might be a better use of time and resources to detail sleep in disorders in which patients show a striking lack of sleep or severely fragmented sleep, in which patterns and the sleep-wake cycle have not yet been established. Although caution should be exerted as sleep in otherwise healthy individuals might deviate from the norm due to sleep-wake disorders, insomnia, cultural and social differences, as well as a genetic tendency to sleep at different times of day. Also the measurement of sleep variables can vary dependent on the type of methodology used e.g. actigraphy vs. PSG. Therefore it could be seen as a more robust and valid assessment to record sleep in patients and controls using the same measuring device whilst controlling for other factors, such as seasonality. Following this, patient data could be examined more closely using time series analysis.
Team Working

As three other Trainee Clinical Psychologists in the same cohort conducted projects with MPS III patients (one studying circadian rhythms, two conducting questionnaire studies on child behaviour and family coping), it was appropriate to work closely together. The current author was involved in conception and design of the studies and took a lead role in the design of the sleep study. Materials for the sleep study were completed by the current author including participant information sheets and the sleep diary, and other materials (salivary sampling instructions and actigraphy instructions) were completed alongside the trainee who investigated circadian rhythms. One form was created on IRAS which all four trainees contributed to. This was helpful to ensure consistency across projects, such as recruitment of MPS III individuals. It avoided families being contacted four separate times inviting them to participate in each project, as a single letter was send explaining all studies. However the IRAS form became a lengthy, complex document as each project had differences as well as similarities. For example the control group for two questionnaire studies consisted of people with intellectual disabilities, rather than typically developing children, hence different recruitment methods were used. It was not possible to submit the IRAS form until technicalities had been decided upon for all projects, therefore deadlines for submission had to be negotiated. For data collection, the current author visited many of the families (2 visits per family), with the remaining families being seen by the trainee investigating circadian rhythms. Home visits were conducted for most families which were preceded by telephone contact. Apart from knowing that each family had a child with MPS III, little else was known about them, particularly for those families who were not known to the Department of Genetic Medicine where recruitment was based. A lone working policy (Appendix N) was developed by all trainees to ensure everyone was clear about their responsibilities to maintain the safety of the researcher.
undertaking the home visit. All sleep data was inputted and analysed by the current author alone.

Working alongside two doctors of Paediatric Metabolic Disease who were experts in MPS III was a significant benefit. In addition to their specialised knowledge of the disorder which informed the design of the study, it allowed trainees to offer projects directly to their patients. The team approach which involved an academic supervisor and two other research fellows was important to make use of each person’s specialised knowledge. For a trainee, it also created a more authentic experience of working in a research environment, rather than working on a student project.

Meeting Families

The researcher met a number of families with children with MPS III, both those participating in this project and people who attended the national MPS conference. During the appointments, some parents talked about the impact that receiving a diagnosis for their child had made on their family and the reality of living with a child with the disorder. Children with MPS III usually begin to lose skills around the age of ten (Cleary & Wraith, 1993), at an age when healthy peers are progressing in their abilities, which can be heartbreaking for parents. This discrepancy was even more apparent for parents who had a healthy child. As a researcher, talking with families could be emotive at times, such as when one mother explained how it upset her to watch old home videos of her 14 year old son, as it was a reminder of the skills he had already lost. The researcher maintained a warm, empathetic approach when seeing families, whilst being careful not to fall into the therapeutic role of a psychologist. All parents were aware of the MPS society and other supportive agencies, and they were each given a full list of relevant agencies in case they required further support. The team working approach was helpful for the researcher, as feelings and reflections about the work could be shared and understood by colleagues. The
researcher felt privileged to have had the opportunity to meet the children and their
families, to be able to understand more about their experiences. Meeting families was a
reminder of the importance of the project and the impact an incurable condition can have
on families, which can sometimes get forgotten when researchers do not meet their
participants, as in some questionnaire studies. It gave the researcher added incentive and
bolstered motivation to complete the project. Talking with parents also highlighted the
need for research into rare disorders, which can be overlooked given the prevalence of
other disorders and the financial limitations for research.

Parents of children with developmental disabilities experience greater stress than
parents of healthy children (Doo & Wing, 2006) and clinical levels of anxiety and
depression (Aspil, 2012). The researcher was careful to minimise any additional demands
that the project would cause. All families with children with MPS III, apart from one
family who lived locally, were visited at home to preclude the need for them to travel. The
information that parents were asked to record in the sleep diary was considered carefully to
ensure that all necessary information was collected to afford interpretation of actigraphic
data, while ensuring the diary was as quick and easy to complete as possible. There is an
array of sleep questionnaires available, but some are lengthy and time-consuming; the
Children’s Sleep Habits Rating Scale could be completed in less than ten minutes with the
researcher present to answer any queries. Generally, parents reported that they found the
research protocol straightforward and not particularly burdensome. An individualised
report was created for parents of each child with MPS III detailing their child’s sleep
patterns. Although this created an extra demand on the researcher in addition to
completing the thesis, it was considered fair to compensate families for the effort that they
had expended in this project. It also made the researcher feel satisfied that this project
might have helped individual children, as doctors could make decisions on treatment using
their individualised results. Parents noted in the sleep diary whether their child slept away
from home on any nights. Two children spent some nights away from home, such as in respite care. From visual inspection of the data the researcher informed families about any differences in the child’s sleep between locations. If sleep varied between locations, parents could inspect the child’s daytime activities and bedtime routine more closely in future to expose any differences which could account for altered sleep.

**Salivary Sampling**

The process of taking saliva samples from children was completed by their parents, as it was decided that children would find it less anxiety provoking with a familiar person. The suction catheter was chosen rather than a cotton swab to eliminate the risk of a child swallowing the swab. Typically parents reported that they found the equipment tricky to use the first time, but it became easier with practice. Most parents were able to take the required number of samples, however a small number of parents were unable to take some samples. The parents of the youngest children with MPS III found it most difficult to take saliva samples, as the children were very active and did not want to sit still for long, whereas the older children tended to be slower and more amenable to the intervention. Overall saliva sampling by suction catheter could be recommended for use in future studies involving children with MPS III or other related disorders. The night-time samples were taken between 10pm and midnight when most of the children were in bed asleep. The first of these night-time samples was taken on the first day of actigraphic recording, therefore most children (both MPS and controls) had to be woken up for this procedure. This would have interrupted their normal sleep, however as the process was identical for both groups any effects should be constant across groups. However it is possible that MPS children and typically developing children do not react similarly to being woken up thus time taken to return to sleep and tiredness the following day could be issues.
Clinical Implications

Melatonin, hypnotic medications and behavioural interventions have all been attempted to improve sleep in children with neurodevelopmental disorders. As sleep onset latency was high in children with MPS III, parents should be given advice on behavioural strategies to manage the bedtime routine. Melatonin has been reported to be the most effective pharmacological intervention for sleep in MPS III patients (Fraser, Wraith, & Delatycki, 2002), which is understandable given the atypical endogenous melatonin levels. Evidence on the effectiveness of exogenous melatonin to improve sleep in children with neurodevelopmental disorders has been mixed. The most compelling evidence is for reducing sleep onset, but there has been no sound evidence of any benefits on sleep duration, nocturnal awakenings, or early morning waking (Phillips & Appleton, 2004; Willey & Phillips, 2002). However, there are concerns about its use with children, its long-term usage, and use with children with epilepsy (Sheldon, 1998; Stores, 2003).

Light therapy has been used with individuals with abnormal circadian rhythms, in an attempt to stabilise the sleep-wake cycle and improve sleep. It has been reported that indirect bright light has successfully improved sleep-wake disturbances in elderly patients with dementia (VanSomeren, Kessler, Mirmiran, & Swaab, 1997). Light therapy has also been used with children with intellectual disabilities associated with neurologic disorders, all of whom displayed abnormal sleep-wake cycles (Guilleminault, McCann, Querasalva, & Cetel, 1993). The treatment resulted in a normal sleep-wake pattern in some children, but it failed to help others. No research has investigated light therapy with MPS III patients, which could be a possible area for further investigation.

Many of the sleep difficulties identified on the Children’s Sleep Habits Rating Scale should be addressed when giving behavioural advice to parents. Advice on managing dangerous behaviours, such as playing with appliances, should be given priority. Parenting programmes have been demonstrated to reduce child problem behaviours, decrease
parental stress, and increase parental competence and confidence (Sanders, 1999; Sanders, Markie-Dadds, Tully, & Bor, 2000; Taylor, Schmidt, Pepler, & Hodgins, 1998). Some of the behaviours seen in MPS III are more likely to be amenable to behavioural treatment, such as managing occasions when the child moves to another’s bed during the night, dangerous/disruptive behaviours and being afraid of sleeping alone/in the dark. The cause of a problem will inform treatment. For example difficulty settling to sleep could be due to a delayed sleep phase, behavioural insomnia, or anxiety, all of which require different approaches to treatment.

Actigraphy is a cost-effective, unobtrusive way of gaining objective, detailed sleep information in a child’s natural environment. For children with MPS III, where disturbed sleep is part of the behavioural phenotype, actigraphy should be used routinely with all patients to detail their sleep patterns and inform the use of interventions. For example actigraphy might reveal that sleep latency is significantly affected by activity levels the proceeding day or by bedtimes, which would suggest different adaptations. Actigraphy could also provide a baseline to which medical or behavioural interventions can be evaluated.

Sleep disturbance is not only a problem for the individual but it can affect the whole family. Parents and siblings can become stressed when a child cannot settle at night, awakes during the night and displays disruptive behaviour, or wakes up early in the morning. Also a disrupted sleep-wake cycle means that a child might sleep and wake at unusual times, making it difficult to keep a regular daily routine or to plan activities/events. Clinicians should be alert to signs of stress, anxiety or depression in family members and be open to having discussions with parents how they are coping. In addition to providing information about the child’s diagnosis and relevant agencies, other details should be given about organisations where parents can gain support for themselves and where to go if they recognise they are experiencing emotional difficulties.
Further research

As sleep can vary from one night to the next in individuals with MPS III, further research should focus on whether any sleep patterns can be deciphered. Circadian rhythms do not appear to follow the typical 24-hour cycle, but can sleep be predicted? Actigraphic recording over a longer period would shed more light on this. Seven-to-ten days recording was sufficient to gain an overview of sleep over weekdays and weekends, as well as days and nights where the quantity and quality of sleep varied. However a longer period of monitoring would allow any patterns to become clearer and more of the variability across time to be captured. For example one participant in the present study wore the actigraph for ten nights, but on the following night after the watch was removed, her father reported that she did not sleep for the whole night. It might also be possible to predict the quantity and quality of sleep from other variables, such as levels of activity the preceding day. This information would help parents to have more control over the situation, or at least to be better prepared for a disrupted night of sleep ahead.

Previous research has found variation between the sleep of younger and older individuals with MPS III, which corresponds with the middle and end stage of the disorder. Findings from the current study showed that sleep deteriorated (greater sleep onset latency, lower sleep efficiency), as children aged and progressed into the final stage. There is scope for further research with a larger sample to clarify more precisely how sleep varies at different stages of MPS III. Also pubertal status might impact sleep and should be considered alongside age. As previous studies have shown minimal clinical differences between subtypes (A, B, D or D), the present study did not restrict participation to one subtype. The oldest two children were MPS IIIA, so the possibility remains that sleep problems might be more severe in subtype A. However the four year old participant with subtype A showed few sleep difficulties. Any differences between subtypes should become more apparent in a larger sample. Subtype C is less common and type D is extremely rare,
so it would be unlikely that a large sample could be found with individuals with these subtypes. It would be feasible to compare individuals with subtypes A and B.

Only one previous study has utilised PSG with MPS III patients and found decreased REM sleep but elevated slow wave sleep (Mariotti et al., 2003). The current actigraphic study was unable to provide information on sleep architecture to corroborate this. PSG investigations using a larger sample than Mariotti et al.’s (2003) six patients would be needed to confirm their findings and to explore any differences between subtypes and stages of the disorder.

**Summary**

Overall the empirical paper and literature review add to the limited evidence base of MPS III and it is anticipated that it will be of interest and value to clinicians in the field. This study is the first to utilise actigraphy with individuals with MPS III and the first to combine actigraphy, questionnaire, sleep diaries and melatonin analyses. The trends found in the current study towards lower levels of melatonin at night and higher levels during the day in MPS III confirmed the previous report of altered circadian melatonin production in urine samples of children with MPS III (Guerrero, Pozo, Diaz-Rodriguez, Martinez-Cruz, & Vela-Campos, 2006). With advances in knowledge about sleep problems in MPS III, it is hoped that this project will be used to inform the development of treatments for sleep difficulties associated with the disorder. The strengths and limitations of this project have been discussed and recommendations have been made for clinical practice and future research. Completing this research has been stimulating, as well as challenging at times. Meeting families with a child with a degenerative and life-limiting condition put the researcher’s struggle in perspective, and kept the inspiration for completing this project alive.
References


Royal College of Paediatrics and Child Health (2000). Guidelines for the ethical conduct of medical research involving children Royal College of Paediatrics and Child Health. *Archives of Disease in Childhood, 82*, 2, 177-182.


Appendix A: Sleep Medicine Guide for Authors

The primary emphasis of the journal will be clinical and to this end, a number of different types of articles will be published. Each type will be aimed to provide clinically important information needed to keep up to date with the practice of sleep medicine, written in a way to foster interdisciplinary understanding and make clinical information accessible to all practitioners.

Article Types
Sleep Medicine publishes the following types of articles:

• Original articles dealing with diagnosis, clinical features, pathophysiology, etiology, treatment (by all relevant modalities, including pharmacological, instrumental, surgical, behavioural, nutritional), genetics, epidemiology, natural history and prognosis of human sleep disorders will be considered for publication, provided these have not been previously published except in abstract form or have not been submitted simultaneously elsewhere. Reports may also include technical aspects of sleep medicine, which are relevant for diagnosis, pathophysiology, etiology, treatment and natural history. Basic research articles will also be published where they have a direct impact on or shed considerable light on clinical aspects of sleep. Submission of original articles based on animal or human experimental studies are encouraged, and these articles should include a comment in the abstract and discussion about the potential clinical relevance of the study.

• Review articles on all aspects of clinical sleep medicine and related basic science that contribute to understanding clinical sleep medicine will be published. Reviews will be timely, emphasize areas undergoing new development, and include both state of the art reviews and multi-author discussion of controversial areas.

Manuscript Preparation
Use double spacing throughout, including the reference section. Manuscripts should be organized as follows: Title page, Abstract, Introduction, Methods, Results, Discussion, References, Legends, and Tables and Figures.

Title Page
Authors’ full names, academic or professional affiliations, and complete addresses must be included on the title page. The corresponding author must be indicated by an asterisk, and his/her full contact details must be included (telephone and fax numbers and e-mail address).

Abstract
A structured abstract of approximately 200 words is mandatory at the beginning of each article. The abstract should be organized by: Objective or Background, Methods, Results, and Conclusions. Review articles and case reports do not need a structured abstract.

Keywords
6-8 items must be included on the title page. Authors are encouraged to choose their own key words, but Medical Subject Headings (issued with the January Index Medicus, latest edition) may be used as a guideline.

References
References to literature must be indicated by Arabic numerals which run consecutively through the paper. Where a reference is cited more than once in the text the same
number should be used each time. Reference style should follow the “Vancouver” style described in the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (published in N Engl J Med 1997;336:309-315). The titles of journals should be abbreviated in conformity with Index Medicus. The following are sample styles:


Please ensure that references are complete, i.e. that they include, where relevant, the author’s name, article or book title, volume and issue number, publisher and publisher’s location, and page reference.

This journal should be abbreviated as Sleep Med.

**Figure and Table Legends**
Legends should be typed double spaced on a separate page and numbered with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers or letters are used to identify parts of the illustrations, each should be explained clearly in the legend. The legends should permit the figures to be understood with reference to the text. If the figure has been published previously a credit line should be included.

**Figures**
Figures of good quality should be submitted online as a separate file. Letters, numbers and symbols should be clear throughout and should be large to permit photographic reduction.

Be sure that all spelling is correct, that there are no broken letters or uneven type, and that abbreviations used are consistent with those in the text. Use a label on the back of each figure to indicate the article’s running title and the top of the figure. Do not write directly on the back of photographs. Do not trim, mount, clip or staple the illustrations. Submit photomicrographs in the final desired size. The colour transparency or negative should be supplied, in addition to colour prints.

Photographs of recognizable persons should be accompanied by a signed release from the patient or legal guardian authorizing publication. Masking eyes to hide identity is not sufficient.

**Tables**
Tables should be submitted online as a separate file and should bear a short descriptive title. If a table must exceed one typewritten page, duplicate all headings on the second sheet. Number tables in the order in which they are cited in the text. Every column in the table should have an abbreviated heading. Define all abbreviations and indicate the units of measurements for all values. Explain all empty spaces or dashes. Indicate footnotes to the table with the superscript symbols cited in order as you read the table horizontally.
### Appendix B: Quality Assessment of Studies

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Appendix C: American Journal of Intellectual and Developmental Disabilities

Guide for Authors

Information for Authors

Manuscript Submission

American Journal on Intellectual and Developmental Disability (AJIDD) uses a Web-based manuscript submission and peer-review system called AllenTrack. Manuscripts should be submitted electronically to ajidd.allentrack.net. Given that all manuscripts will be reviewed anonymously, the author’s name and other identifying information should appear only on the cover page. Potentially identifying information in the text should be removed prior to submission. The journal’s Editor and Associate Editors oversee manuscript reviews. Once a manuscript is submitted, an Editor-in-Charge is assigned who is responsible for assigning the peer reviewers and deciding on the disposition of all manuscripts (acceptance, rejection, or requests for revision). The initial review process ordinarily takes from 8 to 10 weeks, and revisions are often requested. Once a manuscript is accepted for publication, the remainder of the production process is coordinated by AAIDD’s Publications Department (journals@aaidd.org).

Corresponding authors who require assistance in submitting their manuscripts through AllenTrack should contact the editorial office via e-mail at leonard.abbeduto@ucdmc.ucdavis.edu. AllenTrack can convert most word-processing files (e.g., Word, WordPerfect, Text, Postscript, and Rich Text Format).

Ethical Standards

All investigations using human participants must have been approved by the human subjects review committee of the author’s institution. Submission of a manuscript to AJIDD while that paper is under review by another journal is unacceptable. Presentation of a manuscript in electronic form on the Internet is considered to constitute publication and may be grounds for rejection of the paper by this journal.

Form

Manuscripts should be prepared in accordance with the 2009 Publication Manual of the American Psychological Association (APA, 6th edition). All sections of the manuscript (including quotations, references, and tables) should be double-spaced with a 1-inch margin on all sides. References must be in APA style. An abstract of no more than 150 words is required. The preferred length of manuscripts is 20–30 typed pages or less, including references, but somewhat greater length may be accepted, depending on the complexity and importance of the research. Brief reports are generally 5–10 manuscript pages and contain a limited number of findings in comparison to research articles. Authors are encouraged to submit shorter, more concise manuscripts.

Abbreviations and Terminology

Abbreviations should be held to a minimum and spelled out in their first use. The names of groups or experimental conditions are usually not abbreviated. The full names of tests should be given when they are first mentioned, with the common shortened form in parentheses with a citation of the source.

When context makes it clear whether an author is referring to people with intellectual disabilities or when it is otherwise unnecessary to refer to intellectual level or diagnostic category, authors should use the most descriptive generic terms, such as children, students, or people or individuals (not persons), without using qualifiers such as “with intellectual disabilities,” “with handicaps,” or “with developmental disabilities.” The journal adheres to AAIDD’s use of people-first language. Prepositional constructions such as “students with intellectual disabilities” or “individuals who have intellectual disabilities” are preferred over adjectival constructions such as “intellectual disabilities people,” except when clear communication dictates occasional use of adjectival designations. Because “normal” has multiple meanings and may inappropriately imply abnormal where it is not applied, this word should not be used. Instead, more operationally descriptive terms such as intellectually average pupils or typical participants should be used.

Numerical and Illustrative Presentations

The metric system should be used for all expressions of linear measures, weight, and volume. Tables and figures should be kept to a minimum. Information should be presented only once—whether in the text or in a table or figure. For this reason, short tables may be deleted or combined into larger ones during the copyediting process. Tables must be created using the table function of a word-processing program. All columns should be provided with headings. AllenTrack accepts figures in JPEG, TIFF, GIF, EPS, PDF, or Postscript formats with a minimum requirement of 200 dpi. Figure captions should be included in the manuscript text file, but other types of lettering may appear on the figures themselves. All such lettering should be of professional quality and large enough to withstand a reduction of approximately 50%. Release forms (signed, dated, and witnessed) must accompany photographs of human subjects. Care should be taken to conceal the identity of persons in such photographs. Authors must also secure permission to use any copyrighted tables or figures.
Footnotes

Content footnotes are not used. An author note can be used to (a) acknowledge grant support or help in carrying out the research or in preparation of the manuscript, (b) noting change in affiliation of an author, or (c) stating the availability of supplementary information.

Data-Sharing

After research results are published, authors do not withhold the data on which their conclusions are based from other competent professionals who seek to verify the substantive claims through reanalysis and who intend to use such data only for that purpose, provided that the confidentiality of the participants can be protected and unless legal rights concerning proprietary data preclude their release. For further information, check our Web site: www.aaid.org.

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The points of view expressed in AJIDD’s articles are those of the authors and do not necessarily represent the official policy or opinion of AAIDD.

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Appendix D: Consent Forms

Consent Form for Parents of Children with MPS III

Michelle Lomax, Elaine Cross, Sheena Aspil, Louise Mahon
University of Manchester in collaboration with Central Manchester University Hospital
Department of Genetic Medicine

[An Investigation of Sleep and Circadian Rhythm, Behaviour, and Family Functioning in MPSIII]

Statement of Consent

I understand that I am being asked to consent for my child .....................................................who has MPS III and I as the parent/guardian to participant in a research project investigating sleep circadian rhythm and activity levels, behaviour and family coping.

I have read the information provided about the study (or had the information read to me) and understand what is expected of my child and myself as a parent during participation in the research.

I was provided with opportunity to ask questions and have had my questions answered. I know that I can ask any additional questions at a later point in time if required.

I understand that relevant sections of any of my/my child’s medical notes and data collected during the study may be looked at by responsible individuals from the research team were it is relevant to my/my child’s taking part in this research study. I give permission for these individuals to have access to my/my child’s records.

I understand that my child’s identity will remain anonymous to people outside of the research team and that my child can withdraw from the research at any point up until the research data has been analysed.

I agree that my/my child’s General Practitioner is informed of my/my child’s participation in this study.
I understand that my/my child’s participation is voluntary and that I am/my child is free to withdraw at any time, without giving any reason, without my/his/her care or legal rights being affected.

I consent to my collecting saliva samples from my child and that these saliva samples will be disposed of at the end of the study in line with NHS protocols.

I consent to my child wearing an actigraph to collect data on sleep and circadian rhythm patterns.

I consent to my completing a sleep diary

Does your child take prescribed melatonin (please select)   Yes / No

If Yes:
I consent to and understand that my child will be asked to stop taking melatonin under medical guidance 2 weeks before participation in the study and will need to refrain from taking melatonin throughout the 10 days duration of the study amounting to 24 days in total without melatonin intake.

Print name of Consenting Parent / Guardian________________________________________

Signature of Parent / Guardian: _________________________________________________

Date:_________________________________________________________________

To be completed by the researcher:

I have read or witnessed the accurate reading of the consent form to the consenting parent / guardian of the participant, and ensured that they have had the opportunity to ask questions and are aware of the right to withdraw from the study at any point up until data analysis has been completed.

Print name of researcher___________________________________________________

Signature of researcher___________________________________________________

Date_________________________________________________________
Consent Form for Parents of Typically Developing Children

Michelle Lomax, Elaine Cross, Sheena Aspil, Louise Mahon

University of Manchester in collaboration with Central Manchester University Hospital Department of Genetic Medicine

[An Investigation of Sleep and Circadian Rhythm, Behaviour, and Family Functioning in MPSIII]

Statement of Consent

I understand that I am being asked to consent for my child .................................................... and I as the parent/guardian to participant in the control group of a research project investigating sleep circadian rhythm and activity levels, behaviour and family coping.

I have read the information provided about the study (or had the information read to me) and understand what is expected of my child and myself as a parent during participation in the research.

I was provided with opportunity to ask questions and have had my questions answered. I know that I can ask any additional questions at a later point in time if required.

I understand that my child’s identity will remain anonymous to people outside of the research team and that my child can withdraw from the research at any point up until the research data has been analysed.

I understand that my/my child’s participation is voluntary and that I am/my child is free to withdraw at any time, without giving any reason, without my/his/her care or legal rights being affected.

I consent to my collecting saliva samples from my child and that these saliva samples will be disposed of at the end of the study in line with NHS protocols.
I consent to my child wearing an actigraph to collect data on sleep and circadian rhythm patterns.

I consent to my completing a sleep diary

Print name of Consent ing Parent / Guardian______________________________

Signature of Parent / Guardian: _______________________________________

Date:_________________________________________________________________

To be completed by the researcher:

I have accurately read or witnessed the accurate reading of the consent form to the consenting parent / guardian of the participant, and ensured that the individual has had the opportunity to ask questions and is aware of the right to withdraw from the study at any point up until data analysis has been completed.

Print name of researcher________________________________________________

Signature of researcher___________________________________________________

Date_______________________________________________________________
Consent Form for Typically Developing Children Aged 14-15

Michelle Lomax, Elaine Cross, Sheena Aspil, Louise Mahon

University of Manchester in collaboration with Central Manchester University Hospital
Department of Genetic Medicine

[An Investigation of Sleep and Circadian Rhythm, Behaviour, and Family Functioning in MPSIII]

Statement of Consent

I understand that I will have to wear a watch like a wrist watch for 10 days which will measure my sleep and how active I am.

I understand that I need to provide a total of 6 saliva samples.

I understand that I, or my mum/dad, will write down what time I go to bed at night and what time I get up in the morning.

I understand that I do not have to take part if I don’t want to do it.

I understand that I can change my mind and stop taking part in this project even after I have decided to do it.

I understand that nobody else apart from the research team will see information about me.

Sign below if you consent to take part

Print name of child ______________________________________________________________

Signature of child: ______________________________________________________________

Date: __________________________
Assent Form for Typically Developing Children Aged 6-13

Michelle Lomax, Elaine Cross, Sheena Aspil, Louise Mahon

University of Manchester in collaboration with Central Manchester University Hospital
Department of Genetic Medicine

[An Investigation of Sleep and Circadian Rhythm, Behaviour, and Family Functioning in MPSIII]

Statement of Assent:

I understand that I will have to wear a watch like a wrist watch for 10 days which will measure
my sleep and how active I am in the day.

I understand that I need to provide a total of 6 saliva samples.

I understand that my mum/dad will write down what time I go to bed at night and what time I
get up in the morning.

I have been told that I do not have to take part if I don’t want to do it.

I understand that I can change my mind and stop taking part in this project even after I have
decided to do it.

I understand that nobody else apart from the research team will see information about me.

☐ I agree to take part in the research.

OR

☐ I DO NOT agree to take part in the research.

Only if child assents:

Print name of child __________________________________________________________

Signature of child: __________________________________________________________

Date:___________________________
Appendix E: NHS National Research Ethics Service Approval Letters

National Research Ethics Service
North West 12 Research Ethics Committee – Lancaster
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 30Z

Telephone: 0161 625 7818
Facsimile: 0161 237 9427

10 March 2011

Dr Dougal Julian Hare
Senior Lecturer in Clinical Psychology
University of Manchester
Division of Clinical Psychology
Zochonis Building, 2nd Floor
Oxford Road
M13 9PL

Dear Dr Hare

Study Title: An Investigation of the sleep, circadian rhythms, behavioural phenotype and family functioning of children with MPS III

REC reference number: 11/NW/0068

The Research Ethics Committee reviewed the above application at the meeting held on 03 March 2011. Thank you for attending to discuss the study.

Ethical opinion

The Chair welcomed you to the REC and thanked you for attending to discuss the study.

The Committee asked how the typically developing participants would be recruited and you said they would be the children of University staff.

The Committee asked whether the MPS III patients are an over researched group of participants and you said that you have a large clinic at Manchester Childrens’ Hospital and some have been very heavily researched but MPS III patients have been under researched for many years as it is hard to treat.

The Committee had found the Participant Information Sheets very detailed and requested that a larger font be used. You told the Committee that they were happy with the wording and had tried to adapt appropriately. The Committee pointed out that the average reading age for adults in the UK is 8 to 9 years and suggested that you try out the sheets on a 9 year old to see if they could understand it.

The Committee asked whether all of the questionnaires would be sent out in the post and you confirmed that they would. The Sanfilippo behaviour scale is still being developed but the others are standard. You stated that at the recent MPS conference you had casually spoken to people and had found them committed to taking part in research.

The Committee suggested that the mainstream recruitment letter was very technical and might be simplified. They also suggested that the brief COPE inventory be revised to omit the reference to operation.

This Research Ethics Committee is an advisory committee to the North West Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

106
You clarified for the Committee that you do not provide treatment but will signpost to the service if required.

You confirmed for the Committee that most families will have one affected child but a significant number will have two.

You stated that an independent nurse practitioner will be assigned to assist with the questionnaires and practicalities.

The Committee was told that there are three centres for MPS in England.

The Committee asked for confirmation that the data on the laptop would be secure and you confirmed that it would be encrypted and that a new and more secure programme had been brought in as of the previous day.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. The Committee suggests that the font size of the Participant Information Sheet is increased. However, on reflection and after further discussion the Committee agreed that no other changes were necessary.

**Ethical review of research sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

**Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

**Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.**

For NHS research sites only, management permission for research (“R&D approval”) should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at [http://www.rdforum.nhs.uk](http://www.rdforum.nhs.uk).

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation’s involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

**Sponsors are not required to notify the Committee of approvals from host organisations.**

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).
Approved documents

The documents reviewed and approved at the meeting were:

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<th>Document</th>
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<th>Date</th>
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<td>GP/Consultant Information Sheets</td>
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<td>28 January 2011</td>
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<td>Participant Information Sheet: For parents of MPS III children - questionnaire components only</td>
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<td>Letter from Sponsor</td>
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<td>CV for Maria Canal</td>
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<td>Participant Information Sheet: For parents of MPS III children - all components</td>
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<tr>
<td>Participant Consent Form: Informed assent for mainstream controls</td>
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<td>Participant Information Sheet: For mainstream neurotypical children aged 6-10</td>
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<td>Participant Consent Form: Behaviour and family functioning MPS III protocol</td>
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<td>Questionnaire: Learning disability casemix scale</td>
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<td>Questionnaire: Multidimensional scale of perceived support</td>
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<td>Questionnaire: Aberrant behaviour checklist</td>
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<td>Questionnaire: Paediatric inventory for parents</td>
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<td>Questionnaire: Developmental behaviour checklist</td>
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<td>Protocol for risk issues that become apparent through data collected</td>
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for research
CV for Elaine Cross 28 January 2011
Template for initial contact letter - mainstream 01 28 January 2011
Protocol for child participants who are in emotional distress 01 28 January 2011
CV for Michelle Lomax 28 January 2011
Protocol for adult participants who are in emotional distress 01 28 January 2011
Original copies of D1 and D3 on IRAS form 3.0 16 February 2011
Questionnaire: Children's sleep habits rating scale
Questionnaire: Brief cope inventory
Questionnaire: The general health questionnaire

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.
We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/NW/0068 Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project

Yours sincerely

Dr Lisa Booth
Chair

Email: carol.ebenezer@northwest.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: April Lockyer
Lorraine Broadfoot
11 March 2011

Dr Dougal Julian Hare
Senior Lecturer in Clinical Psychology
University of Manchester
Division of Clinical Psychology
Zochonis Building, 2nd Floor
Oxford Road
M13 9PL

Dear Dr Hare

Full title of study: An Investigation of the sleep, circadian rhythms, behavioural phenotype and family functioning of children with MPS III

REC reference number: 11/NW/0068

Thank you for your email of 11 March 2011. I can confirm the REC has received the documents listed below as evidence of compliance with the approval conditions detailed in our letter dated 03 March 2011. Please note these documents are for information only and have not been reviewed by the committee.

Documents received

The documents received were as follows:

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<td>Participant Information Sheet: parents of ID controls</td>
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<tr>
<td>Participant Information Sheet: parents of MPS III children</td>
<td>1</td>
<td>28 January 2011</td>
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</table>

All of the above documents were resubmitted using a larger font size as requested.
You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

11/NW/0068 Please quote this number on all correspondence

Yours sincerely

Mrs Carol Ebenezer
Committee Co-ordinator

E-mail: carol.ebenezer@northwest.nhs.uk

Copy to: April Lockyer
Lorraine Broadfoot
Appendix F: NHS Trust Research and Development Approval

Central Manchester University Hospitals
NHS Foundation Trust

Research & Development
1st Floor Fox: Graduate Centre
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL
Tel: 0161 276 4125
Fax: 0161 276 5766
Lynne.Webster@cmuh.nhs.uk
http://clinicalresearch.nw.mht.nhs.uk/

Professor Ed Wraith
Professor in Paediatric Metabolic Disease
Genetic Medicine
St Mary's Hospital
Oxford Road
Manchester
M13 9WL

Dear Professor Wraith

Ref: RO1593-11: E-WRAITH

PIN: RO1593 (Please quote this number in all future correspondence)
Research Study: An Investigation of the sleep, circadian rhythms, behavioural phenotype and family functioning of children with MPS III

Thank you for submitting the above study for approval.

We acknowledge that the University of Manchester has accepted the role of Research Governance Sponsor for this study.

We understand that this study is not adopted by the NIHR Portfolio.

I am pleased to confirm that the Research Office has now received all necessary documentation, and the Trust Director of Research & Innovation has given approval for the project to be undertaken. This approval is in relation to the documentation supplied to us below.

Approval is given subject to the attached conditions – please ensure you and all members of the research team are familiar with these before commencing your research.

Please note: You must tell your Divisional Research Manager – Sarah Leo

• the date that you intend to start recruiting to this study AND
• the date on which the first participant is recruited/consented

The Trust aims for its research projects to recruit their first participant within 30 days of the recruitment start date. If you do not tell us your actual recruitment start date, we will use this approval date. This information is important for monitoring Trust recruitment performance for internal and external assessment.
I would like to take this opportunity to wish you well with your research.

Yours sincerely,

[Signature]

Dr Lynne Webster
Head of Research Office

Date: [Date]

Encs (Internal Authorisations)

c. Ms Elaine Cross
Sarah Leo
Dr Dougall Hare

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<td>10 March 2011</td>
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Version 1.1 - 1/08/09
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<td>Questionnaire: Multidimensional Scale of Perceived Social Support</td>
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<td>Questionnaire: Pediatric Inventory for Parents</td>
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<td>Questionnaire: Children's Sleep Habits Rating Scale</td>
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<td>Questionnaire: Sanfilippo Behaviour Rating Scale</td>
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Appendix G: Invitation Letter to Parents of Children with MPS III

Dear Sir/Madam,

A major research study is being conducted at the University of Manchester to investigate child behaviour and family functioning in families with a child with Sanfilippo Syndrome. This study is part of a large study under the direction of Prof Ed Wraith, Dr. Dougal Hare, Dr. Simon Jones, and Dr. Brian Bigger. We are contacting you to invite you and your family to participate in this research.

Currently our understanding of the behaviours shown by children with Sanfilippo Syndrome is limited. This study aims to gain a detailed understanding of the behaviours typically experienced by children with this diagnosis. We will also be examining what effects these behaviours have on how families function, i.e. how carers deal with stress, what coping mechanism they employ and how to build resilience.

Some families living within the Northwest/Yorkshire are will also have the opportunity to participate in research focusing particularly on the sleep and circadian rhythms of children with Sanfilippo Syndrome.

It is useful to gain more information about sleep, activity levels and behaviours to inform the development and evaluation of clinical interventions, including gene therapy and behavioural interventions. By investigating how families manage these behaviours and what causes parents the most difficulty, clinicians will be better placed to design interventions to support families and their children.

Participation in this study is voluntary and will in no way affect the medical treatment of your child.

If you are interested in hearing more about this project, please phone us on 07983759667, email us at Sanfilippo@listserv.manchester.ac.uk, or return the slip below to Sanfilippo Study, Division of Clinical Psychology, Second Floor Zochonis Building, Brunswick Street, Manchester M13 9PL, and a Researcher will contact you. We are currently recruiting families and look forward to hearing from you.

Yours sincerely

Elaine Cross, Trainee Clinical Psychologist

Louise Mahon, Trainee Clinical Psychologist
Michelle Lomax, Trainee Clinical Psychologist
Sheena Aspil, Trainee Clinical Psychologist

Please telephone me to provide further information about this research project:

Name: __________________________

Telephone number: ________________________

Address: ________________________________

_______________________________________

_______________________________________

Email Address: ___________________________
Appendix H: Participant Information Sheets

Participant Information Sheet for Parents of Children with MPS III

Central Manchester University Hospitals NHS

Participant Information Sheet

Study Title: An Investigation of Sleep, Circadian Rhythms,
Behaviour, and Family Functioning in MPS III

Research Team: Dr Dougal Julian Hare, Dr Brian Bigger, Sheena Aspil,
Louise Mahon, Michelle Lomax, and Elaine Cross (University of
Manchester); Professor Ed Wraith and Dr Simon Jones (Central Manchester
University Hospitals NHS Foundation Trust), Research Assistant.

We would like to invite your child to take part in our research study. We
are asking you to consent on behalf of your child if you feel he/she should
take part. Before you decide, we would like you to understand why the
research is being done and what it would involve. You may wish to
consider whether you think your child would have agreed to join the
study, had he/she been able to make a decision for him/herself. One of
our team will answer any questions you have.

Part 1 tells you the purpose of this study and what will happen to your
child if he/she takes part.

Part 2 gives you more detailed information about the study.

We recommend that you take a minimum of 24 hours to consider the
information below before deciding whether to take part.

Part 1

1.1 What is the purpose of the study?
The study aims to find out more about typical sleep patterns, circadian
(24-hour) rhythms and behaviours in children with MPS III. We will also
investigate how a family’s well-being is affected and how they manage to
cope with difficulties. Differences between children with and without this
condition will be compared, as well as variations between subtypes and
phases of the disorder.
1.2 Why have I been invited to take part?
Your child has been selected to take part because they have a diagnosis of MPS III.

1.3 Do I have to take part?
Participation is voluntary. If you agree that your family will take part, we will ask you to sign a consent form on behalf of your child. You are free to withdraw at any time, without giving a reason. For example if your child exhibits distress or parents feel too stressed to continue, then you don’t have to carry on with the project. This would not affect the standard of care your family receives from your doctor.

1.4 What will participation involve?
Each family will meet a member of the team for 2 appointments. The first appointment will last up to one hour and the second appointment will last about 30 minutes. The study involves:

- If your child takes melatonin, it will be stopped for a total of 24 days for the study.

- Your child will wear a device called an actigraph on his/her wrist (or in their pocket) for 10 days and nights, except for bathing or swimming. The actigraph collects information about sleep and activity levels.

- Parents will take saliva samples from their child (6 samples in total) using equipment which we will provide. Your child should not be given Aspirin or Ibuprofen on the 2 days on which the samples are collected, but an alternative, Paracetamol, can be given. We will demonstrate how to take saliva samples at the first appointment and give you written instructions. The samples will be tested to check levels of melatonin in the body.

- Parents will complete a sleep checklist and a sleep diary over the 10-day period, noting times when your child goes to bed and wakes up, when lights are switched on/off and any other night-time events.

- Parents will complete questionnaires which ask about behaviour and family coping.
Basic demographic information (e.g. age, gender, etc) will be collected. We will need to access relevant sections of your child’s NHS medical records to get information like the stage of the disorder.

**Important Note**

Professor Ed Wraith and Dr Simon Jones have confirmed that no harmful effects can occur by stopping melatonin for the study period. There will still be melatonin in the body, as it is produced naturally by a part of the brain called the pineal gland. We want to observe natural sleep patterns without medication, so some children may have more disrupted sleep for the study period. If you have any questions or concerns about stopping melatonin, please speak to Gill Moss (0161 701 2147) who is an independent nurse and can discuss your decision whether to take part or not.

1.5 What are the risks of taking part?

Wearing an actigraph feels like wearing a wristwatch. Initially it may feel unfamiliar but it is not dangerous in any way. If sleep becomes more irregular after stopping melatonin, it could cause parents to become more stressed. We would encourage you to contact Gill Moss who can provide advice/support during this time. It is possible that questionnaires might raise issues which could be distressing to think about. A list of agencies is provided who can offer additional information/support. Taking saliva samples will not harm your child.

1.6 What are the benefits of taking part?

Each family will be sent a report about your child’s sleep functioning and circadian rhythms, which will assist doctors when working with your child. In the longer-term, the results of the study will help with the development of behavioural interventions, medication and clinical interventions aimed at improving sleep and particular behaviours. Being aware of the needs of children and the demands of caring for child with MPS III will help services provide the best support to families and promote resilience and coping. It will also inform the development and implementation of innovative treatments for MPS III such as gene therapy.

1.7 Expenses
Your travel expenses will be reimbursed. Your child will receive a £10 high street gift voucher as a thank-you for taking part.

1.8 Will my data be kept confidential?

Yes. All data will be confidential and will be handled and stored in accordance with all statutory guidance and procedures. Further information is provided in Part 2.

If you are interested in what you have read so far and considering taking part, please read Part 2 before making a decision.

Part 2

2.1 What happens if I don’t want to continue with the project?

We will discuss with you whether you want to withdraw from the whole project or just certain components. We will need to use information which has been collected up to that point, but this data will not be personally identifiable. If you are in possession of the actigraph, you will need to attend the second appointment to return the actigraph, other equipment and any completed questionnaires.

2.2 What if there is a problem?

If you have a concern about any aspect of the study, you should contact one of the researchers (sanfilippo@listserv.manchester.ac.uk or 07983 759667). If you are not satisfied that the problem has been solved, email Research-Governance@Manchester.ac.uk or telephone 0161 2758093.

2.3 Will my data be confidential?

All data collected about your child will be stored securely in a locked filing cabinet at the University of Manchester. It will only be viewed by members of the research team. Actigraph data will be deleted after being downloaded onto a stand-alone computer. Saliva samples will be stored in a freezer in a laboratory at the University with no personally identifiable information. A laboratory technician will test the samples and the samples will be destroyed at the end of the study.

Data will be entered onto a computer database that will be password protected and encrypted. Each participant will be assigned a number, therefore no names will not be entered onto the database.
We will ask for details of your child’s GP and will send him/her a letter informing them of your child’s participation in this research. During the study if we have any concerns about risk of harm to anyone, then we will have to contact the relevant agency/person to provide support. If possible, we would speak to you first about this.

The results of the study will be published in scientific and clinical journals but no names or any other information that might identify individual participants will be published.

2.4 Who is organising the research?

This research is being conducted as part of the Doctorate in Clinical Psychology at the University of Manchester for Trainee Clinical Psychologists/postgraduate students Elaine Cross, Louise Mahon, Sheena Aspil and Michelle Lomax. It will be carried out under the guidance of Dr Dougal Hare (Academic Supervisor), Dr Simon Jones and Professor Ed Wraith (Clinical Supervisors). It is part-funded by a grant from the MPS Society.

2.5 Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee who protect the rights, safety, dignity and well-being of participants. This study has been reviewed and given a favourable opinion by the North West 12 Research Ethics Committee.

2.6 Further information

If you have any further queries or concerns, please contact a member of our research team at: sanfilippo@listserv.manchester.ac.uk or 07983 759667 or Dr Dougal Hare, Division of Clinical Psychology, 2nd Floor, Zochonis Building, University of Manchester, Brunswick Street, Manchester, M13 9PL.

You can keep this copy of the information sheet.

Please explain this research to your child in the best way you can to help them understand what is involved.
We would like to invite your child to take part in our research study. We are asking you to consent on behalf of your child if you feel he/she should take part. Before you decide, we would like you to understand why the research is being done and what it would involve. One of our team will answer any questions you have.

Part 1 tells you the purpose of this study and what will happen to your child if he/she takes part.

Part 2 gives you more detailed information about the study.

We recommend that you take a minimum of 24 hours to consider the information below before deciding whether to take part.

Part 1

1.3 What is the purpose of the study
The study aims to examine differences in sleep patterns and circadian (24 hour) rhythms in children with and without Sanfilippo syndrome (MPS III). We hope to get a detailed picture of how active children are, as well as the quantity and quality of their sleep. Little is known about typical sleep patterns and wake cycles in children with MPS III, despite the fact that sleep difficulties can impair the quality of life of the child and their family.

1.4 Why have I been invited to take part?
Your child has been selected to take part because he/she is the same age as a participant with MPS III and has no diagnosed condition which affects their sleep.
1.3 Do I have to take part?

Participation is voluntary. If you agree that your family will take part, we will ask you to sign a consent form on behalf of your child. You are free to withdraw at any time, without giving a reason.

1.4 What will participation involve?

Each family will meet a member of the team for 2 appointments. The first appointment will last up to one hour and the second appointment will last about 30 minutes. The study involves:

- Your child will wear a device called an actigraph on his/her wrist (or in their pocket) for 10 days and nights, except for bathing or swimming. The actigraph collects information about sleep and circadian rhythms.

- Parents will take saliva samples from their child (6 samples in total) using equipment which we will provide. Your child should not be given Aspirin or Ibuprofen on the 2 days on which the samples are collected, but an alternative, Paracetamol, can be given. We will demonstrate how to take saliva samples at the first appointment and give you written instructions. The samples will be tested to check levels of melatonin (hormone which affects sleep and circadian rhythms) in the body.

- Parents will complete a sleep checklist and a sleep diary over the 10-day period, noting times when your child goes to bed and wakes up, when lights are switched on/off and any other night-time events.

- Basic demographic information (e.g. age, gender, etc) will be collected.

1.5 What are the risks of taking part?

Wearing an actigraph feels like wearing a wristwatch. Initially it may feel unfamiliar but it is not dangerous in any way. A list of agencies is provided who can offer additional information/support should any parents feel stressed or emotionally distressed during the study.

1.6 What are the benefits of taking part?
The results of the study will help with the development of interventions and medication aimed at improving sleep in children. It will also inform the development and implementation of innovative treatments for MPS III such as gene therapy. Observing the natural sleep and activity patterns of children who are not taking medication will act as a standard against which treatments can be compared.

1.7 Expenses

Your travel expenses will be reimbursed. Your child will receive a £10 high street gift voucher as a thank-you for taking part.

1.8 What if there is a problem?

Any complaint about the way you have been dealt with during the research or any possible harm you might suffer will be addressed. Further information is given in Part 2.

1.9 Will my data be kept confidential?

Yes. All data will be confidential and will be handled and stored in accordance with all statutory guidance and procedures. Further information is provided in Part 2.

If you are interested in what you have read so far and considering taking part, please read Part 2 before making a decision.

Part 2

2.1 What happens if I don’t want to continue with the project?

We will need to use information which has been collected up to that point, but this data will not be personally identifiable. If you are in possession of the actigraph, you will need to attend the second appointment to return the actigraph.

2.2 What if there is a problem?

If you have a concern about any aspect of the study, you should contact one of the researchers (sanfilippo@listserv.manchester.ac.uk or 07983 759667). If you are not satisfied that the problem has been solved, email Research-Governance@Manchester.ac.uk or telephone 0161 2758093.

2.3 Will my data be confidential?
All data collected about you and your child will be stored securely in a locked filing cabinet at the University of Manchester. It will only be viewed by members of the research team. Actigraph data will be deleted after being downloaded onto a stand-alone computer. Saliva samples will be stored in a freezer in a laboratory at the University with no personally identifiable information. A laboratory technician will test the samples and the samples will be destroyed at the end of the study.

Data will be entered onto a computer database that will be password protected and encrypted. Each participant will be assigned a number, therefore no names will not be entered onto the database.

We will ask for details of your GP, but will not routinely contact him/her. During the study if we have any concerns about risk of harm to anyone, then we will have to contact the relevant agency/person to provide support. If possible, we would speak to you first about this.

The results of the study will be published in scientific and clinical journals but no names or any other information that might identify individual participants will be published.

2.4 Who is organising the research?

This research is being conducted as part of the Doctorate in Clinical Psychology at the University of Manchester for Trainee Clinical Psychologists/postgraduate students Elaine Cross, Louise Mahon, Sheena Aspil and Michelle Lomax. It will be carried out under the guidance of Dr Dougal Julian Hare (Academic Supervisor), Dr Simon Jones and Professor Ed Wraith (Clinical Supervisors). It is part-funded by a grant from the MPS Society.

2.5 Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee who protect the rights, safety, dignity and well-being of participants. This study has been reviewed and given a favourable opinion by the North West 12 Research Ethics Committee.

2.6 Further information

If you have any further queries or concerns, please contact a member of our research team at: sanfilippo@listserv.manchester.ac.uk or 07983 759667 or Dr Dougal Julian Hare, Division of Clinical Psychology, 2nd Floor,
You can keep this copy of the information sheet.

Please explain this research to your child in the best way you can to help them understand what is involved.
Information Sheet for Children Aged 6-10

Study Title: Learning about Sleep in Children

Research Team: Dr Dougal Julian Hare, Dr Brian Bigger, Sheena Aspil, Louise Mahon, Michelle Lomax, and Elaine Cross (University of Manchester); Professor Ed Wraith and Dr Simon Jones (Central Manchester University Hospitals NHS Foundation Trust), Research Assistant.

We are asking if you would join in a research project. Research is a way we try to find the answers to questions. Before you decide if you want to take part, read these sheets. It will help you understand what will happen if you take part. To help you decide, you can talk to your family, friends, or anyone else you choose. Ask us about anything which you don’t understand.

Part 1

What is the point of the research?
We want to find out how much sleep children get and if this is peaceful or not. We also want to find out if children are moving around lots or if they are quite still.

Why have I been asked to take part?
You have been asked to take part because:
1) You are healthy.
2) You are the same age as another child in the study.
Do I have to take part?
No. It is your choice. If you agree to take part we will ask you to sign a form to say that you agree. We will also ask your parents to sign a form. You can stop taking part at any time during the research and you don’t have to tell us why.

What will happen to me if I take part?
Your parents will meet one of our team 2 times. You can come too but you don’t have too.

- You will wear something called an actigraph on your wrist for 10 days and nights. You only take it off for washing yourself and swimming. The actigraph collects information about your sleep and how much you move around.
- Your parents will get some of your saliva in a tube for us to test.
- Your parents will fill in a form about your sleep. They will also write in a sleep diary. They will write down when you go to bed and wake up, when lights are switched on/off and any other events that happen at night.
- We will ask for details like your age.

Will taking part hurt me?
Wearing an actigraph feels like wearing a normal watch. If you’re not used to wearing a watch, it might feel strange at first but it is not dangerous.

What’s good about taking part?
We hope that the information we get might help doctors. They want to make better medicines to help children who are poorly and don’t sleep well.

Thank you for reading so far.

Please read Part 2 if you want to find out more.

Part 2

What if I don’t want to do the research anymore?
Just tell your parents or one of our team. Nobody will be angry with you.

What if something goes wrong?
If you are worried about anything please tell your parents or one of the research team. Your parents can talk to us for you.

Will my details be kept private?
Only your parents and our team will know which children are taking part. All details will be kept safe and locked away.

Did anyone check the research is ok to do?
This project has been checked by a Research Ethics Committee. This is a group of people who make sure that the research is fair.

You can keep this sheet.
Participant Information Sheet for Young People Aged 11-15

Study Title: Investigating Sleep and Activity Levels in Young People

Research Team: Dr Dougal Julian Hare, Dr Brian Bigger, Sheena Aspil, Louise Mahon, Michelle Lomax, and Elaine Cross (University of Manchester); Professor Ed Wraith and Dr Simon Jones (Central Manchester University Hospitals NHS Foundation Trust), Research Assistant.

We are asking if you would join in a research project which is investigating sleep and activity levels in young people. Before you decide if you want to take part, it is important to understand why the research is being done and what it will involve for you. So please read this leaflet carefully. To help you decide, you can talk to your family, friends, or anyone else you choose. Ask us about anything which you don’t understand.

We suggest that you take at least 24 hours to think about the information below before deciding whether to take part.

Part 1

1.1 What is the point of the research?
We want to see how much sleep young people get and how active they are. We hope to get detailed information on whether each person’s sleep is interrupted or peaceful. We will compare the results of children who have no medical illnesses with those who have a condition called Sanfilippo syndrome. Your results will help us to see what normal sleep and activity levels look like.

1.2 Why have I been invited to take part?
You have been invited to take part because:
   1) You have no medical conditions which affect your sleep.
2) You are the same age as another young person in our study.

1.3 Do I have to take part?
No. It is your choice. If you agree to take part we will ask you to sign a form. We will also ask your parent/s to sign a form. You are free to stop taking part at any time during the research without giving a reason.

1.4 What will happen to me if I take part?
Your parent/s will meet a member of the team for 2 appointments. You can come too, but you don't have to. The first appointment will last about one hour and the second appointment will last about 30-60 minutes. The study will involve:

- Wearing something called an actigraph on your wrist for 10 days and nights. **You only remove it for bathing or swimming.** The actigraph collects information about your sleep and activity levels.

- Your parents will take some samples of your saliva. We will test these to see how much melatonin is in your body. Melatonin is a hormone which affects your sleep and body-clock.

- Your parents will complete a sleep checklist and a sleep diary over the 10-day period. They will write down times when you go to bed and wake up, when lights are switched on/off and any other night-time events.

- We will ask for basic details like your age.

1.5 Is there anything to be worried about if I take part?
Wearing an actigraph feels like wearing a normal watch. If you’re not used to wearing a watch, it might feel strange at first but it is not dangerous.

1.6 What are the benefits of taking part?
We hope that the information we get might help with the treatment of children with Sanfilippo syndrome in the future.

Thank you for reading so far. If you are still interested, please read Part 2.
Part 2

2.1 What happens if I don’t want to carry on with the project?

You can stop taking part at any time. We would need to use information which has been collected up to that point. We would ask that someone in your family comes to the second appointment to return the actigraph.

2.2 What if there is a problem?

If you are worried about any part of the study, the researchers can be contacted at sanfilippo@listserv.manchester.ac.uk or 07983 759667. If you or your parents are still not happy, email Research-Governance@Manchester.ac.uk or telephone 0161 2758093.

2.3 What will happen to my information?

All data which is collected about you will be locked away at the University. It will only be seen by members of the research team. Computer files will be in a special code and protected with a password. Your saliva samples will be destroyed at the end of the study.

We will ask for details of your family doctor, but will not usually contact him/her. During the study if we are worried that you or someone else is being harmed, then we would have to tell somebody else.

2.4 Who is organising the research?

This research is being carried out as part of a University of Manchester course (Doctorate in Clinical Psychology) by Trainee Clinical Psychologists/postgraduate students Elaine Cross, Louise Mahon, Sheena Aspil and Michelle Lomax. It will be carried out with Dr Dougal Hare (Academic Supervisor), Dr Simon Jones and Professor Ed Wraith (Clinical Supervisors). A charity (MPS Society) are part-funding this research.
2.5 Who checked that this research is ok to do?

Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is fair. This project has been checked by the North West 12 Research Ethics Committee.

2.6 Further information

If you or your parents have any further questions, please contact a member of our research team at sanfilippo@listserv.manchester.ac.uk or 07983 759667 or Dr Dougal Hare, Division of Clinical Psychology, 2nd Floor, Zochonis Building, University of Manchester, Brunswick Street, Manchester, M13 9PL.

You can keep this copy of the information sheet.
Appendix I: Participant Demographic Sheets

Demographics Sheet for Children with MPS III

**Central Manchester University Hospitals NHS**

**Demographic Questions about your Child with MPS III**

*Study Title: An Investigation into Sleep and Circadian Rhythms*

<table>
<thead>
<tr>
<th>Child Name:</th>
<th>________________________________</th>
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<tbody>
<tr>
<td>Date of Birth:</td>
<td>________________________________</td>
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<tr>
<td>Gender:</td>
<td>________________________________</td>
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<td>Ethnicity:</td>
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<td>Date of Diagnosis:</td>
<td>________________________________</td>
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<tr>
<td>Diagnosis Genetic Subtype:</td>
<td>________________________________</td>
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</table>

*Has your child ever received (Please circle)*

<table>
<thead>
<tr>
<th>A bone marrow transplant</th>
<th>No</th>
<th>Yes</th>
<th>? (Don’t know)</th>
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<tbody>
<tr>
<td>Gene Replacement Therapy</td>
<td>No</td>
<td>Yes</td>
<td>? (Don’t know)</td>
</tr>
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</table>

*Child’s Medical Status (Please circle)*

<table>
<thead>
<tr>
<th>Deafness?</th>
<th>No</th>
<th>Yes</th>
<th>? (Don’t know)</th>
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<tbody>
<tr>
<td>Blindness?</td>
<td>No</td>
<td>Yes</td>
<td>? (Don’t know)</td>
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<tr>
<td>Cerebral Palsy?</td>
<td>No</td>
<td>Yes</td>
<td>? (Don’t know)</td>
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<td>Other: ____________________________________________________________</td>
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</table>

*Current Medications (Please list any medication and dosage schedule)*
1. ____________________________________________________________

2. ____________________________________________________________

3. ____________________________________________________________

4. ____________________________________________________________

**G.P. Details**

Name: ________________________________________________________

Address: ______________________________________________________

______________________________________________________________

______________________________________________________________

Telephone number: ____________________________________________
Demographic Questions about your Child

Study Title: An Investigation into Sleep and Circadian Rhythms

Child Name: __________________________________________

Date of Birth: ________________________________________

Gender: ______________________________________________

Ethnicity _____________________________________________

Current Medications (Please list any medication and dosage schedule)

1. ______________________________________________________

2. ______________________________________________________

3. ______________________________________________________

4. ______________________________________________________

G.P. Details

Name: _________________________________________________

Address: ______________________________________________

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Telephone number: ____________________________________________
Appendix J: Children’s Sleep Habits Rating Scale

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<th>Site Number</th>
<th>Patient Number</th>
<th>Patient Initials</th>
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**Children’s Sleep Habits Rating Scale**

☐ Week #_____ Day #_____ ☐ End of Study

Please check the box that applies to your child best

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<thead>
<tr>
<th>Item</th>
<th>Usually 5-7 times/week</th>
<th>Sometimes 2-4 times/week</th>
<th>Rarely 0-1 times/week</th>
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<td>31.</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Version 1.0
June 9, 2010

Shire HGT (Confidential) Page 1 of 2
Children's Sleep Habits Rating Scale

☐ Week #_____ Day #_____ ☐ End of Study

<table>
<thead>
<tr>
<th>司数</th>
<th>Usually 5-7 times/week</th>
<th>Sometimes 2-4 times/week</th>
<th>Rarely 0-1 time/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>32. Hard time getting out of bed</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>33. Takes long time to be alert</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>34. Seems tired</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>35. Sleeps during day, other than planned nap</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>36. Tired/sleeps watching TV</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>37. Tired/sleeps riding in car</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

At what age did your child begin to have sleep difficulties? ____________

What is the nature of the sleep problem? ________________________________

What treatments have you tried for your child’s sleep problem?

☐ Medication

What was tried? ________________________________

Effectiveness? ________________________________

☐ Behavioral treatments

What was tried? ________________________________

Effectiveness? ________________________________

Does your child have seizures? ☐ Yes ☐ No

If Yes, do you think that there is a relationship between sleep disturbance and your child’s seizures? ☐ Yes ☐ No

Describe: ________________________________

Do you think your child’s sleep problems affect his/her behavior? ☐ Yes ☐ No

If so, how? ________________________________
Appendix K: Scoring of the Children’s Sleep Habits Rating Scale

**Scoring:** Usually = 3, Sometimes = 2, Rarely/Never = 1
R indicates items which are reverse scored

**Subscales:**

<table>
<thead>
<tr>
<th>Bedtime resistance (6 items)</th>
<th>Sleep onset delay (1 item)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goes to bed at the same time R</td>
<td>Falls asleep in 20 minutes R</td>
</tr>
<tr>
<td>Falls asleep in own bed R</td>
<td></td>
</tr>
<tr>
<td>Falls asleep in other’s bed</td>
<td></td>
</tr>
<tr>
<td>Needs parent in room to sleep</td>
<td></td>
</tr>
<tr>
<td>Struggles at bedtime</td>
<td></td>
</tr>
<tr>
<td>Afraid of sleeping alone</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep anxiety (4 items)</th>
<th>Night waking (3 items)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needs parent in room to sleep</td>
<td>Move’s to other’s bed at night</td>
</tr>
<tr>
<td>Afraid of sleeping the dark</td>
<td>Awakes once during night</td>
</tr>
<tr>
<td>Afraid of sleeping alone</td>
<td>Awakes more than once</td>
</tr>
<tr>
<td>Trouble sleeping away</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Night behaviours (2 items)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Disruptive behaviour at night (awakens screaming, singing, laughing)</td>
<td></td>
</tr>
<tr>
<td>Dangerous behaviour at night (running outside, playing with appliance)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parasomnias (6 items)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wets the bed at night</td>
<td></td>
</tr>
<tr>
<td>Talks during sleep</td>
<td></td>
</tr>
<tr>
<td>Restless and moves a lot</td>
<td></td>
</tr>
<tr>
<td>Sleep walks</td>
<td></td>
</tr>
<tr>
<td>Grind teeth during sleep</td>
<td></td>
</tr>
<tr>
<td>Alarmed by scary dream</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep disordered breathing (3 items)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Snores loudly</td>
<td></td>
</tr>
<tr>
<td>Stops breathing</td>
<td></td>
</tr>
<tr>
<td>Snorts and gasps</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daytime sleepiness (9 items)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wakes by himself/herself R</td>
<td></td>
</tr>
<tr>
<td>Wakes up in negative mood</td>
<td></td>
</tr>
<tr>
<td>Others wake child</td>
<td></td>
</tr>
<tr>
<td>Hard time getting out of bed</td>
<td></td>
</tr>
<tr>
<td>Long time to be alert</td>
<td></td>
</tr>
<tr>
<td>Seems tired</td>
<td></td>
</tr>
<tr>
<td>Sleeps during the day, other than planned nap</td>
<td></td>
</tr>
<tr>
<td>Tired/sleeps watching TV</td>
<td></td>
</tr>
<tr>
<td>Tired/sleep riding in car</td>
<td></td>
</tr>
</tbody>
</table>

Appendix L: Amendment to NRES to Recruit Across Britain

National Research Ethics Service
NRES Committee North West - Lancaster
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ
Tel: 0161 625 7818

16 August 2011

Dr D Hare
Senior Lecturer in Clinical Psychology
University of Manchester
Division of Clinical Psychology
2nd Floor, Zochonis Building
Oxford Road
Manchester
M13 9PL

Dear Dr Hare

Study title: An Investigation of the sleep, circadian rhythms, behavioural phenotype and family functioning of children with MPS III

REC reference: 11/NW/0068
Amendment number: 3
Amendment date: 05 August 2011

The above amendment was reviewed by the Sub-Committee in correspondence.

Due to the fact that there are few children with MPS III in the North West of England and Yorkshire areas the amendment requests an expansion of the recruitment catchment area. The expansion includes all geographical areas in England, Wales and Scotland. There will be an option of families meeting the researchers at St Mary’s Hospital, a local community venue or at home.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 3</td>
<td></td>
<td>05 August 2011</td>
</tr>
<tr>
<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>3</td>
<td>05 August 2011</td>
</tr>
</tbody>
</table>

This Research Ethics Committee is an advisory committee to the North West Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England
Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/NW/0068: Please quote this number on all correspondence

Yours sincerely

Dr L. Booth
Chair

E-mail: carol.ebenezer@northwest.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr L. Webster, R&D, Central Manchester University Hospitals NHS Foundation Trust

NRES Committee North West - Lancaster
Appendix M: Amendments to NRES for Recruitment of Controls

16 August 2011

Dr D Hare
Senior Lecturer in Clinical Psychology
University of Manchester
Division of Clinical Psychology
2nd Floor, Zochonis Building
Oxford Road
Manchester
M13 9PL

Dear Dr Hare

Study title: An Investigation of the sleep, circadian rhythms, behavioural phenotype and family functioning of children with MPS III

REC reference: 11/NW/0068
Amendment number: 4
Amendment date: 12 August 2011

The above amendment was reviewed by the Sub-Committee in correspondence.

The amendment relates to the Control Group Data Collection for the Sleep and Circadian Rhythm studies. It seeks to expand recruitment into the group to include children of students at the University of Manchester in addition to children of staff. This will give a larger pool of potential participants for the group. An email giving brief information about the study will be sent to students and staff.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 4</td>
<td></td>
<td>12 August 2011</td>
</tr>
<tr>
<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>4</td>
<td>12 August 2011</td>
</tr>
</tbody>
</table>
Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/NW/0068: Please quote this number on all correspondence

Yours sincerely

[Signature]

Dr L Booth
Chair

E-mail: carol.ebenezer@northwest.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr L Webster, R&D, Central Manchester University Hospitals NHS Foundation Trust
19 October 2011

Dr D Hare
University of Manchester
Division of Clinical Psychology
2nd Floor, Zochonis Building
Oxford Road
Manchester
M13 9PL

Dear Dr Hare

Study title: An Investigation of the sleep, circadian rhythms, 
behavioural phenotype and family functioning of children 
with MPS III

REC reference: 11/NW/0068
Amendment number: 5
Amendment date: 23 September 2011

The above amendment was by the Sub-Committee in correspondence.

The amendment relates to the control group data collection for the sleep and circadian rhythm studies. In order to recruit sufficient numbers of typically-developing children for the group it is proposed to recruit children of parents not connected to the university. Potential recruitment will be via email or word of mouth.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document Listing Proposed Changes</td>
<td>Amendment 5</td>
<td>23 September 2011</td>
</tr>
<tr>
<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>5</td>
<td>23 September 2011</td>
</tr>
</tbody>
</table>

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.
R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/NW/0068: Please quote this number on all correspondence

Yours sincerely

L. Brown
Dr Lisa Booth
Chair
E-mail: carol.ebenezer@northwest.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms L Mahon, Trainee Clinical Psychologist, Division of Clinical Psychology, University of Manchester
         Ms A Lockyer, University of Manchester

An advisory Committee to NHS North West
R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/NW/0068: Please quote this number on all correspondence

Yours sincerely

L. Brown
Dr Lisa Booth
Chair

E-mail: carol.ebenezer@northwest.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms L Mahon, Trainee Clinical Psychologist, Division of Clinical Psychology, University of Manchester

Ms A Lockyer, University of Manchester

An advisory Committee to NHS North West
Appendix N: Lone Working Procedure

<table>
<thead>
<tr>
<th>LONE WORKING PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior to Lone Working</strong></td>
</tr>
<tr>
<td>The Lone Worker should contact a Buddy from within the research team and provide them with:</td>
</tr>
<tr>
<td>- Name, address and telephone number of the family they are visiting</td>
</tr>
<tr>
<td>- Phone on arrival at destination and agree time for completion of visit (for example, 1 hour)</td>
</tr>
<tr>
<td>- Ensure their personal phone and research phone are fully charged and turned on before entering the family’s home</td>
</tr>
<tr>
<td>- Put an alarm on their mobile phone to sound at the agreed time for completion of visit</td>
</tr>
</tbody>
</table>

The Buddy should ensure that they;
- Have the name, address and telephone number of the family being visited |
- Have their own mobile phone fully charged, turned on and in sight at all times during the visit |
- Place an alarm on their mobile phone to sound at the agreed time for completion of visit |

| **During Lone working** |
| The Lone Worker should explain the Lone Working Policy to the family they are visiting, and ensure that they are aware of the agreed upon time for completion of the visit. The Lone Worker should have the research phone turned on and in sight at all times during the visit. |

The code word for sharing that you are in trouble and need of assistance is PINK FOLDER. If the Lone Worker phones their Buddy and uses the term PINK FOLDER in any context the Buddy should reply with three questions;
- Are you alone? |
- Are you safe? |
- Should I call the police? |

The Lone Worker should reply with a Yes or No response to each question. If the Buddy is unsure of the Lone Worker’s responses then they should call the police immediately, give them the family’s address and ask them to call on the family to ensure the Lone Worker’s safety. |

| **After Lone Working** |
| The Lone Worker should call the Buddy immediately after completing their visit to confirm their safety. If the Lone Worker has not made contact within 30 minutes of the agreed time of completion of the visit then the Buddy should; |
| - Call the research phone |
| - Call the Lone Worker’s personal mobile phone |
| - Call the family’s phone |

If there is no response from calling the three phone numbers twice, then call the Police immediately, give them the family’s address and ask them to call on the family to ensure the Lone Worker’s safety. |
Appendix O: Sleep Diary

Start a new table each morning.

<table>
<thead>
<tr>
<th>Day and Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning: Time the lights are turned on:</td>
</tr>
<tr>
<td>Morning: Time he/she got out of bed:</td>
</tr>
<tr>
<td>Evening: Time he/she went to bed:</td>
</tr>
<tr>
<td>Evening: Time the lights were turned off:</td>
</tr>
<tr>
<td>Night time events e.g. seizures</td>
</tr>
</tbody>
</table>

Note times the watch is removed and put back on.