

Circadian rhythms, sleep and behaviour in intellectual and developmental disabilities: a systematic review of sleep and challenging behaviour and actigraphic assessment of circadian functioning in MPS III (Sanfilippo syndrome)

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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Abstract

Sleep disturbance and behavioural difficulties are both prevalent problems in the intellectual and developmental disability population and can have a significant impact on quality of life for the individual and their family. This thesis investigated sleep, behaviour and circadian rhythm functioning in children with intellectual and developmental disabilities, and is presented in three sections. The first two papers have been prepared in accordance with the author guidelines of the journals proposed for submission, excluding tables and figures for ease of reading.

The first paper is a systematic review of the literature examining the relationship between sleep disturbance and challenging behaviour in children with intellectual and developmental disabilities. 15 studies were included in the review and overall there were consistent findings of an association between the presence of sleep disruption and increased behavioural difficulties. A causal relationship could not be inferred due to the cross-sectional methodology of studies. Other factors, such as parental wellbeing, child level of intellectual disability and comorbidity of physical health conditions, need to be considered to understand the complexity of this relationship.

Children with the neurodevelopmental disorder mucopolysaccharidosis type III (MPS III or Sanfilippo syndrome) present with high rates of sleep disturbance and challenging behaviour. The second paper investigates circadian rhythm functioning and activity levels in children with MPS III, compared to typically developing controls. Objective measurement of circadian rhythm and activity levels was obtained through actigraphic recording for 7-10 days. Children with MPS III had increased fragmentation of circadian rhythm, less stability of rhythm in relation to external cues and a differential pattern of activity across the day compared to controls. Overall, results were indicative of a disruption of circadian rhythm function in children with MPS III. The implications for clinical practice and future research are discussed.

The third paper provides a critical appraisal of the overall research process, including further consideration of the strengths and limitations, implications for clinical practice, wider context of the research and personal reflections. An account of the project that was originally proposed with the MPS III population is also presented, alongside reflections on its termination.

Declaration

No portion of the work referred to in this 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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Paper One

A systematic review of the relationship between sleep disturbance and challenging behaviour in children with intellectual disabilities

Prepared in accordance with author guidelines for submission to Journal of Applied Research in Intellectual Disabilities (Appendix 1)

Word count: 7480

Abstract

Background

Sleep disturbance and challenging behaviour are prevalent problems in children with intellectual and developmental disabilities [IDD], and can result in numerous disadvantages for the individual and their family.

Method

Medline, PsycINFO and Embase were searched for studies reporting on the relationship between sleep and behaviour in children with IDD. Inclusion criteria were that the study: (i) assessed sleep in children and adolescents with IDD, (ii) contained a specific measure of daytime behaviour, and (iii) examined the relationship between sleep and behaviour. A quality assessment tool was developed to evaluate studies.

Results

Fifteen studies met criteria for inclusion, which investigated both specific IDD conditions (e.g. Fragile X, Cornelia de Lange, Down, Prader-Willi, and Smith Magenis syndromes) and mixed samples of IDD conditions. One study was rated as strong quality, thirteen studies were of moderate quality and two were rated as weak quality. Overall, results revealed a significant association between sleep problems and challenging behaviour in IDD, with sleep problems predictive of challenging behaviour in two studies. Findings in relation to the relationship between sleep disturbance and self-injurious behaviour were inconsistent. All studies were cross-sectional, therefore a causal relationship could not be inferred.

Conclusion

Further research is required to explain the nature of the relationship between sleep and challenging behaviour in IDD and explore possible mediating factors. Clinical implications, recommendations for future research and study limitations are discussed.

Keywords: sleep, behaviour, intellectual disability, developmental, systematic review

Introduction

Sleep disturbance in intellectual and developmental disability

Children with intellectual and developmental disabilities [IDD], including autistic spectrum disorders [ASD], experience higher rates of sleep disturbance than their typically developing [TD] peers (Didden & Sigafoos, 2001; Doran *et al.*, 2006; Krakowiak *et al.*, 2008; Quine, 2001). Prevalence rates vary depending on age, severity of cognitive impairment and the definition of sleep disturbance, but have been reported from 13% to 86% (Didden & Sigafoos, 2001; Jan & Freeman, 2004). The restorative and neurocognitive functions of sleep for children are well established (Sadeh, 2007). Consequently, sleep disruption for children with a pre-existing intellectual vulnerability is likely to further disadvantage cognition and learning abilities (Jan *et al.*, 2008). Sleep disturbance also impacts on family functioning. Parents of children with IDD and sleep problems report high stress levels and poor psychosocial wellbeing (Chu & Richdale, 2009; Doo & Wing, 2006) and secondary disrupted sleep in parents and caregivers of children with IDD is also a risk factor for reduced wellbeing and family quality of life (Meltzer, 2008).

Sleep and behaviour

Challenging behaviour has been defined as behaviour that impacts on the safety of the individual or others, damages the environment and/or impedes daily and social functioning (Emerson, 2001). For the purposes of the current review, the definition of challenging behaviour was considered in relatively broad terms, including behaviours that are challenging for family or carers (e.g. aggression, non-compliance, hyperactivity). Research to date indicates a higher prevalence of challenging behaviour in individuals with IDD (Lowe *et al.*, 2007; Janssen *et al.*, 2002; Emerson *et al.*, 2001). Both national guidance, such as 'Valuing People' (Department of Health, 2001), and research focused on the management of behavioural difficulties in the IDD population identify challenging behaviour as a priority for services, as it often confers serious disadvantages for the individual and their family. Associations have been reported between challenging behaviour and increased family or carer stress, reduced quality of life and limited social participation opportunities (Emerson, 2001; Gerber *et al.*, 2011; Hastings, 2002; Holden & Gitlesen, 2006).

The relationship between sleep disruption and daytime behavioural difficulties has been a focus of research in the TD child and adolescent population and several studies have reported an association between behaviour problems and insufficient or disturbed sleep (Astill *et al.*, 2012; Hall *et al.*, 2012; Sadeh *et al.*, 2002). Emotional problems and poor attention regulation, which arguably underlie the expression of some challenging behaviours in children, have also been linked with sleep disturbance (Chorney *et al.*, 2008; Dahl, 1996; Dahl & Harvey, 2007; Paavonen *et al.*, 2002). Although some studies have relied purely on parent report, the relationship between sleep disturbance and daytime behavioural problems has been corroborated through other sources. Bates *et al.* (2002) showed that parental reports of child sleep disturbance were predictive of independent teacher reports on behaviour and school adjustment. Furthermore, longitudinal studies have demonstrated that childhood sleep difficulties are predictive of behavioural and emotional difficulties in later life (Gregory *et al.*, 2005; Smedje *et al.*, 2001). For example, Gregory & O'Connor (2002) followed children over an 11-year period and demonstrated that sleep disturbance at age four predicted behavioural (e.g. aggression, inattention) and emotional (e.g. anxiety, depression) difficulties in adolescence.

There are a number of mechanisms whereby sleep disturbance may affect daytime behaviour in both IDD and TD child and adolescent populations. Given its negative effect on attention regulation and consequent

daytime sleepiness (Fallone *et al.*, 2001; Sadeh, 2007), disrupted sleep may impede opportunities to learn appropriate behaviour or routines. Simultaneous parental sleep disruption may result in increased stress or negative parent-child interactions, potentially leading to the expression of behavioural and emotional difficulties in the child. Both difficulties (sleep and behaviour) may also be reflective of permissive parenting practices that limit the implementation of boundaries (Polimeni *et al.*, 2007); however, given that not all sleep disturbance is behaviourally-based, this may not explain the relationship for some children. Furthermore, in relation to the IDD population, behavioural difficulties are considered part of the behavioural phenotypes of some neurodevelopmental conditions (e.g. Rett, Smith-Magenis, MPS III (Sanfilippo) and Angelman syndromes), which also have reportedly high rates of sleep disturbance (De Leersnyder *et al.*, 2006; Didden *et al.*, 2004; Fraser *et al.*, 2005; Young *et al.*, 2007). It is therefore possible that underlying neurological mechanisms may offer some explanation of the relationship. The link between sleep and behavioural/psychological functioning in children has been described as bi-directional (Owens & Palermo, 2008) and any causal interpretations must necessarily be cautious based on the complexity of factors involved.

Review rationale

Both sleep disturbance and challenging behaviour are prevalent problems in the IDD population and in TD children daytime behavioural difficulties are associated with sleep problems. This association has also been examined in IDD populations, but, to date, no systematic review has examined the evidence for a relationship between sleep disturbance and daytime behavioural difficulties in children with IDD conditions. Understanding the nature of the relationship between sleep and daytime behaviour aids assessment and the development of effective interventions for children and families. Moreover, it emphasises the importance of conducting multi-dimensional, comprehensive assessments in clinical practice, including a consideration of physical factors, when children with IDD present with challenging behaviour. Previous reviews have reported on the relationship between sleep disturbance and challenging behaviour in adults with IDD (de Winter *et al.*, 2011) and in individuals with pervasive developmental disorders (PDD; Hollway & Aman, 2011), therefore these groups were excluded from the present review.

Review aims

The aims of the current review were: i) to identify extant literature on sleep disturbance and daytime behaviour in children with IDD, ii) to draw conclusions about the nature of the relationship where possible, iii) to critically evaluate the research methodologies used, and iv) to offer recommendations for further research in this area.

Method

Search strategy

Medline (1946-2013), PsycINFO (1950-2013) and Embase (1974-2013) were searched in May 2013. The search was limited to English language, peer reviewed journals and human studies. Combinations of search terms (presented in Table 1) were searched for in all fields and MeSH terms were used where indicated. Terms were selected to broadly investigate all aspects of difficult or challenging behaviour and intellectual disability. Reference lists of relevant papers were also hand searched.

Table 1. Search term combinations

All fields	All fields (one of)	All fields (one of)	Limits
<i>Sleep (MeSH)</i>	<i>Behavio*</i> AND <i>Self injur*</i> AND <i>Aggression</i>	<i>Intellectual disab* (MeSH)</i> <i>Learning disab* (MeSH)</i> <i>Developmental disab*</i> <i>Developmental delay*</i> <i>Mental retard*</i>	English language Human studies Peer-reviewed journals

Selection criteria

For inclusion in the review, studies were required to: i) include an assessment of sleep in children and adolescents with IDD, ii) contain a specific measure of daytime behaviour, and iii) examine the relationship between sleep and behaviour. Studies investigating sleep and behaviour in mixed age samples (i.e. children and adults with IDD) were only included if they considered groups individually in analysis or if the mean age of the sample was ≤18 years.

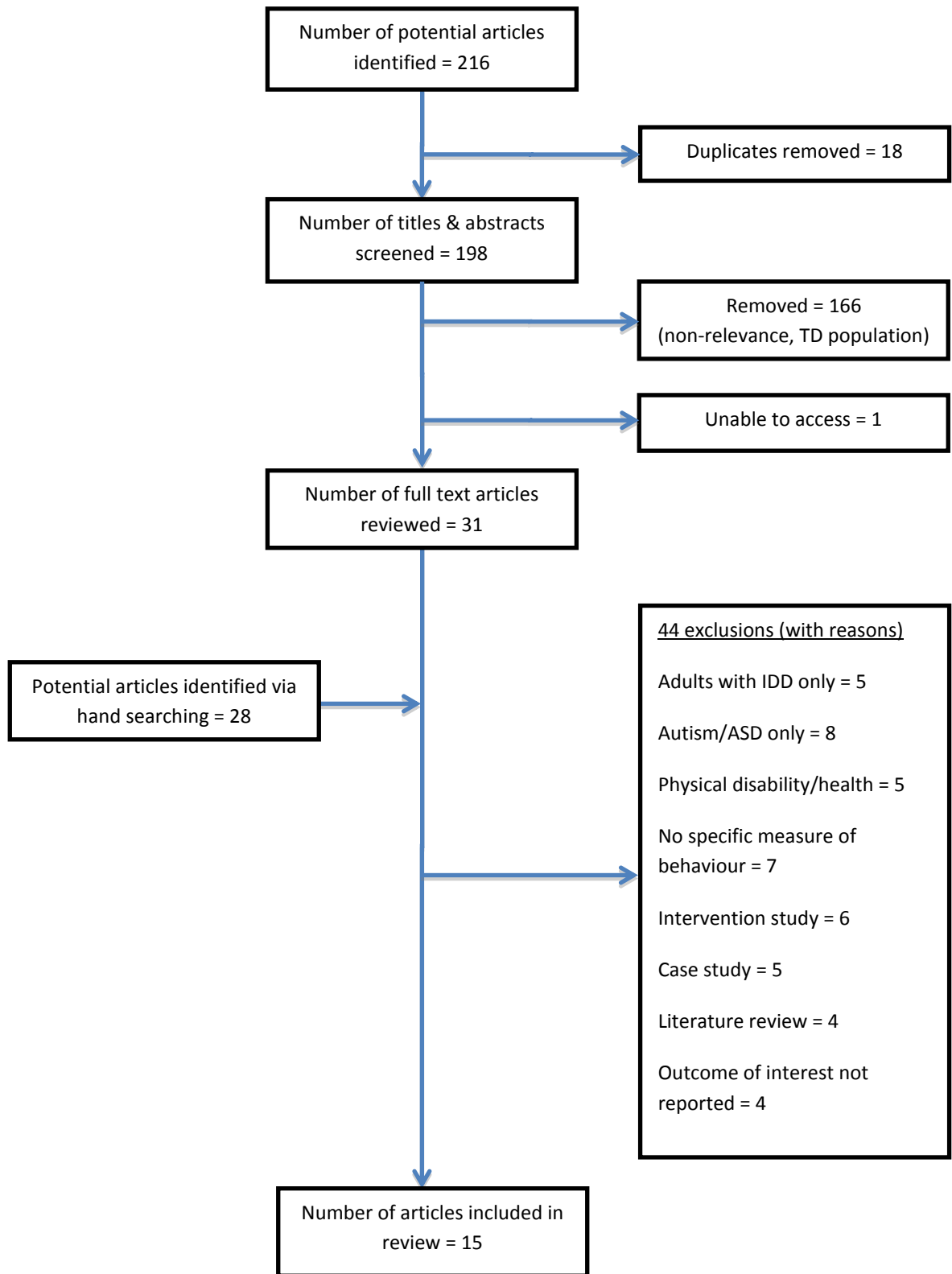
Studies were excluded if they: i) only included adults with IDD, ii) only included individuals with ASD, iii) were intervention studies, iv) only reported on behaviour in relation to general level of adaptive function, v) only reported on daytime sleepiness as a measure of daytime behaviour, and vi) used qualitative methodology. So-called “grey literature”, reviews and case studies were also excluded.

Quality assessment

A quality assessment tool (Appendix 2) was developed based on component factors recommended by the Effective Public Health Practice Project [EPHPP] quality assessment tool for quantitative studies (Thomas *et al.*, 2004). Adaptations and additional components were included in relation to methodological considerations in ID research (Smiley, 2005). Given the variation in assessment measures and methodologies employed, the use of meta-analysis was not considered appropriate in the current review.

Studies were awarded a score (either 0-2 or 0-1) for each methodological component. Studies scoring in the upper third of total scores (20 – 28) were designated *strong* quality, between 11 – 19 were considered *moderate* quality and those scoring ≤10 were considered *weak* quality. Independent quality assessment by two reviewers was not possible due to time and resource restrictions. If the author was unsure regarding inclusion of a study or quality ratings, a second opinion was obtained as recommended (Petticrew & Roberts, 2006).

Figure 1. Flow chart of study selection process (adapted from Moher et al., 2009)



Results

The initial search yielded 198 articles after removing duplicates. Figure 1 presents the process of study selection. All titles/abstracts were screened and 166 papers were subsequently excluded based on non-relevance. 31 articles were reviewed in full and 28 potentially relevant articles were further identified through screening reference lists. Of these, 16 studies satisfied inclusion criteria. Two papers reported on the same experimental data (Richdale, 2003; Richdale *et al.*, 2000) and were therefore treated as one study, as per recommendations of Moher *et al.* (2009). 15 studies (16 published papers) were thus included in the current review.

Study characteristics

Table 2 presents the characteristics, methodology and relevant results (specifically in relation to sleep and behavioural outcomes) of all studies included in the review. Studies are numbered according to publication date. Of the studies reviewed, the majority explored behavioural difficulties across a range of domains; however one study (6) focused only on self-injurious behaviour [SIB] and one specifically measured ADHD symptomatology as an indication of behavioural difficulties (1). The latter study was included in the review as the ADHD measure utilised (ADHD-SC4; Gadow & Sprafkin, 1997) has been shown to correlate with other behavioural assessments (Sprafkin *et al.*, 2001). Eight studies (1, 4, 6, 7, 9b, 10, 11 and 12) investigated sleep and behaviour within specific neurodevelopmental genetic conditions, whereas the remaining studies utilised mixed samples of IDD conditions. All studies had medium – large sample sizes. A cross-sectional design, with postal parent-report questionnaires, was used in the majority of studies. Six studies had a control comparison group, matched on various different demographics. Of these, five studies used a TD control group (1, 3, 5, 9a and 10). Where the sample of interest was a specific neurodevelopmental genetic condition, one study (6) employed a mixed IDD group as the control comparison. The remaining studies explored experimental groups with no comparison.

A variety of questionnaire measures were employed to assess sleep and behavioural difficulties. Eight studies used standardised, validated questionnaire measures (2, 6, 7, 8, 11, 12, 13 and 14), four used idiosyncratic measures (4, 9a/b, 10 and 15) and one study utilised diary reports (3). Two studies (1 and 5) employed objective assessment of sleep (polysomnography [PSG] or actigraphy), alongside questionnaire measures. Four studies (9a, 12, 14 and 15) additionally investigated the relationship between parent stress/family functioning, sleep and behaviour as a secondary factor and one study also explored child anxiety levels (2). Geographically, six studies were conducted in the UK (2, 7, 12, 13, 14 and 15), four in the USA (1, 4, 5 and 11), three in Australia (3, 9a/b and 10), one in the Netherlands (8) and one across the UK and USA (6).

Table 2. Overview of methodology and findings

Author, year & country	Aims	Sample; age range	Design	Comparison group (matched)	Diagnosis confirmation	Assessment methods – sleep; behaviour	Analysis	Relevant findings	Quality rating (score)
1. Mason <i>et al.</i>, 2011 USA	Sleep and ADHD features in WS	WS: $n=35$; NR (mean=9.3 yrs), TD: $n=35$; NR (mean=9.5 yrs)	Btw. group comparison, PSG, obs. and questionnaire (parents)	TD control group (matched for age, gender & ethnicity)	Genetically confirmed	Overnight PSG & sleep questionnaire (NR); ADHD-SC4	Group comparison (t -test, McNemar's test)	Sig. difference in sleep problems and ADHD features (WS>TD). No sig. difference in sleep among WS subjects based on ADHD vs. no-ADHD features (based on PSG data and parent report).	<i>Moderate</i> (18)
2. Rzepecka <i>et al.</i>, 2011 UK	Sleep, anxiety and CB in ID/ASD	ID: $n=31$, ASD-ID: $n=55$, ASD-no ID: $n=81$; 5-18 yrs	Cross-sectional, postal questionnaire (parents)	None	Recruited from specialist provision, previous ADOS/ID assessment	CSHQ ($r_{t-r}=.62-.79$; $\alpha=.76$); ABC-C ($\alpha=.80$)	Pearson correlations, Multiple regression	Sig. positive correlation btw. sleep and CB ($p<.001$, $e.s.=.61$) across sample. Sleep strongest predictor of CB, explained 31.4% of variance ($p<.001$, $e.s.=.39$).	<i>Moderate</i> (19)
3. Cotton & Richdale, 2010 Australia	Sleep and CB across variety of conditions	ASD: $n=34$, DS: $n=12$, PWS: $n=12$, ID: $n=24$, TD: $n=33$; 3 – 16 yrs	Btw. group comparison, cross-sectional (2 week) diary report (parents)	TD control group (matched for age)	Recruited from specialist provision and/or condition specific support group	Idiosyncratic sleep diary; beh. diary – visual analogue scales (NR)	Group comparison (Kruskal-Wallis ANOVA), Spearman correlations	Difficult daytime beh. associated with bedtime resistance across all groups inc. control ($p<.001$). Poor sleep quality was associated with difficult daytime beh. (ASD/TD; $p<.001$), restlessness (all groups; $p<.01$) and over-activity (ASD/PWS; $p<.01$).	<i>Moderate</i> (14)
4. Kronk <i>et al.</i>, 2010 USA	Sleep correlates in Fragile X	Fragile X: $n=1295$; NR (mean=15.5 yrs)	Cross-sectional, on-line/ telephone questionnaire (parents)	None	Identified through Fragile X foundation, previous genetic test	Idiosyncratic sleep questionnaire (NR); Health, beh. and QoL questionnaire – Likert scales (NR)	Group comparison (χ^2), Logistic regression (Controlled for age)	Younger children had more sleep problems. After controlling for age, presence of sleep problem associated with difficult beh. for males & females across domains: listening/compliance ($p<.02$), social interaction ($p=.003$), ability to adapt ($p<.05$), mood ($p<.01$).	<i>Strong</i> (20)
5. Goodlin-Jones <i>et al.</i>, 2009 USA	Relationship between sleep, daytime sleepiness and beh. function in ASD/DD	DD: $n=57$, ASD: $n=68$, TD: $n=69$; 2 – 6 yrs	Cross sectional, actigraphy and questionnaire (parents)	TD controls (matched for gender, socio-demographics)	Diagnostic assessment (ADOS, VABS, MSEL)	Actigraphy & CSHQ ($r_{t-r}=.62-.79$); CBCL ($\alpha=.96$)	Linear regression (Controlled for diagnostic group)	Actigraphy data not associated with difficult daytime beh. Sleep problems (parent report) sig. associated with internalising and externalising beh. across all groups ($p=.0001$). Difference reported in level of beh. difficulties	<i>Moderate</i> (19)

Author, year & country	Aims	Sample; age range	Design	Comparison group (matched)	Diagnosis confirmation	Assessment methods – sleep; behaviour	Analysis	Relevant findings	Quality rating (score)
								(DD/ASD>TD), but p value = NR.	
6. Hall et al., 2008 USA/UK	Health, sleep and SIB in CdLS	CdLS: $n=54$, ID: $n=46$; NR (mean=13.8 yrs)	Btw. group comparison, cross-sectional postal questionnaire (parents/carers)	Mixed aetiology ID control group (matched for age, gender, level of ID and mobility)	Identified through CdLS support groups and/or specialist provision	Infant sleep questionnaire ($r_{t-r}=.92$); CBI ($r_{t-r}=.76-.86$) (SIB scale only)	Group comparison (t -test), Pearson correlations	No sig. difference in sleep for SIB display vs. no SIB display in either CdLS ($p=.60$) or ID group ($p=.37$). No association btw. severity of SIB and sleep problems in either group ($p=.87$ and $p=.44$, respectively).	Moderate (17)
7. Johnson et al., 2005 UK	Sleep and beh. patterns in NF1	NF1: $n=64$ (43% ID); 3 – 18 yrs	Cross-sectional, postal questionnaire (parents)	Compared against normative data (not matched)	Regional genetics centre database and medical records	Simonds & Parraga sleep questionnaire ($r_{t-r}=.83-1.0$); SDQ ($r_{t-r}=.62$; $\alpha=.73$)	Group comparison (Mann-Whitney U) (No comparison of NF1-ID vs. NF1-no ID)	Children with frequent sleep disturbance (vs. no sleep disturbance) had sig. increased total beh. problems ($p=.002$) and sig. higher scores on conduct ($p=.041$), inattention/hyperactivity ($p=.002$) and emotionality ($p=.002$) subscales. No sig. group difference for peer relationships or pro-social beh.	Moderate (16)
8. Didden et al., 2002 Netherlands	Sleep and CB in IDD	ID (all levels): $n=286$; 1 – 19 yrs	Cross-sectional, postal questionnaire (parents) and teacher report	None	Recruited from specialist provision	Simonds & Parraga sleep questionnaire – adapted ($r_{t-r}=.83-1.0$); ABC ($r_{t-r}=.55-.69$; $\alpha=.85-.94$)	Group comparison (Mann-Whitney U), Stepwise logistic regression	Sig. higher CB scores for children with severe sleep problems vs. no sleep problem: hyperactivity, irritability, non-compliance, temper tantrums ($p<.001$); aggression, screaming ($p<.01$); impulsivity ($p<.05$). No difference for SIB ($p=.27$). Irritability ($p<.01$) sig. correlated with sleep problems in regression model, alongside ID level ($p<.05$).	Moderate (17)
9a. Richdale et al., 2000; 9b. Richdale, 2003 Australia	Parental stress, sleep and beh. in IDD; Sleep in Fragile X	ID (all levels): $n=52$ (inc. ASD $n=7$); 2 – 19 yrs TD: $n=25$; 2 – 17 yrs Fragile X: $n=13$; 3 – 19 yrs	Btw. group comparison, cross-sectional questionnaire (parents)	TD control group (matched for age)	Recruited from specialist provision, parents reported diagnosis where possible (e.g. DS, ASD, Fragile X)	Idiosyncratic sleep questionnaire – visual analogue scales (NR), ESS ($\alpha=.84$), apnoea and narcolepsy scales (NR); DBC ($r_{t-r}=.83$; $\alpha=.67-.91$)	Group comparison (t -test, ANOVA, Mann-Whitney U), Correlations	Children with ID had sig. more sleep problems and CB compared to controls ($p<.001$). Across both ID and controls, children with sleep problems had increased CB, but difference only reached sig. in ID group ($p=.016$). Presence of sleep problem was sig. associated	Moderate (14)

Author, year & country	Aims	Sample; age range	Design	Comparison group (matched)	Diagnosis confirmation	Assessment methods – sleep; behaviour	Analysis	Relevant findings	Quality rating (score)
10. Richdale et al., 1999 Australia	Sleep and beh. in PWS	PWS: $n=16$, TD: $n=16$; 4 -16 yrs (Subset of larger cohort of PWS inc. adults)	Btw. group comparison, cross-sectional postal questionnaire (parents)	TD control group (matched for age and gender)	Identified through PWS support group, genetic status not known	Idiosyncratic sleep questionnaire – visual analogue scales (NR) & ESS ($\alpha=.84$); DBC ($r_{t-r}=.83$; $\alpha=.67-.91$)	Group comparison (ANOVA), Correlations	with total CB, disruptive and self-absorbed subscales ($p<.05$) in ID group, but only anxiety subscale ($p<.05$) in controls. For Fragile X cohort, children with sleep problem (vs. no sleep problem) had sig. increased beh. difficulties ($p=.024$). Children with PWS had sig. more sleep problems ($p<.01$) and CB ($p<.001$) compared to controls. Sleep problems (daytime sleepiness, narcolepsy, snoring) correlated with beh. problems in PWS group ($p<.001$, $p<.05$, and $p<.05$, respectively). Fewer sig. correlations btw. sleep and beh. in TD group.	Moderate (15)
11. Bouras et al., 1998 USA	Correlates of maladaptive beh. in SMS	SMS: $n=35$, 4 – 20 yrs (Subset of larger cohort inc. PWS and ID groups)	Cross-sectional, questionnaire (parents)	None	Previous genetic test (parent report), completed VABS	Sleep History Questionnaire (NR); CBCL ($\alpha=.96$), Self-injury checklist ($IRR=.91$), Stereotypy checklist (NR)	Correlations, Stepwise regression	Sleep problems positively correlated with total CB ($p<.001$) and specific domains: aggression ($p<.001$); attention, delinquent beh., mood, social problems ($p<.01$). Sleep problems strongest predictor of CB (37% of variance; $p<.001$). Age and level of delay also associated with difficult beh.	Moderate (13)
12. Stores et al., 1998 UK	Psychological associations of sleep disturbance in DS	DS (moderate – severe LD): $n=91$; 4 – 19 yrs	Cross-sectional, postal questionnaire (parents)	None	Identified through SEN & mainstream schools	Simonds & Parraga sleep questionnaire – adapted ($r_{t-r}=.83-1.0$); ABC ($r_{t-r}=.55-.69$; $\alpha=.94$)	Group comparison (Kruskal-Wallis ANOVA, Mann-Whitney U)	Children with sleep problems showed sig. greater CB across domains: overall beh. ($p<.01$), irritability ($p<.01$) and hyperactivity ($p<.001$).	Moderate (13)

Author, year & country	Aims	Sample; age range	Design	Comparison group (matched)	Diagnosis confirmation	Assessment methods – sleep; behaviour	Analysis	Relevant findings	Quality rating (score)
13. Wiggs & Stores, 1996 UK	Sleep and CB in LD	Severe LD: $n=209$ (inc. ASD $n=25$); 5 – 16 yrs	Cross-sectional, postal questionnaire (parents)	None	Identified through SEN schools, parents reported diagnosis where possible (e.g. DS, ASD)	Simonds & Parraga sleep questionnaire – adapted ($r_{t-r}=.83-1.0$), plus open-ended questions on settling and waking; ABC ($r_{t-r}=.55-.69$; $\alpha=.94$)	Group comparison (t-test)	Children with sleep problems showed sig. more types of CB ($p<.001$) and increased severity of beh.: aggression, screaming, temper tantrums, non-compliance, hyperactivity ($p<.001$); SIB, impulsivity, irritability ($p<.01$). Younger children more likely to have sleep problems.	<i>Moderate</i> (17)
14. Quine, 1991 UK	Sleep disturbance in LD	Severe LD: $n=166$, 0 – 18 yrs	Cross-sectional, questionnaire and interview (parents, teachers)	None	Not clearly specified in text	Sleep index (based on settling & waking problems from the BSQ) ($\alpha=.78$); BSQ ($\alpha=.72$), DAS ($r_{t-r}=.87-.96$)	Group comparison (χ^2 , ANOVA), Multiple regression	Sleep problems sig. correlated with number of CB domains. Children with sleep problems were sig more likely to have daytime CB ($p<.001$). Beh. difficulties directly accounted for 32% of variance in sleep problems ($p<.001$).	<i>Weak</i> (10)
15. Clements et al., 1986 UK	Prevalence of sleep problems and correlates in LD	Severe LD: $n=155$; 0 – 16 yrs	Cross-sectional, questionnaire and interview (parents)	None	Recruited from specialist provision and presented with beh. disturbance for inclusion	HBS schedule (NR); Idiosyncratic schedule of beh./QoL factors (NR)	Group comparison (χ^2 , log linear analysis)	Sleep problems sig. associated with some CB domains: SIB, 'non-socially directed difficult beh.' (e.g. tantrums, destructiveness) ($p<.01$); ability to adapt routines ($p<.05$). No sig. association with social aggression ($p>.05$).	<i>Weak</i> (8)

Key – Abbreviations: ID=intellectual disability, DD=developmental disability, LD=learning disability, TD=typically developing, ASD=autistic spectrum disorders, DS=Down syndrome, CdLS=Cornelia de Lange syndrome, NF1=neurofibromatosis 1, WS=Williams syndrome, PWS=Prader-Willi syndrome, SMS=Smith-Magenis syndrome, CB=challenging behaviour, SIB=self-injurious behaviour, beh.=behaviour, QoL= Quality of Life, SEN=Special Educational Needs, NR=not reported in paper, inc.=including, obs.=observations, btw.=between, sig.=significant(ly)
 r_{t-r} =test-retest validity, α =Cronbach's alpha (internal consistency), IRR=inter-rater reliability, e.s.=effect size

Assessments: CBCL=Child Behaviour Checklist, ABC=Aberrant Behaviour Checklist, ABC-C=Aberrant Behaviour Checklist – Community, SDQ=Strengths & Difficulties Questionnaire, BSQ=Behaviour Screening Questionnaire, DAS=Disability Assessment Schedule, CBI=Challenging Behaviour Interview, PSG=polysomnography, CSHQ=Child Sleep Habits Questionnaire, ADOS=Autism Diagnostic Observational Schedule, VABS=Vineland Adaptive Behaviour Scales, ESS=Epworth Sleepiness Scale, DBC=Developmental Behaviour Checklist, HBS=Handicaps, Behaviour and Skills Schedule, MSEL=Mullen Scales of Early Learning

Strong quality = 20 – 28; Moderate quality = 11 – 19; Weak quality = ≤ 10

Data synthesis

Mixed IDD samples

There were eight studies that examined the relationship between sleep and behaviour in samples of mixed IDD conditions and most employed parental-report questionnaire methodology. Six studies were rated as *moderate* quality (scoring between 14 – 19) and two received *weak* ratings. No studies with a mixed IDD sample received a *strong* rating.

Moderate quality

Of the *moderate* quality studies, three employed a matched TD control group (3, 5 and 9a). These three studies highlighted associations between sleep disturbance and challenging behaviour across both IDD and control groups, although for the control group this relationship only reached significance in two of the studies (3 and 5). Sleep problems were associated with the overall presence of challenging behaviour, as well as specific types of behavioural difficulty. One study (3) noted that difficult daytime behaviour was associated with sleep disturbance in relation to both bedtime resistance and actual sleep quality, potentially highlighting a relationship with both behaviourally and physiologically-based sleep problems. This study was limited by a lack of standardised assessment measures and potentially limited power for some of the analyses. When objective assessment of sleep (actigraphy) was employed in children with ASD or DD, compared to TD controls (5), it was found that actigraphic sleep data had no associations with difficult daytime behaviour in any group. However, parental report of sleep disturbance was significantly associated with problematic behaviour across all groups. This highlights the potential impact that parental perception of difficulties may have on the reports of this relationship. Diagnostic group was controlled for in the analyses of this study and authors reported that children in the DD and ASD groups presented with a significantly higher level of behavioural difficulties, compared to TD controls. There was, however, no statistical information reported in relation to this comparison and any potential difference in the actual relationship between sleep and behaviour across different diagnostic groups was not investigated.

Three further *moderate* quality studies explored mixed IDD samples with no comparison group (2, 8 and 13). In accordance with findings from the aforementioned studies, each of these also reported a significant relationship between sleep disruption and challenging behaviour. Two studies (8 and 13) compared groups of children based on the presence of sleep disturbance and found significantly increased behavioural difficulties in those with sleep problems. Children with sleep disturbance showed more types of challenging behaviour and increased severity of behaviour. One study (8) highlighted this relationship when parental report of sleep disturbance was compared to independent teacher report of behavioural difficulties. There was inconsistency within these studies regarding the specific relationship between sleep and SIB. One study (13) indicated that children with sleep disturbance showed increased SIB, but the other study (8) reported no association. This latter study (8) also found in a subsequent regression analysis that only the behavioural subscale, 'irritability', remained associated with the presence of sleep problems, alongside level of ID. The further *moderate* quality study (2) utilised regression analysis in a large sample of children with ID and/or ASD and found that sleep disturbance was the strongest predictor of overall challenging behaviour, with medication use being the second strongest predictor. The study was limited by a lack of consideration of the nature of these relationships between diagnostic groups (i.e. ID, ASD with ID and ASD without ID).

Weak quality

The two studies using mixed IDD samples that were rated as *weak* in quality (14 and 15) also reported significant associations between sleep difficulties and challenging behaviour in large samples of children presenting with severe ID. Using regression analysis, one study (14) highlighted that behaviour difficulties were directly associated with sleep disturbance, but that the child's level of delay and communication skills also influenced both difficulties. The second study (15) conversely reported no relationship between sleep disruption and the child's functional ability. These studies were both limited by a lack of control group, use of non-standardised assessment tools and lack of clarity regarding statistical analyses.

Specific condition samples

Of the eight studies that examined sleep and behaviour in specific neurodevelopmental genetic conditions, one study (4) received a *strong* quality rating, with the other studies rated as *moderate* quality (scores ranging from 13 – 18).

Strong quality

The methodologically *strong* study reported, in a large sample of children with Fragile X, that sleep disturbance was positively associated with problematic behavioural characteristics, including poor compliance, social interactions, ability to adapt and mood. Sleep disruption was not a primary characteristic of Fragile X, but it was found to be more likely in children who presented with behavioural difficulties. There was also a significant association between sleep and child health, with poorer health and more comorbid conditions (e.g. seizures, diagnosis of ASD) increasing likelihood of sleep problems. The study was limited by the lack of a control group or a standardised sleep assessment measure.

Moderate quality

Five *moderate* quality studies employing cross-sectional, questionnaire methodology reported on sleep and behaviour in NF1 (7), Fragile X (9b), PWS (10) SMS (11) and DS (12). Across conditions, a consistent finding was that sleep disturbance was significantly associated with increased daytime behavioural difficulties. This relationship was consistent whether studies utilised group comparison (i.e. children with sleep problems versus no sleep problems) (7, 9 and 12) or correlational analysis (10 and 11). Behavioural difficulties that related to sleep across all conditions included hyperactivity, mood/emotionality, aggression and disruptive behaviour, alongside the total behavioural difficulty score on the various subscales utilised. Regression analysis was conducted in one study (11) and sleep problems were the strongest predictor of challenging behaviour in children with SMS, with level of delay emerging as the second strongest predictor. The authors tentatively suggested the existence of a causal role for sleep disturbance in the manifestation of behavioural difficulties, given that increased daytime nap length was associated with reduced challenging behaviour. However, this interpretation may be over simplistic, failing to take into account the potential impact of additional variables, such as an increase in time spent asleep during the day inherently reducing the amount of time for displaying challenging behaviour, rather than the expression of behaviour per se. The study was limited by a relatively small sample size for the use of regression analysis. One study employed a TD control group (10) and concluded that both sleep and behavioural difficulties were more prevalent in children with PWS than TD controls. Additionally, sleep problems were correlated with more types of challenging behaviour in the PWS group, whereas there were fewer significant correlations between sleep and behaviour in the TD group. In the PWS sample, sleep disturbance was primarily related to excessive daytime sleepiness, whilst in the other studies the notion of sleep problems tended to represent difficulties with

sleep at night. One study (12) with a large sample of children with DS noted that the presence of any sleep problem was related to increased challenging behaviour, but children with specific sleep maintenance difficulties (i.e. night waking) consistently had the highest rates of behavioural problems. A further study (7), investigating children and adolescents with NF1, found that although challenging behaviour was related to sleep disturbance, there was no difference in the expression of pro-social behaviour between groups with or without sleep problems. This is suggestive of the complexity behind the relationship between sleep and manifestations of daytime behaviour. The study was limited, however, by no subsequent comparison of these relationships in individuals with NF1 presenting with or without ID. Sample size may have limited the power necessary for these analyses.

Two further *moderate* studies investigated sleep and behaviour in specific neurodevelopmental genetic conditions and conversely reported no significant associations between sleep and the manifestation of behavioural difficulties. One study (1) utilised overnight PSG in a medium sample of children with WS, compared to matched TD controls. Although children with WS had increased sleep disturbance and ADHD features compared to controls, there was no association between sleep disturbance and presence of ADHD features within the WS group. This was a consistent finding based on both PSG and parent report data. Sleep was also investigated in a medium sample of individuals with CdLS, compared to a matched ID control group (6). Although a comprehensive behaviour assessment was completed, the study focused specifically on the presence and severity of SIB. There were no significant associations between sleep and SIB in either the CdLS or control ID group; however the presence of health problems was associated with SIB severity in the CdLS group. Limitations of the study included a mixed sample of children and adults with CdLS, with no consideration of age in analyses. Taken at face value, the findings from these two studies are inconsistent with other results reporting an association between sleep disturbance and behavioural difficulties in IDD conditions. This may be partially explained by the focus on the measurement of specific behavioural manifestations (i.e. ADHD symptomatology and SIB) in these two studies, rather than assessment of challenging behaviour overall.

Additional findings

Four studies of *moderate – weak* quality (9a, 12, 14 and 15, respectively) included a measure of parenting stress or family functioning. All studies reported that sleep problems were significantly associated with increased parental stress and/or poorer family functioning. Regression analysis was utilised in one *weak* quality study (14), which suggested that parental and family impact variables had a direct impact on variance in sleep problems and also mediated the relationship between behavioural difficulties and sleep. However, the study did not use a control group or a standardised measure of sleep, and both the recruitment process and confirmation of diagnosis were relatively unclear. Therefore, the results should be considered with caution. One study employed a control group (9a). This highlighted that both sleep and behavioural problems were related to increased parental stress across IDD and TD control groups, but found that sleep problems in particular were more likely to be a source of increased parental stress in the IDD group. Two studies (12 and 15) reported specifically that sleep maintenance difficulties had a greater impact on parental stress and family functioning than other types of sleep problem.

Child anxiety was examined as an additional factor in one study rated towards the higher end of *moderate* quality (2). Based on parent-report questionnaire data in a large ID/ASD sample, it was found that anxiety levels were independently associated with both sleep disturbance and challenging behaviour. Hierarchical regression analysis demonstrated that anxiety explained some of the variance in challenging behaviour,

although sleep problems remained the strongest predictor. There was no exploration of any potential differences in the nature of these relationships between different diagnostic groups.

Discussion

The primary aim of this review was to identify extant literature on sleep disturbance and daytime behaviour in children with various IDD conditions. Only one study was rated as methodologically *strong*, thirteen studies received *moderate* ratings and two studies were rated as *weak*. Overall, studies demonstrated evidence of a relationship between sleep problems and difficult behaviour in IDD conditions, both when specific neurodevelopmental genetic conditions and mixed IDD samples were investigated. Across the reviewed studies, sleep disruption was related to overall behavioural difficulties, as well as specific behaviour manifestations (such as hyperactivity, aggression, non-compliance and disruptive behaviour) and factors related to mood (e.g. emotionality, irritability). Evidence was based on both between group comparisons (i.e. sleep problems versus no sleep problems) and correlation or regression analyses. Two studies indicated that sleep disturbance was predictive of challenging behaviour. There was tentative evidence that the type of sleep disturbance may have an impact on the nature of this association and the severity of behavioural difficulties, given that specific sleep maintenance problems had a more negative effect in two studies. However, the nature of an association between sleep and behaviour remains largely un-established and, as a whole, studies were simply indicative of a bidirectional relationship between the two factors (Owens & Palermo, 2008).

The findings of reviewed studies are generally consistent with previous research into the correlates of sleep disturbance in adults with IDD (de Winter *et al.*, 2011), individuals with ASD (Hollway & Aman, 2011; Sikora *et al.*, 2012) and also within the TD child and adolescent population (Astill *et al.*, 2012; Bates *et al.*, 2002; Hall *et al.*, 2012; Sadeh *et al.*, 2002). Across studies there was evidence of an association between behavioural problems and insufficient or disturbed sleep. Further support for this relationship comes from: i) single-case experimental studies, in which sleep deprivation was found to exacerbate problematic behaviour (DeLeon *et al.*, 2004; O'Reilly & Lancioni, 2000), and ii) research involving behavioural or pharmacological interventions for sleep problems that have reported concurrent improvements in daytime behaviour (Braam *et al.*, 2010; Carr *et al.*, 2007; Dahl *et al.*, 1991; Minde *et al.*, 1994). However, there are inconsistencies in this area, with some studies reporting no change in daytime behaviour as a consequence of behavioural interventions for sleep (Thackeray & Richdale, 2002; Wiggs & Stores, 1999). This suggests complexities in the association between sleep and behavioural problems which require further investigation. If potentially the same underlying relationship between sleep and behaviour exists in both IDD and TD populations, then it is important to consider the factors which could explain why the prevalence of sleep and behavioural difficulties is increased in IDD populations (Didden & Sigafos, 2001; Doran *et al.*, 2006; Krakowiak *et al.*, 2008; Quine, 2001). Communication difficulties, sensory differences, circadian rhythm dysfunction, comorbid health problems or parental stress may conceivably be initial factors to investigate.

In relation to the expression of SIB as a specific form of challenging behaviour, the findings of the present review are inconsistent. Two *moderate* studies reported no significant associations between SIB and sleep disturbance, whereas one *moderate* study found that children with sleep problems were significantly more likely to present with SIB. Previous studies have indicated that adults with IDD and sleep disturbance are more likely to show SIB than individuals without sleep problems (Brylewski & Wiggs, 1999; Symons *et al.*, 2000). This inconsistency is therefore difficult to synthesise with the findings of other reviewed studies, but

it is feasible that these differences relate to the multi-factorial aetiology and function of SIB, including a significant neurological component (Clarke, 1998). Furthermore, there is evidence that the expression of SIB increases with age (Davies & Oliver, 2013) and therefore this discrepancy may relate to the age group of study samples. Several reviewed studies also reported an association between sleep problems and parental stress/family functioning, with the presence of sleep disturbance being associated with poorer outcomes. Given the established independent impact of both sleep and behavioural difficulties on parental and family functioning (Chu & Richdale, 2009; Hastings, 2002; Holden & Gitlesen, 2006; Meltzer, 2008), parental wellbeing and coping seems to be an important variable to consider in further investigations of the nature of the relationship between sleep and challenging behaviour.

Methodological considerations

All of the studies reviewed were cross-sectional in design, which limited the ability to draw any conclusions about the causative relationship between sleep and challenging behaviour. Sleep problems may be both a cause and effect of difficult daytime behaviour, or both difficulties may be related to third underlying factor. All of these are clinically viable explanations and longitudinal or experimental studies are required to explain the relationship further. There were differences in the methodologies used to confirm diagnoses. In some studies which investigated specific genetic conditions, researchers had clear diagnostic evidence; whereas most studies relied on recruitment through specialist provision or support groups. Only two of the reviewed studies conducted independent assessments of ID level. It is possible that samples were more likely to consist of children with identified sleep and/or behaviour problems as the studies may have been of increased interest to these families. However, most studies appeared to attempt to draw representative samples through their recruitment methodologies and only one *weak* quality study specified behavioural disturbance as part of the inclusion criteria.

Most studies relied on subjective parental report of sleep and behavioural difficulties, which may have been open to reporter bias or influenced by factors relating to parental wellbeing. Nonetheless, it is important to note that parental reports of sleep have been shown to correlate strongly with objective measurement, such as PSG or actigraphy (Holley *et al.*, 2010). Additionally, one study provided evidence of an association by comparing parental reports of sleep to independent teacher assessment of behaviour. There was little consistency in the assessment measures used for sleep and behaviour, which limited comparison between study outcomes to some extent. Two studies measured specific behavioural constructs (i.e. ADHD features and SIB) and this may have accounted for the discrepancy in findings within these studies. Samples often included a broad age range, including both children and adolescents with IDD. Age was not always controlled for in analyses and several studies reported that age itself was directly related to both prevalence of sleep problems and behavioural difficulties. 'Sleep disturbance' can incorporate a range of different problems (e.g. bedtime resistance, increased sleep latency, night waking, parasomnias, and sleep-wake cycle disruption). Only some reviewed studies specifically considered the link between challenging daytime behaviour and the type of sleep disturbance shown by children in their analysis. Further examination of the type of sleep disturbance would aid understanding of the relationship between sleep and behavioural difficulties and may also explain any apparent inconsistencies in the literature.

Physical factors (e.g. health conditions, pain, respiratory problems) have been shown to relate to sleep and behaviour in both IDD and TD populations (Bandla & Splaingard, 2004; de Winter *et al.*, 2011; Hysing *et al.*, 2007; Palermo & Kiska, 2005; Tietze *et al.*, 2012). Only a few studies measured comorbidity or accounted for this in analyses, suggesting that this may have acted as a confounding variable in some analyses. The studies which investigated mixed samples of IDD conditions generally lacked the statistical power required to

undertake comparisons between different diagnostic groups. Although this was problematic in some respects, the fact that sleep problems have been independently noted in many of the specific conditions included in the samples highlighted the importance of conducting pragmatic, clinically relevant research in order to elucidate the relationship between sleep and behaviour and provide appropriate support for families.

Clinical implications

Increasing understanding of the relationship between sleep problems and difficult behaviour has significant implications for children with IDD and their families. Clinicians need to be aware of this association and ensure that both factors are considered in assessment when families present to services in relation to only one difficulty (i.e. sleep or behavioural problems). Anecdotal evidence suggests that families are more likely to present with difficulties in relation to challenging behaviour, thus sleep problems are likely to be the additional consideration. Failure to undertake a comprehensive assessment could result in potential factors for intervention being overlooked. Additionally, based on knowledge of this relationship, sleep disruption may be considered as a potential risk factor for behavioural difficulties (or vice versa) allowing targeted early intervention to be implemented for any anticipated difficulties. There is evidence to suggest that professionals working with children and families would benefit from further education in sleep (Stores & Crawford, 1998; Stores & Wiggs, 1998), which would enable high quality assessment and intervention.

The prevalence of sleep disturbance in children with IDD indicates a largely unmet need for effective interventions. Further understanding of the complexity of the relationship between sleep and behaviour problems could allow for appropriate, systemic interventions to be developed and evaluated. Behavioural interventions for sleep disturbance in children with IDD have been shown to be effective (Jan *et al.*, 2008; Montgomery *et al.*, 2004) and use of these behaviourally-based strategies by parents may have additional longitudinal benefits if extrapolated for the management of any daytime behaviour difficulties. Furthermore, it may arguably be useful for established parenting interventions in IDD to place additional emphasis on sleep disturbance. Developing effective interventions for both sleep and behavioural difficulties is likely to have a positive impact on parental wellbeing and family functioning and improve the quality of life for the individual child.

Future research

There is a need for longitudinal research in IDD populations to enable potential conclusions to be drawn about any causal relationships between sleep disturbance and behavioural difficulties in children. Multi-centre studies may be required to obtain sample sizes which allow for comparison of different IDD conditions or age groups. Examination of the link between challenging behaviour and specific types of sleep disturbance is also important. Future studies should attempt to account for the impact of comorbid physical health problems (e.g. pain, epilepsy, respiratory problems), level of ID and medication use, and should utilise TD control groups to allow for comparisons regarding the nature of the relationship between sleep and behaviour. Psychosocial factors, in particular the potential mediating effect of parental stress and wellbeing, should also be measured.

The use of objective measurement of sleep (PSG or actigraphy) would rule out the potential impact of bias from parental reports and would also allow for a more comprehensive assessment of the relationship between behavioural problems and differing types of sleep disturbance. Alternatively, given that these methods are expensive, studies could compare parental report of sleep disturbance to independent professional or carer reports of daytime behaviour in order to mitigate any tendencies to report both sleep

and behaviour difficulties. Research into the effectiveness of either behavioural or pharmacological interventions for sleep disturbance in IDD should also consider daytime behaviour as a relevant outcome for children and families. Finally, on a conceptual basis, it is useful for future research to consider sleep difficulties as a distinct problem from challenging behaviour per se.

Review limitations

There was no pre-existing quality assessment tool that was considered suitable for the purposes of the present review. Consequently, a scoring system was developed based on an existing tool and factors relevant to ID research (Thomas *et al.*, 2004; Smiley, 2005). This may have introduced an element of bias into the quality assessment process and, although a second opinion was sought where needed, it was not possible to establish inter-rater reliability for the bespoke tool. It would be beneficial to further refine the descriptions and justification of the boundaries between each rating. Search terms utilised may also require some development, given the large number of included studies that were identified via hand-searching reference lists. The review was restricted to peer-reviewed, English language journals and excluded single case studies or case series, as well as “grey literature” and reviews. This was deemed necessary in order to refine the focus of the review; however potentially relevant studies may have been excluded, especially when taking into account the rarity of some neurodevelopmental genetic conditions.

Conclusion

This review has highlighted evidence of a relationship between sleep disturbance and challenging behaviour in children with IDD. Children with sleep problems were consistently more likely to present with challenging behaviour in the studies reviewed and sleep was predictive of behavioural difficulties in two studies. Further research is required to explain the nature of this relationship. Sleep disturbance and challenging behaviour are prevalent problems in the IDD population and can confer numerous disadvantages for the individual and their family. Understanding this relationship and developing effective interventions is therefore paramount for services.

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Paper Two

Actigraphic investigation of circadian rhythm and activity levels in children with mucopolysaccharidosis type III (Sanfilippo syndrome)

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(Appendix 3)

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Abstract

Background

Sleep disturbance is part of the behavioural phenotype of the rare genetic condition, mucopolysaccharidosis [MPS] type III. A growing body of evidence suggests that underlying disturbance in circadian rhythm functioning may explain sleep problems within the MPS III population.

Method

Actigraphic data were recorded in eight children with MPS III over 7-10 days and compared to age-matched typically developing controls. Parameters of circadian rhythmicity and activity levels across a 24-hour period were analysed.

Results

Statistically and clinically significant differences between the two groups were noted. Analysis indicated that children with MPS III showed significantly increased fragmentation of circadian rhythm and reduced stability with external cues (*zeitgebers*), compared to controls. Average times of activity onset and offset were indicative of a phase delayed sleep-wake cycle for some children in the MPS III group. Children with MPS III had significantly higher activity levels during the early morning hours (midnight – 6am).

Conclusion

Results are consistent with previous research into MPS III and suggest that there is an impairment in circadian rhythm functioning in children with this condition. The implications for clinical practice and management of sleep difficulties are discussed.

Introduction

Sleep and circadian rhythms in intellectual and developmental disability

There is evidence that sleep disturbance and disorder are more prevalent in the intellectual and developmental disability [IDD] population (Quine, 2001; Krakowiak *et al.*, 2008). Prevalence estimates have been reported as high as 85% (Didden & Sigafos, 2001; Jan & Freeman, 2004); although rates vary with age, level of disability and parental perceptions of sleep problems. Settling difficulties (increased sleep latency), frequent night waking, parasomnias, co-sleeping and daytime sleepiness are the most common difficulties described by parents (Cotton & Richdale, 2010; Robinson & Richdale, 2004). There is evidence that deficient or disrupted sleep can confer numerous disadvantages for the individual, including adverse effects on cognition, physical health and daytime behaviour (Jan *et al.*, 2008; Sadeh, 2007). Poor parental psychological wellbeing is also associated with sleep disturbance in children with IDD (Chu & Richdale, 2009; Doo & Wing, 2006).

A number of explanations for sleep disruption within the IDD population exist, including medical conditions, pain, sensory differences and environmental factors (Richdale & Wiggs, 2005; Tietze *et al.*, 2012). In addition to these factors, a growing body of research has identified underlying circadian rhythm disruption as a further explanation of sleep problems in IDD. Circadian rhythms are internally generated cycles that occur across a 24-hour period. They are influenced by internal biological factors and external environmental cues [*zeitgebers*] and include the sleep-wake cycle, hormone production, and body temperature. Variation in circadian rhythm functioning has been reported in children and adults with autistic spectrum disorders (Glickman, 2010; Hare *et al.*, 2006a, 2006b; Wiggs & Stores, 2004), Smith-Magenis syndrome (De Leersnyder *et al.*, 2006), Rett syndrome (Nomura, 2005) and Angelman syndrome (Takaesu *et al.*, 2012), amongst other IDD conditions. The specific circadian rhythm differences highlighted have included both phase advanced and delayed sleep syndrome, irregular sleep-wake patterns, increased fragmentation of rhythmicity and reduced stability or association with external *zeitgebers*.

Endogenous melatonin plays a role in the regulation of several bodily rhythms, including the sleep-wake cycle. Consistent with reported sleep disturbance, abnormalities in levels of melatonin or in melatonin production have been identified in autism (Melke *et al.*, 2008), Angelman syndrome (Takaesu *et al.*, 2012) and Smith-Magenis syndrome (De Leersnyder *et al.*, 2001). Specifically in Smith-Magenis syndrome, a complete inversion of the circadian rhythm of melatonin release has been described and related to the sleep disturbance and daytime behavioural difficulties seen in this condition (De Leersnyder *et al.*, 2001, 2006). Accordingly, exogenous melatonin is often used as treatment for sleep disturbance in IDD (Gringas *et al.*, 2012; Sajith & Clarke, 2007), although the potential value of behavioural sleep hygiene interventions is not dismissed (Jan *et al.*, 2008).

Sleep in MPS III

The mucopolysaccharide [MPS] disorders comprise a group of inherited metabolic diseases in which specific lysosomal enzymes are absent or deficient, causing cellular accumulation of glycosaminoglycans (GAGs). This accumulation impairs cellular function across organs (Cleary & Wraith, 1993; Muenzer, 2004). MPS III, or Sanfilippo syndrome, is characterised by a deficiency in one of four enzymes involved in the metabolism of the glycosaminoglycan heparin sulphate. There are four corresponding subtypes (MPS III A, B, C and D) based on the specific enzyme alteration (Valstar *et al.*, 2008). MPS III is the most common of the MPS disorders, with incidence estimated at 1 in 20, 000 live births (Cleary & Wraith, 1993). It is characterised by a

clinical course divided into three phases, involving progressive mental and physical deterioration (Valstar *et al.*, 2008; Cleary & Wraith, 1993). In the first stage (between 1-4 years), developmental delay becomes increasingly apparent after an initial period of normal development. The second phase usually begins from 3 to 4 years and is marked by an increasing loss of function, severe sleep disturbance and behavioural difficulties, including hyperactivity and aggression. The third period, from approximately 10 years old, sees increased motor difficulties, seizures and respiratory complications. Life span is significantly reduced, with death often reported in the second or third decade (Valstar *et al.*, 2008). Current clinical treatment for MPS III focuses on symptom management, although potential therapies which attempt to modify the progression of the disease (enzyme replacement therapy, gene therapy and hematopoietic stem cell transplantation) are under development (de Ruijter *et al.*, 2011).

Sleep disturbance is consistently reported in MPS III, with incidence rates of 87-92% (Bax & Colville, 1995; Colville *et al.*, 1996; Ruijter *et al.*, 2008; Fraser *et al.*, 2005), and is therefore described as part of the behavioural phenotype of the condition (Cross & Hare, 2013). Parental report studies have identified a broad spectrum of sleep difficulties, including difficulty initiating sleep, frequent night/early morning waking and disruptive behaviour at night (e.g. wandering, singing) (Bax & Colville, 1995; Colville *et al.*, 1996; Fraser *et al.*, 2005; Mahon *et al.*, 2013). Clinicians managing individuals with MPS III have also highlighted these as the main presenting difficulties (Fraser *et al.*, 2002). In addition, daytime sleepiness has been reported, although less commonly than other sleep difficulties (Fraser *et al.*, 2002, 2005; Mahon *et al.*, 2013). Objective measurement of sleep in MPS III has been carried out in two studies. Actigraphic analysis¹ undertaken with eight individuals with MPS III subtype A or B revealed significantly longer sleep onset latencies and increased daytime sleep in the MPS III group compared to controls (Mahon *et al.*, 2013). There were also trends towards increased night waking and reduced sleep efficiency in the MPS III group. Increased age was associated with longer sleep onset latency and diminished sleep efficiency for MPS III individuals. Parent questionnaire responses indicated significantly greater sleep disturbance across all domains in the patient group compared to controls. Mariotti *et al.* (2003) used polysomnography² [PSG] and electroencephalogram [EEG] to investigate sleep in a small sample of individuals with MPS III subtype A. In comparison to controls, there was reduced overall nocturnal sleep duration, REM sleep and slow wave sleep, alongside greater daytime sleep in the MPS III group. It was reported that older individuals with MPS III showed an irregular and fragmented sleep-wake pattern, with no identifiable circadian rhythm.

There is growing evidence that sleep disturbance in MPS III may be explained by an abnormality in the diurnal release of melatonin. Levels of melatonin production in MPS III have been shown to be significantly lower at night and higher during the day (Guerrero *et al.*, 2006). Mahon *et al.* (2013) also found no significant variation in melatonin concentration across three time points within a 24-hour period in MPS III patients. This suggests an alteration in circadian melatonin production, given that levels can be differentiated across time in typically developing children. Descriptive analysis also indicated that melatonin levels were reduced at night and higher in the morning in the MPS III group compared to controls (Mahon *et al.*, 2013). Taken together, these findings directly correspond with subjective and objective reports of the type of sleep disturbance seen in MPS III (e.g. difficulty initiating sleep at night, night waking, difficulty

¹ Actigraphy records body movement via a device worn on the wrist (an actigraph), to differentiate between sleep and wake states. It allows for measurement of sleep in naturalistic settings over several weeks and generates sleep-wake parameters, circadian rhythm parameters and levels of activity.

² Polysomnography is a comprehensive method of sleep assessment that records biophysiological changes occurring across sleep-wake states, including eye and limb movements, heart rhythm, breathing and brain waves (EEG). It allows for highly accurate measurement and differentiation of sleep architecture (Ancoli-Israel *et al.*, 2003).

waking up and daytime sleepiness), and parallel research into sleep disturbance and an inversion of the circadian rhythm of melatonin release observed in Smith-Magenis syndrome (De Leersnyder *et al.*, 2001, 2006). Although a comprehensive review is beyond the scope of this paper, it can be noted that alterations in circadian functioning have been demonstrated in murine models of MPS III. Canal *et al.* (2010) reported that MPS IIIB mice showed weaker circadian rhythm cycles, increased activity levels during rest phases and a marked late peak of activity within the light/dark cycle.

There is limited research into treatment for sleep disturbance in MPS III. Fraser *et al.* (2005) found that almost 60% of families reported some degree of success with behavioural strategies, although only 37% of their overall sample had tried behavioural intervention. Colville *et al.* (1996) described a brief behavioural intervention that resulted in clinically significant improvements for four out of five families. There is undoubtedly scope for further research into the acceptability and effectiveness of behavioural intervention for sleep in MPS III. Given the abnormalities in diurnal melatonin concentration, exogenous melatonin is often the pharmacological treatment of choice, with some level of effectiveness reported by parents in approximately 70% of individuals with MPS III (Fraser *et al.*, 2005). Finding effective treatment is critical given that sleep disturbance has a major impact on individuals with MPS III and their families. Parents report disruption in their own sleep pattern and in that of siblings (Colville *et al.*, 1996) and both parents and clinicians have described associations between sleep difficulties and increased daytime challenging behaviour (Fraser *et al.*, 2002, 2005). Sleep disturbance places extra strain on parents who are already coming to terms with their child's diagnosis and its emotional, social, and financial burdens. Previous research has indicated that parents of children with MPS III experience clinically significant levels of depression and anxiety (Grant *et al.*, 2013; Ucar *et al.*, 2010). There are, therefore, significant clinical implications for families if an increased understanding of sleep and circadian rhythmicity in MPS III results in tailored, effective interventions.

Aims and hypotheses

The present study formed part of a wider investigation into MPS III undertaken at the University of Manchester in conjunction with the Department of Genetic Medicine, St Mary's Hospital, Manchester. Previous studies have reported on behavioural phenotypes (Cross & Hare, 2013), parental coping (Grant *et al.*, 2013) and actigraphic assessment of sleep (Mahon *et al.*, 2013). This paper presents further analysis of the data collated by Mahon *et al.* (2013). The primary aim was to examine circadian rhythm functioning related to the activity/rest cycle in children with MPS III through objective actigraphic assessment. This was fundamentally an exploratory study; however based on previous research, it was hypothesised that children with MPS III would exhibit a significantly different pattern of circadian functioning, compared to typically developing [TD] controls.

Method

Participants

In accordance with Mahon *et al.* (2013), all families of a child with MPS III under the care of St Mary's Hospital, Manchester, or registered with the MPS Society UK were sent a recruitment letter. Diagnosis was verified through urine/specific enzyme analysis and the presence of sleep disturbance was not a prerequisite to participation. Exclusion criteria were: i) concurrent involvement in an enzyme replacement study; ii) previous bone marrow transplant; iii) serious disease affecting another organ; or iv) child considered near

the end of life. Ten families of children with MPS III expressed an interest in participating; however two families were subsequently withdrawn from the study due to a technical problem with actigraphic recording and one child's additional health complications. Consequently, a total of eight children with MPS III took part in the study, 5 males and 3 females, aged 2-15 years (mean = 9 years 3 months, SD = 4.86). Individual demographic information is presented in Table 1. All children had a diagnosis of MPS III subtype A or B. The two eldest children with MPS III subtype A had epilepsy. Older children were prescribed more medications, including medication for sleep (melatonin, chloral hydrate, zopiclone). Given the established effect of exogenous melatonin on circadian rhythmicity (Samel *et al.*, 1991), this treatment was discontinued two weeks prior to data collection. All other medication was unchanged throughout data collection. Previous interventions for sleep had been attempted for four children with MPS III (including melatonin, herbal medication and behavioural techniques) with limited effectiveness as reported by parents. Eight children, 4 males and 4 females, aged 3-15 years (mean = 8 years 7 months, SD = 4.85) formed an age-matched (within 1 year), TD control group. These children were not taking any medication and did not have developmental disability, neurological disorder, brain injury, sleep disorder or mental health difficulties.

Table 1. Demographic information of MPS III participants

Participant ID	Sex	Age (yrs)	MPS III subtype	Ethnicity	Current medication/intervention (effectiveness ¹)	Previous sleep intervention (effectiveness ¹)
MPS1	Male	2	B	Pakistani	None	None
MPS2	Male	4	A	White Polish	None	None
MPS3	Male	5	B	White British	None	Behavioural advice (<i>parents had already tried techniques</i>)
MPS4	Male	10	B	Pakistani	Melatonin ² (<i>good for settling</i>) Loperamide	Herbal medicine (<i>no effect after first week</i>)
MPS5	Female	10	B	Pakistani	Walking (<i>helpful</i>) Risperidone (<i>no effect</i>)	None
MPS6	Female	11	A	White British	Gonapeptyl	None
MPS7	Male	14	A	White British	Chloral hydrate, Zopiclone (<i>short term effects only</i>), Levetiracetam, Ibuprofen, Hyoscine	Melatonin (<i>short term effect only</i>) Behavioural techniques (<i>no effect</i>)
MPS8	Female	15	A	White British	Zopiclone, Clonazepam, Midazolam, Sodium Valproate, Senokot, Movicol, Omeprazole, Glycopyrrolate, Morphine, Paracetamol	Melatonin (<i>no effect</i>) Temazepam (<i>initial effect but discontinued due to distress/tearfulness</i>)

¹ Effectiveness of intervention for sleep as reported by parents.

² Melatonin treatment ceased 2 weeks prior to data collection.

Procedure

All eligible families of a child with MPS III were sent a letter providing brief details of the project and asking them to make initial contact with the researchers (Appendix 4). Interested families were given participant information sheets (Appendix 5) and a home visit was subsequently conducted to obtain consent and collect demographic data. The control group comprised of children of colleagues from the University of Manchester or local NHS Trust. Written informed consent was obtained from a parent of each child. In the control group,

participants aged 14 to 15 years gave their informed consent and assent was also obtained from those aged 6 to 13 years (Appendix 6). The research protocol was approved by a local NHS Research Ethics Committee and NHS Trust Research and Development (Appendix 7). Further details of the procedure can be found in Mahon *et al.* (2013).

Actigraphy

Either a *Cambridge Neurotechnology AW4* or *Respironics Actiwatch 2* actigraph was used to obtain data as production of the *Cambridge Neurotechnology AW4* actigraph was discontinued during the study. These are equivalent models of actigraph produced under different names allowing for comparability of data. All children wore the actigraph on their non-dominant wrist continuously for 7-10 days as recommended (Acebo *et al.*, 1999) and were asked to remove it only when washing or swimming. Data was sampled across 15 second epochs. To ensure comparability of data across subjects and to limit any seasonal impact on circadian functioning, all data was collected during a standard school week within a six-month period.

Circadian rhythm and activity parameters

Actigraph data was downloaded and analysed using Actiware version 5.5 to provide the following non-parametric indices of rhythmicity (Van Someren *et al.*, 1999) as defined by Hare and colleagues (2006a, 2006b):

- i. *L5 and M10 onset*: specify the average time of the start of the least active 5-hour period [L5] and the most active 10-hour period [M10] across a circadian cycle and provide an indication of the extent to which an individual's circadian cycle is coordinated with a normal 24-hour cycle.
- ii. *Relative amplitude*: is derived from the normalised difference between the most active 10-hour period and least active 5-hour period in an average 24-hour pattern and indicates the quantity of activity, with a range of 0-1 (higher values represent a greater divergence between most and least active phases).
- iii. *Intradaily variability*: indicates fragmentation of an individual's rhythm, through assessing the frequency and extent of transitions between rest and activity, and is derived as a ratio of the mean squares of the differences between all successive hours and the mean squares of difference within the grand mean. Derived scores range from 0-2, with higher values indicative of increased fragmentation.
- iv. *Interdaily stability*: specifies the invariability of 24-hour rhythm between days and is the 24-hour value from a chi-square periodogram, normalised for number of data points. It provides an indication of the strength of the linkage of the circadian rhythm to external *zeitgebers* that are deemed to be stable within the period of recording (e.g. daylight), with a range of 0-1 (higher values indicate greater stability). The parameter is derived by examining the regularity of the pattern of data points across each day of recording.
- v. *Periodicity*: specifies the time of the peak correlation of the 'best fit' circadian rhythm cycle.

In addition, overall levels of activity were measured across each of the four quadrants of a 24-hour period (midnight – 6am; 6am – 12pm; 12pm – 6pm and 6pm – midnight). This data allowed for assessment between groups of potential differences in activity at particular time points during the day. Total activity counts were also generated for each day and averaged across the recording period.

Statistical analysis

SPSS version 20 was utilised for further analysis of actigraphic data using non-parametric statistics (Mann-Whitney U, Spearman's Rank correlation). Two-tailed tests were adopted throughout, with a significance level of 0.05.

Results

Circadian rhythm analysis

Non-parametric circadian rhythm analysis (Van Someren *et al.*, 1999) was performed on the actigraph data obtained from all participants. Data was averaged over the recording period where appropriate, as indicated by previous research (Acebo *et al.*, 1999; Hare *et al.*, 2006a, 2006b). Table 2 presents descriptive statistics of circadian rhythm parameters for the MPS III and control groups, alongside inferential analyses. As can be seen, mean intradaily variability was significantly greater in the MPS III group compared to controls ($U = 6.5$, $z = -2.68$, $p = .007$, $r = 0.67$ [large effect]), indicating increased fragmentation of rhythm across the recording period. Additionally, mean interdaily stability was significantly lower in the MPS III group than in the control group ($U = 13.0$, $z = -1.99$, $p = .046$, $r = 0.5$ [large effect]), showing less stability of rhythm across days in relation to external *zeitgebers*. Despite a lower mean relative amplitude in the MPS III group, this was not significantly different to controls ($U = 16.0$, $z = -1.68$, $p = .093$, $r = 0.42$ [medium-large effect]). Mean periodicity (peak correlation of circadian rhythm) did not differ between groups ($U = 29.5$, $z = -0.27$, $p = .785$, $r = 0.06$), but the standard deviation for periodicity was much greater in the MPS III group, with some children showing either a slightly phase advanced or delayed circadian rhythm cycle (see Figure 1). Further analysis via calculation of z-scores indicated that half of the MPS III group demonstrated significantly different periodicity scores to controls. Two children showed significantly phase advanced circadian rhythms (23½ hours, $z = -4.54$ and 23¾ hours, $z = -3.19$), whereas two children demonstrated significantly phase delayed circadian rhythms (24½ hours, $z = 2.18$ for both children). Figure 2 presents individual MPS III group periodicity z-scores compared to controls. This variation within the MPS III group accounts for the non-significance of mean periodicity group comparisons.

Table 2. Comparison of circadian rhythm parameters for MPS III and control groups

	MPS III (n=8)		Controls (n=8)		U (2 tailed)	p
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Relative amplitude	0.85 (0.19)	0.94 (0.13)	0.95 (0.02)	0.95 (0.04)	16.0	0.93
Intradaily variability	0.88 (0.12)	0.86 (0.22)	0.71 (0.08)	0.73 (0.14)	6.5	0.007**
Interdaily stability	0.50 (0.12)	0.50 (0.20)	0.62 (0.08)	0.62 (0.14)	13.0	0.046*
Periodicity ¹	1446.25 (18.85)	1455 (35)	1448.75 (7.44)	1445 (7.50)	29.5	0.785

¹24-hour time converted to minutes

* $p < 0.05$, ** $p < 0.01$

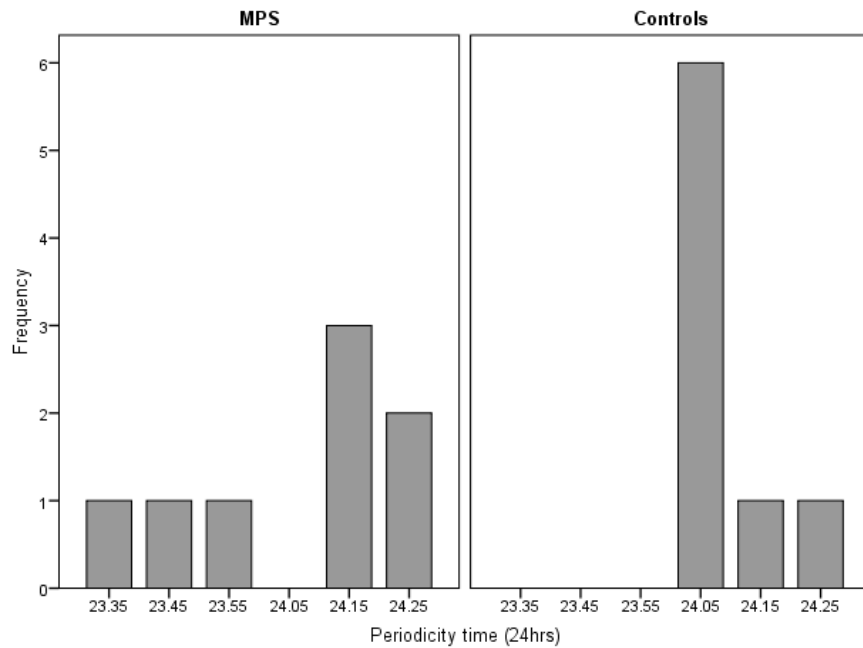


Figure 1. Periodicity (time of peak correlation) for MPS III and control group

The data for L5 onset (least active 5-hour period) and M10 onset (most active 10-hour period) indicated wide variability in both phases within the MPS III group. There was a bimodal L5 onset of 11pm and 2am in the MPS III group (range = 9pm to 3am), compared to a mode of 11pm for L5 onset in the control group (range = 10pm to 1am). The mode for M10 onset was 12pm in the MPS III group (range = 8am to 12pm) and 9am for controls (range = 8am to 12pm). Taken together, these modal figures illustrated a later onset of wakefulness and activity for children with MPS III, combined with wider variation in the onset of their least active period. For three children with MPS III, these parameters were indicative of phase delay in the sleep-wake cycle (L5 = 2am, M10 = 11am; L5 = 3am, M10 = 12pm; and L5 = 2am, M10 = 12pm).

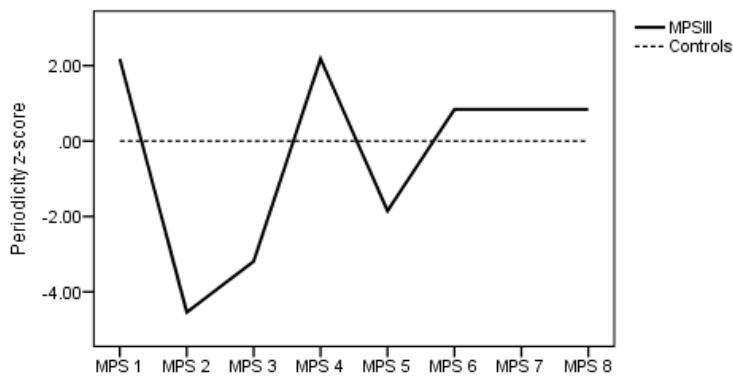


Figure 2. Periodicity z-scores for MPS III group compared to controls

Activity analysis

Activity levels were averaged over the recording period for each quadrant of a 24-hour period (midnight – 6am; 6am – 12pm; 12pm – 6pm and 6pm – midnight). Individual data for the MPS III group is presented in Table 3, with group comparisons in Table 4.

There was wide variation in activity levels amongst the children with MPS III. Five out of eight children had higher activity counts towards the end of the day in the fourth quadrant (6pm – midnight), in comparison with their level of activity during the morning (6am – 12pm). This is further suggestive of a phase delayed sleep-wake cycle. The youngest three children, and in particular those in the second phase of the disorder (aged 4 and 5 years), displayed the highest overall levels of activity. The three children with MPS III who had the lowest overall activity levels, which included the eldest two children (14 and 15 years), showed the least discrepancy in level of activity across the 24-hour period. Figure 3 depicts activity levels averaged for the MPS III group compared to controls across time. This illustrates an attenuated trajectory of activity for children with MPS III, with little observable difference in activity levels between the second (6am – 12pm) and fourth (6pm – 12pm) time quadrants.

Table 3. Activity levels in children with MPS III averaged over recording period

Time quadrant	Participant ID (age)							
	MPS1 (2)	MPS2 (4)	MPS3 (5)	MPS4 (10)	MPS5 (10)	MPS6 (11)	MPS7 (14)	MPS8 (15)
Midnight – 6am	9.33	6.59	6.47	2.72	7.87	4.25	7.08	27.14
6am – 12pm	42.18	125.32	172.36	15.10	23.12	78.29	21.01	35.89
12pm – 6pm	116.45	153.93	198.21	21.09	112.32	145.79	49.11	53.77
6pm – Midnight	128.86	61.75	62.07	23.15	102.29	52.39	24.71	54.25
Total daily activity	296.82	347.59	439.11	62.05	245.61	280.72	101.92	171.05

Group comparisons (see Table 4) indicated a significantly greater mean level of activity for children with MPS III within the first time quadrant (midnight – 6am), compared to controls ($U = 11.0$, $z = -2.21$, $p = .027$, $r = 0.55$ [large effect]). There were no statistically significant differences between groups in the mean activity scores for the third quadrant (12pm – 6pm; $U = 20.0$, $z = -1.26$, $p = .208$, $r = 0.31$ [medium effect]) or fourth quadrant (6pm – midnight; $U = 30.0$, $z = -0.21$, $p = .834$, $r = 0.05$). Although visual inspection of the data suggested that activity levels were lower in the MPS III group for the second quadrant (6am – 12pm) compared to controls, this difference did not initially reach statistical significance ($U = 18.0$, $z = -1.47$, $p = .141$, $r = 0.38$ [medium-large effect]). However, following removal of one extreme score within the MPS III group, a statistically significant difference between groups was detected ($U = 10.0$, $z = -2.08$, $p = .037$, $r = 0.52$ [large effect]). There was no significant difference between groups in mean total activity scores across the recording period ($U = 21.0$, $z = -1.16$, $p = .248$, $r = 0.29$ [small-medium effect]).

Table 4. Comparison of activity levels for MPS III and control groups

	MPS III (n=8)		Controls (n=8)		U (2 tailed)	p
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Midnight – 6am	8.93 (7.64)	6.84 (4.16)	3.79 (2.12)	4.03 (4.01)	11.0	0.027*
6am – 12pm	64.16 (57.17)	39.03 (92.02)	100.52 (23.38)	104.72 (42.86)	10.0	0.037*#
12pm – 6pm	106.33 (60.60)	114.39 (101.62)	142.99 (37.42)	158.19 (66.59)	20.0	0.208
6pm - Midnight	63.68 (36.10)	58.00 (66.61)	56.58 (19.31)	59.34 (27.99)	30.0	0.834
Total daily activity	243.12 (126.23)	263.16 (215.69)	304.51 (55.38)	311.27 (103.24)	21.0	0.248

*p<0.05

#Inferential analysis after removal of extreme score

Spearman’s rank correlational analyses were conducted for both circadian rhythm and activity parameters. Despite some observable differences in activity parameters across age in the MPS III group, age was not significantly correlated with any variables in either the MPS III or control group. There was a trend towards a negative relationship between age and relative amplitude in the MPS III group ($r = -0.70, p = .056$) indicating, in line with descriptive statistics, that older children had less differentiation between the most and least active phases across the 24-hour period. The established relationship between circadian rhythm parameters was evident, with a strong negative correlation across both groups between intradaily variability and interdaily stability ($r = -0.83, p < .001$) and intradaily variability and relative amplitude ($r = -0.52, p = .041$).

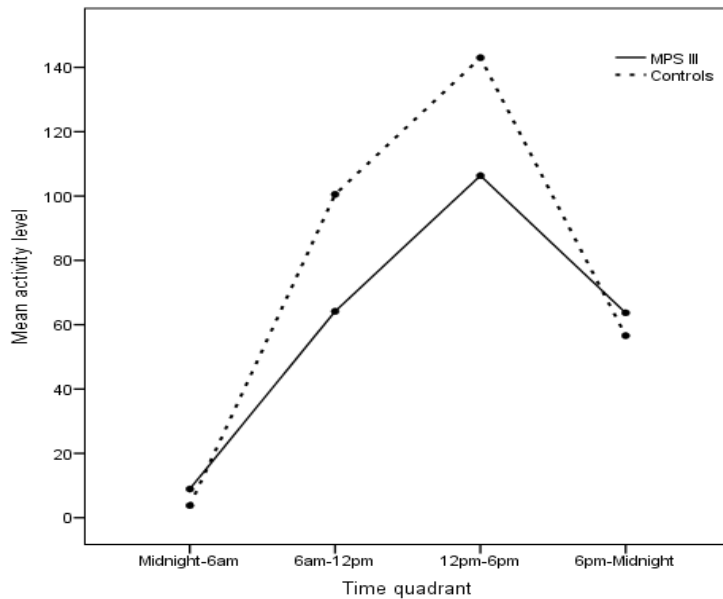


Figure 3. Average activity levels for MPS III and control group across a 24-hr period

Discussion

Actigraphic assessment of circadian rhythm and activity parameters revealed clinically and statistically significant differences between children with MPS III and TD controls. These results confirmed the general hypothesis. Children with MPS III demonstrated significantly increased variability and fragmentation of circadian rhythm (intradaily variability) across a 7-10 day period, with less stability of rhythm across days in relation to external *zeitgebers* (reduced interdaily stability). There was a trend towards lower relative amplitude in the MPS III group, suggesting that there was less differentiation between the most and least active phases over the 24-hour period compared to TD controls. For children with MPS III, individual periodicity scores and times of activity onset and offset were indicative of incidences of both phase delayed and phase advanced sleep-wake cycle, although phase delay was more common. There was also greater variability of activity onset and offset times within the MPS III group, which is consistent with results for intradaily variability and interdaily stability parameters.

Analysis of activity level patterns showed a shallower rhythm of activity in the MPS III group, which was attenuated in its rise and fall. This finding is also in line with a trend towards lower relative amplitude (i.e. less differentiation between periods of activity and rest) in individuals with MPS III. Children with MPS III had significantly higher levels of activity in the early morning hours (midnight – 6am) compared to controls. Descriptive analysis suggested lower activity levels in the MPS III group between 6am and 12pm and, after the removal of one extreme score, this difference was found to be statistically significant. This is consistent with a later onset of the most active 10-hour period in the MPS III group and provides evidence of a later onset of wakefulness and activity, which corresponds with phase delayed circadian rhythm functioning.

Taken together, both circadian rhythm and activity parameters were indicative of disrupted circadian rhythm functioning in children with MPS III and this may offer some explanation of the significant sleep disturbance within this population (Bax & Colville, 1995; Colville *et al.*, 1996; Ruijter *et al.*, 2008; Fraser *et al.*, 2005). There was evidence of established circadian rhythm patterns within the MPS III group, but circadian functioning was quantitatively different to controls. This finding is consistent with previous research utilising PSG, which reported irregular sleep-wake patterns in individuals with MPS III (Mariotti *et al.*, 2003). With PSG authors also found that some individuals with MPS III demonstrated no identifiable circadian rhythm of the sleep-wake cycle; however this finding was not replicated in the present study. This inconsistency may be accounted for by the fact that Mariotti *et al.* (2003) also included adults with MPS III in their sample, who would have been at a later stage of the disease. An increased fragmentation of sleep and circadian functioning has previously been highlighted particularly in older individuals with MPS III (Mahon *et al.*, 2013; Mariotti *et al.*, 2003). Accordingly in the present study, there was a trend towards reduced differentiation between most and least active phases and greater disruption in patterns of activity levels in older children with MPS III, providing further tentative evidence that sleep and circadian rhythm disturbance may be related to disease progression.

The finding that levels of activity were significantly higher in the MPS III group in the early morning (midnight – 6am) extends previous reports of increased nocturnal wakefulness in MPS III (Mahon *et al.*, 2013; Mariotti *et al.*, 2003). These bouts of activity may likely relate to episodes of night behaviours and parasomnias as reported by parents (Mahon *et al.*, 2013). The reduction in activity levels between the hours of 6am and 12pm and a later onset of wakefulness in the MPS III group may fit with parent and clinician reports of daytime sleepiness (Fraser *et al.*, 2002, 2005). Both these findings, along with non-parametric indices of rhythmicity, are suggestive of phase delayed circadian functioning in MPS III, although further investigation with a larger sample is required to confirm this. Descriptive analysis of activity data also

demonstrated that children in the second phase of MPS III (age 4 and 5 years) had the greatest levels of activity throughout the day. This corresponds with clinical reports of hyperactivity during this period (Bax & Colville, 1995; Cleary & Wraith, 1993; Valstar *et al.*, 2008).

Evidence of an impairment in circadian rhythm functioning in MPS III is consistent with reports of an abnormality in endogenous melatonin concentrations (Guerrero *et al.*, 2006; Mahon *et al.*, 2013). Melatonin secretion normally coincides with the onset of darkness, peaks during the night and is inhibited in the early morning with light onset. Paradoxically, melatonin production in MPS III has been demonstrated to be significantly lower at night and higher during the day (Guerrero *et al.*, 2006), corresponding with sleep onset difficulties and night waking, and daytime sleepiness, respectively. In the present study, this could potentially offer an explanation for higher activity levels between the hours of midnight – 6am and lower activity between 6am – 12pm in children with MPS III. An abnormality of melatonin rhythm is also consistent with significantly lower interdaily stability within the MPS III group, given the relationship between melatonin secretion and external *zeitgebers* (e.g. light). As a consequence, both lines of research point towards a potential intrinsic alteration in circadian clock functioning in MPS III, which is also consistent with murine models of the condition (Canal *et al.*, 2010). The identification of circadian rhythm disturbance in MPS III is also in line with previous research into sleep and circadian functioning in various IDD conditions (De Leersnyder *et al.*, 2006; Hare *et al.*, 2006a, 2006b; Nomura, 2005; Takaesu *et al.*, 2012; Wiggs & Stores, 2004). Being 'out of sync' with environmental *zeitgebers* and the sleep-wake pattern of others is likely to have a major impact on quality of life for the individual and those who care for them. Learning opportunities or valued activities may be hindered (Jan *et al.*, 2008) and expressions of challenging behaviour may be increased (Didden *et al.*, 2002; Wiggs & Stores, 1996), placing further strain on family functioning. It is, therefore, of central importance to address sleep-wake difficulties in individuals with MPS III.

Limitations

Given the rarity of MPS III, the sample size was small and thus variability within the data may have limited detection of statistically significant results. Accordingly, some effect sizes for non-significant results were indicative of difference between groups. With a larger sample size, relative amplitude and further activity level comparisons may have reached statistical significance. There were observable clinical differences in circadian rhythm functioning across age (and consequently, disease stage) in the MPS III group, with increased disruption in circadian rhythm generally in older children. However, the small sample size limited the statistical power to detect significant relationships based on age/stage of disease and thus prevents any firm conclusions from being drawn. It was also not possible to make any comparisons between MPS III subtypes A and B, which could be a critical factor given that subtype A is considered more severe (Héron *et al.*, 2010) and both eldest children were diagnosed with subtype A. The eldest two children with MPS III also had epilepsy, which has been shown to relate to sleep and behavioural difficulties (Cortesi *et al.*, 1999), but it was not possible to investigate or control for the potential impact of this comorbid condition.

Although exogenous melatonin was withdrawn prior to actigraphic monitoring, some children were prescribed further hypnotic medications (chloral hydrate, zopiclone). It is possible, therefore, that circadian rhythm parameters may have been further disrupted for these children without medication use; although the effect may have only been minimal as there is evidence of that these medications have little effect on sleep architecture (Guilleminault *et al.*, 1993). More likely is the potential impact of these medications on measurement of activity across the 24-hour period, based on a side effect profile of increased daytime lethargy and somnolence (Palermo *et al.*, 2002). This may partially explain the overall lower levels of activity in the two eldest children with MPS III taking these medications, although other circadian parameters were

nonetheless indicative of disrupted rhythmicity. Medication side effects is one of the challenges posed by research into rare conditions (Griggs *et al.*, 2009) and it may be particularly difficult to overcome in the MPS III population, given the common comorbidity of physical complaints.

Utilising actigraphy enabled objective, naturalistic monitoring of circadian rhythm and activity levels and was generally well tolerated by all children and families. Recordings were collected during weekdays and at the weekend across both groups to allow for reliable comparisons, which captured natural variability across time. Potential confounding variables were minimised as data was collected for minimum of 7 days (Acebo *et al.*, 1999) within 6 month period, during school term time. Data indicated that all families complied with instructions regarding wearing the actigraph, with removal only for short periods. Although some research has indicated that actigraphy is less accurate in discriminating between sleep-wake states in populations where sleep is fragmented (Ancoli-Israel *et al.*, 2003), it generally correlates highly with PSG data (Jean-Louis *et al.*, 2001). The results of the present study largely correspond with findings obtained with PSG in an MPS III population (Mariotti *et al.*, 2003). Actigraphy has been used to differentiate sleep-wake states in individuals with physical disabilities to an acceptable degree of reliability with PSG, albeit slightly lower than for individuals without physical disability (Laakso *et al.*, 2004). Despite this, it may have been beneficial to include measurement of any restrictions on physical activity in the MPS III group (e.g. time spent in a wheelchair, use of restraint), given that this is a common factor in MPS III (Valstar *et al.*, 2008). There are further potentially relevant factors that could have been recorded, including school attendance, behavioural difficulties, sleep routines and parental management strategies, and family composition. As data had been collected previously it was not possible to obtain this information; however these factors may have enhanced analysis and interpretation of circadian parameter and activity results.

Future research

International, multi-centre research into circadian functioning and sleep in MPS III would allow for validation of the present findings in a larger sample and would enable comparisons between MPS III subtypes and across stages of disease progression. Longitudinal analysis with actigraphy may also allow for exploration into potential differences in ultradian rhythm functioning, which, given the variability within the MPS III sample, may warrant investigation. Simultaneous measurement of melatonin and cortisol concentration levels across the 24-hour period would also enhance understanding of circadian clock functioning and its relative contribution to sleep disturbance within this population. There is evidence that intrinsic circadian clock functioning has an influence on respiratory systems (Stephenson, 2007) and a high prevalence of sleep-disordered breathing has been reported across all MPS conditions (Lin *et al.*, 2010). Therefore further work could usefully examine whether there is a relationship between nocturnal breathing difficulties and circadian rhythm functioning in MPS III.

The relationship between sleep problems and daytime challenging behaviour in IDD populations has been identified in a number of studies (Cotton & Richdale, 2010; Didden *et al.*, 2002; Hollway & Aman, 2011; Wiggs & Stores, 1996, 2004). Given the high reported rates of behavioural difficulties in MPS III (Ucar *et al.*, 2010; Valstar *et al.*, 2008), combining actigraphy with measurement of daytime behaviour would allow for objective investigation of this potential relationship. Additionally, further research may examine the relative contributions and effectiveness of behavioural and pharmacological interventions for sleep problems in MPS III.

Clinical implications

An increased understanding of circadian rhythm functioning and sleep patterns of children with MPS III has significant implications for individuals and families. 'Sleep problems' in IDD populations are by no means equivalent issues and should not be treated so. In the present study, actigraphic monitoring of children with MPS III was suggestive of both phase delayed and phase advanced circadian rhythmicity. Estimating individual circadian functioning is therefore critical in order to guide appropriate treatment choices, together with the timing of any treatment administration (e.g. melatonin, bright light therapy) (Bjorvatn & Pallesen, 2009). Employing actigraphy in clinical practice with MPS III populations would aid assessment and enable interventions to be targeted to individual difficulties. It would also provide a baseline of sleep and circadian rhythm functioning in a condition involving progressive developmental decline, which may allow for effective evaluation of new treatments targeting disease progression (de Ruijter *et al.*, 2011; Mahon *et al.*, 2013).

Enhancing parental understanding of their child's circadian rhythm and sleep disruption may inherently relieve some of the associated anxiety and stress regarding sleep; although the impact of caring for a child with sleep difficulties is by no means dismissed. By providing an explanation for the sleep problem, any negative perceptions that parents may hold in relation to their child's sleep or parenting abilities could potentially be altered. Using actigraphy would enable these individual sleep patterns to be identified and explained to parents, allowing for implementation of daytime and bedtime routines that fit with the individual child's circadian rhythm. Evidence supports the use of behavioural intervention for sleep problems in children with IDD (Jan *et al.*, 2008; Montgomery *et al.*, 2004); therefore there should be routine screening for sleep difficulties in children with MPS III, comprehensive assessment of the nature of sleep disturbance and implementation of subsequent tailored interventions incorporating behavioural strategies. This has the potential to also improve parental sleep patterns (Wiggs & Stores, 1998). Based on parent and clinician report, exogenous melatonin has been suggested as the most effective pharmacological treatment for sleep problems in MPS III (Fraser *et al.*, 2002, 2005); however its limited, short-term effects in some cases may be explained by an increased disruption of circadian rhythm functioning. Alternative treatments, such as light therapy and pharmacological agents acting upon the endogenous melatonin system, are considered for the circadian rhythm disorder, Smith-Magenis syndrome (De Leersnyder *et al.*, 2001, 2003), and may be worth investigation as treatment options in MPS III.

Conclusion

This study provides further evidence for the notion of an impairment in circadian rhythm functioning in children with MPS III. Further research is required to investigate this difference longitudinally, across MPS III subtypes and in relation to the circadian rhythm of endogenous melatonin and cortisol systems. Given the high prevalence of sleep problems in MPS III and the negative impact of childhood sleep disturbance on individual and family functioning, these findings are particularly relevant for clinical management of sleep in MPS III. It remains imperative to attempt to ascertain the underlying aetiology of sleep and circadian rhythm disturbance, in order that appropriate behavioural and pharmacological interventions can be targeted for the individual.

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Paper Three

Critical Appraisal

Word count: 5497

Introduction

This thesis aimed to investigate sleep and challenging behaviour in children with intellectual and developmental disabilities [IDD], with a subsequent specific focus on circadian rhythm functioning in the neurodevelopmental genetic condition, mucopolysaccharidosis type III [MPS III]. Sleep is an important subject for research and service provision in IDD given the prevalence of sleep disturbance within this population (Didden & Sigafos, 2001; Doran, Harvey & Horner, 2006; Krakowiak *et al.*, 2008) and its negative impact on functioning (Chu & Richdale, 2009; Jan *et al.*, 2008). Paper one, a systematic literature review, highlighted an association between sleep disturbance and challenging behaviour in children with IDD. Sleep disruption was predictive of behavioural difficulties in two reviewed studies. All studies were cross-sectional in design and therefore a causal relationship between these factors could not be inferred. Paper two, the empirical paper, reported an abnormality in circadian rhythm functioning in children with MPS III.

The following paper aims to provide a critical appraisal of the overall research process. Further consideration of the research strengths and limitations, implications for clinical practice, the wider context of the research and personal reflections will be discussed. For various reasons, completion of the current project focusing on circadian rhythms, sleep and behaviour was commenced in March 2013; therefore an account of the original project with the MPS III population is also presented, alongside reflections on its termination.

Literature review

Topic selection

There were a number of potential topics related to the study of sleep that would have been suitable for the purposes of a systematic literature review. It was observed that many experimental studies had been conducted with adult populations (Wiggs, 2007) and, based on the focus of the empirical paper, investigating research within a child IDD population was deemed more appropriate. Initially, the topic of circadian rhythm disruption in neurodevelopmental disorders was considered; however identifying suitable search terms, which would incorporate all rare conditions, was considered impractical within the timeframe of thesis completion (i.e. subsequent to the change of project). An awareness of sleep disturbance and behavioural difficulties, such as aggression, destructiveness, agitation and hyperactivity, as common comorbid presenting difficulties in children with MPS III (Bax & Colville, 1995; Valstar, Ruijter, van Diggelen, Poorthuis & Wijburg, 2008), fostered interest in investigating the potential relationship between these factors in other IDD conditions.

Study identification and selection

It is noteworthy that a significant number of potentially relevant papers were identified through hand searching reference lists. This suggests that search terms could possibly have been refined or developed to increase the efficiency of the systematic review process. One of the difficulties encountered was that some papers had a main focus on challenging behaviour as the outcome of interest, whereas others concentrated on sleep in general. Some studies may therefore have been missed when combining both these topics in the initial electronic search. This is an example of the common conflict between sensitivity and specificity of the search in systematic reviews (Petticrew & Roberts, 2006). The advantage of systematic reviews is their thorough, unbiased and replicable nature (Petticrew & Roberts, 2006) and, although hand-searching is an established part of the process, over reliance in the current review may have negated these assets of the

systematic process to some extent. However, there is also evidence that hand-searching is more sensitive than electronic searching in some respects (Hopewell, Clarke, Lefebvre & Scherer, 2007).

Eight studies were excluded as they only considered investigated sleep and behaviour in individuals with autistic spectrum disorders [ASD], suggesting that this relationship has been a focus in this condition. Inclusion of these papers may have been beneficial in some respects to extend the findings of the review, particularly given that some mixed IDD samples did include individuals with a diagnosis of ASD. However, a recent review of sleep in pervasive developmental disorders had been published (Hollway & Aman, 2011) and therefore it was deemed redundant to re-analyse these studies. A lack of a specific measure of daytime behaviour was the other predominant reason for exclusion of studies. Some studies investigated the relationship between sleep and general adaptive level of functioning or autistic symptom severity, rather than behavioural difficulties per se. Although these are undoubtedly critical factors to consider and did include measurement of behavioural aspects, they were considered to be different constructs and therefore excluded.

Quality assessment and data extraction

Time was taken to consider the quality assessment method that should be applied to the review. There was no existing quality assessment tool which included all the criteria relevant to research in IDD and/or sleep. Mahon (2012) used an idiosyncratic quality checklist for the assessment of research into sleep in neurodevelopmental genetic disorders that demonstrated face validity, and this was developed further for the current review. As recommended, the main potential sources of bias within the research area were considered and the checklist was utilised to guide an overall assessment of the study (Petticrew & Roberts, 2006). Having completed the systematic review process and with an enhanced understanding on the type of research within the field, the description of each quality criterion could be further refined. It may also be useful to consider the relative weighting of scores of each different methodological criterion; some factors, such as presence of a control group, diagnosis confirmation and statistical analysis, may have warranted a higher weighting than other quality assessment factors. Quality assessment rating should ideally take place with two reviewers, however due to time and resource constraints it was not possible to achieve such standards. In line with recommendations, any uncertainty was resolved through discussion with the research supervisor (Moher, Liberati, Tetzlaff & Altman, 2009). It would be beneficial to establish co-rater reliability prior to submission for publication.

Some reviewed studies had investigated multiple factors in relation to sleep and behaviour and, in line with the review aims, it was decided to predominantly focus on reporting results relevant to the relationship between sleep and behaviour. This, in itself, introduced an element of complexity when attempting to synthesise findings, given that studies used a range of measures to assess behavioural difficulties. Although it was possible to discuss the types of behavioural difficulties that showed a relationship with sleep to some extent, this was by no means a comprehensive account of the intricacies of different types of challenging behaviour. The researcher was reminded that systematic reviews are fundamentally an identification and appraisal of existing literature (Petticrew & Roberts, 2006) and that the aim of the review was to comment on the nature of any identifiable relationship between sleep and behaviour and provide an evaluation of the current research base. However, it was deemed necessary to comment on some of the other factors that studies identified as being associated with sleep and behavioural difficulties (e.g. level of intellectual disability and parental wellbeing), given that these are important considerations in furthering an understanding of the relationship. The findings of methodologically *weak* quality studies were included, but discussed separately. This decision was based on the fact that the findings were largely consistent with the

majority of *moderate* quality papers and also that detailed study information had been presented in table format, allowing the reader to form their own judgements regarding the studies. The researcher was aware that reporting findings of lower quality studies is not always routine practice in systematic reviews (Petticrew & Roberts, 2006).

Clinical implications

The review was considered to be of use to clinicians working in services for children with IDD, who would benefit from being aware of the association between sleep and behavioural problems. It highlighted the importance of undertaking comprehensive assessment with families, adopting a biopsychosocial approach to understanding presenting difficulties. There may be scope for an increased focus on sleep hygiene strategies as an early intervention in IDD populations; however, in view of the diversity of sleep disturbance problems, thorough assessment and subsequent implementation of tailored interventions is likely to be more beneficial. Evidence indicates that professionals may benefit from further training in sleep difficulties and intervention (Stores & Crawford, 1998; Stores & Wiggs, 1998). Having completed a systematic literature review in this area, the researcher was aware of the impact on their own clinical practice within a paediatric psychology service. Research has indicated that, similarly to IDD populations, children with physical health conditions or repeated hospital admissions are at risk of disrupted sleep patterns (Bandla & Splaingard, 2004; Melnyk, 2000; Palermo & Kiska, 2005). Consequently, findings from the literature review were presented at a paediatric psychology team meeting and an initiative will be commenced to provide sleep hygiene information to all inpatient wards.

Empirical paper

Topic area

Sleep disturbance is a significant problem in MPS III. Many parents report an extremely disrupted sleep pattern in their child where, for example, two or three nights of relatively adequate sleep duration may be subsequently followed by a child being awake all night (S. Jones & E. Wraith, personal correspondence, March 2012). This variability is undoubtedly confusing and frustrating for parents, causing disruption to daily family life and functioning. Attempting to increase understanding of sleep and circadian rhythm functioning in MPS III is therefore a worthy area of research. Considering the parallel case of Smith-Magenis syndrome, research into circadian rhythm functioning in this condition has aided the development of effective interventions for sleep disturbance (De Leersnyder, Claustrat, Munnich & Verloes, 2006; De Leersnyder *et al.*, 2001) and broadened understanding of the potential reasons for the disruption of sleep in IDD populations.

Owing to the change of project at a relatively late stage, it was initially a somewhat daunting prospect to embark on the investigation of circadian rhythm functioning in MPS III, as it was a largely new topic area for the researcher. It was necessary to review general literature on sleep and circadian rhythms in both typically developing [TD] and IDD populations in an attempt to develop a comprehensive understanding. It was also important to dedicate time to become familiar with the actigraphic analysis software, in order to understand how circadian rhythm parameters were derived and be able to interpret data meaningfully.

Methodology

Although sleep disturbance is prevalent in the MPS III population, families were not recruited based on the presence of sleep problems. This increased the generalizability of results from the empirical paper. It is important to note that the sample only consisted of children with MPS III subtype A or B; therefore it is not possible to draw firm conclusions about the circadian rhythm functioning of children with MPS III subtypes C or D. However, sleep disturbance is a factor across all MPS III subtypes, so it is a possibility that circadian functioning is disrupted across all conditions. MPS III subtypes C and D have the lowest incidence rates, thus it can be a challenge to obtain samples with all subtypes in an already rare condition.

The sample size was small, but this is often a feature of research into rare genetic disorders and it was offset to some extent by the use of objective measurement of circadian functioning via actigraphy. Taking into consideration the fact that the number of children with MPS III in the UK was estimated at sixty-eight at the time of recruitment (Mahon, 2012), a sample size of eight actually involved 11.7% of the population. This is a strength of the research and its ability to generalise to other children with MPS III. It was not possible however, to consider any statistical differences between MPS III subtypes, age/stage of the condition, or to control for comorbidity of physical health conditions (e.g. epilepsy) within the constraints of the sample size. International, multi-site research would be the only feasible way to obtain a large enough sample and the statistical power required to undertake such comparisons. Medical trials in MPS III often utilise this methodology for this precise reason. There were medium to large effect sizes for some non-significant circadian rhythm and activity group comparisons, indicating that a significant difference may have been detected with a larger sample. After visual inspection of the data for influential data points, one extreme score in the MPS III group was removed. Consequently, a significant difference between MPS III and control groups for one of the activity level parameters (level of activity between 6am and midday) was detected. This decision was made after consideration of how to treat outliers in statistical analyses (Osbourne & Overbay, 2004) and was based on the impact of outliers on power in an already small sample (Barnett & Lewis, 1994).

Actigraphy allowed for measurement of circadian rhythm parameters in a naturalistic context and thus children were in their usual sleep environment, with the normal *zeitgebers* that they would be exposed to. This ecological validity is one of the fundamental benefits of actigraphic recording, especially given that the devices were well tolerated by the children in the present study (Mahon, 2012). Previous research has also highlighted the practicality of discrete actigraphic recording and its applicability to a range of research questions in IDD populations (Hare, Jones & Evershed, 2006). A disadvantage of actigraphy is that it does not allow sleep architecture or phase (i.e. REM/non-REM) to be investigated. This information can only be obtained via polysomnography [PSG] which is considered the “gold-standard” of sleep investigation (Ancoli-Israel *et al.*, 2003). However, PSG is expensive, disruptive to normal sleep circumstances and generally only conducted over a short period of time. There is evidence that sleep stages can be disrupted in neurodevelopmental disorders (Hoban, 2000), and PSG has been utilised in an MPS III population (Mariotti *et al.*, 2003) with some consistent results to the present study. Future studies may benefit from employing both PSG and actigraphic recording in MPS III. In the present study, actigraphic data was averaged over the recording period as recommended (Acebo *et al.*, 1999), to allow for group comparisons. There is, therefore, scope for future work to also examine circadian rhythm and activity parameters over individual consecutive nights in MPS III. This would potentially enhance understanding of longitudinal sleep-wake patterns.

Taking into consideration findings from the current literature review and the behavioural phenotype of MPS III (Cross & Hare, 2013), in hindsight it would have been useful to obtain measures of child behaviour and

parental wellbeing levels in conjunction with actigraphic recording. Although numbers would have only been small, this may have allowed for descriptive analysis of the impact of disrupted circadian rhythm functioning and any potential relationship between sleep-wake and behavioural parameters. For example, it was noted that the three youngest children with MPS III had the highest overall activity levels and it would have been beneficial to know if parents viewed this potential 'hyperactivity' as problematic. However, it was crucial to minimise any additional demands that the project placed on parents as much as possible (Mahon, 2012). With this in mind, although it would also have been beneficial for other hypnotic medications alongside melatonin to be discontinued prior to recording, this was not an essential criteria for inclusion given that parents were reluctant to stop medication (Mahon, 2012).

Wider context

There is a growing research base into the behavioural phenotypes of individual syndromes and conditions. It was therefore considered relevant to reflect on the utility of studying one specific factor (circadian rhythm functioning) in one rare condition (MPS III). Behavioural phenotyping has aimed to improve understanding of the gene-environment interaction (Oliver, Berg, Moss, Arron & Burbidge, 2011; Oliver & Woodcock, 2008) and, it has been argued, can lead to the development of more targeted, effective interventions for individuals and their families (Dykens, 1995; Oliver & Woodcock, 2008). Syndromes with greater prevalence rates have typically been the focus of research, however understanding less prevalent conditions remains crucial and can arguably still aid understanding of the interaction between biological, behavioural, psychosocial and environmental factors. Understanding life-limiting conditions in particular, such as MPS III, is arguably vital for promoting quality of life and identifying effective support and intervention. On the other hand, it has been proposed that the concept of a behavioural phenotype overemphasises genetic and biological factors, and could lead to behaviour being viewed as inevitable, resulting in reduced attempts to intervene (see O'Brien & Yule, 1995, for a discussion). Descriptions of behaviour across IDD conditions are often not captured in a 'one size fits all' approach; the same behaviour in different conditions may have a different underlying aetiology. Therefore, investigating specific behavioural factors can shed light onto the processes and interactions underlying behaviour and may allow more sophisticated models of genotype-phenotype relationships to be developed (Horsler & Oliver, 2006; Oliver & Woodcock, 2008). In the present study, an increased understanding of circadian rhythm functioning and sleep disturbance in MPS III offers an understanding of disease presentation, potential ideas regarding disease progression and intervention, and recommendations for future research. Parallels have also been drawn with circadian rhythm functioning in Smith-Magenis syndrome throughout (De Leersnyder *et al.*, 2006; De Leersnyder *et al.*, 2001), and linking research ideas across these two conditions has proven useful.

Clinical implications

Sleep disturbance has numerous disadvantages for individuals with IDD and their families. Understanding the reason behind sleep disturbance is likely to be important for families of children with MPS III and the health professionals working with them. Knowledge of the aetiology behind sleep disruption, such as circadian rhythm dysfunction, is critical to guide appropriate pharmacological and behavioural intervention (Bjorvatn & Pallesen, 2009) and may also conceivably relieve parental stress or guilt regarding their child's sleeping habits. The effectiveness of behavioural interventions or light therapy for sleep in MPS III may be areas for further investigation. It would be useful to explore any association between sleep and behavioural difficulties in MPS III based on the findings from the present literature review. It is feasible that targeted, effective interventions to improve sleep disturbance may influence the expression of daytime behaviour and this is a worthwhile area for future research.

Original project

Overview of the project

The initial project focused on parenting interventions in neurodevelopmental genetic disorders. A systematic literature review was commenced investigating the evidence for the use of manualised parenting interventions in neurodevelopmental conditions and/or IDD. The aim of the original empirical paper was to trial a manualised parenting programme with parents of children with MPS III.

Background and aims

Given that children with IDD present with higher rates of behavioural problems than their typically developing [TD] peers (Lowe *et al.*, 2007; Janssen, Schuengel & Stolk., 2002; Emerson *et al.*, 2001), there is a need for effective, acceptable interventions to support parents to manage these difficulties. Behavioural difficulties can cause significant disadvantages in relation to quality of life, parental wellbeing and family functioning (Emerson, 2001; Gerber *et al.*, 2011; Hastings, 2002; Holden & Gitlesen, 2006) and, without intervention, can become more severe over time (Einfeld *et al.*, 2006). Children with MPS III often present with significant behavioural problems in the second phase of the condition, including destructiveness, aggression, agitation and hyperactivity (Bax & Colville, 1995; Valstar *et al.*, 2008). Clinical reports (S. Jones & E. Wraith, personal correspondence, March 2012) suggest that parents struggle to manage these behaviours and have described receiving no or little support from services in relation to behaviour management (Bax & Colville, 1995). There is limited research into parental and family functioning in MPS III due to the predominant focus on medical management, but two studies have indicated that parents experience clinically significant levels of anxiety and depression (Grant *et al.*, 2013; Ucar *et al.*, 2010). Consequently, psychosocial intervention in MPS III, specifically in relation to support for behavioural difficulties, was considered to be an important and beneficial area of research.

The Triple P positive parenting programme is a multi-level intervention designed to enhance parental skills and confidence, and simultaneously reduce problematic child behaviour. There is evidence for the effectiveness of the programme, as well as high levels of parental satisfaction and acceptance (Sanders, 1999; Thomas & Zimmer-Gembeck, 2007). A specific programme, Stepping Stones Triple P, has been developed to support parents of a child with IDD and has demonstrated positive outcomes in relation to child behaviour and parenting confidence (Plant & Sanders, 2007; Tellegen & Sanders, 2013). To date, there have been no studies investigating Stepping Stones with conditions involving developmental regression. Grant *et al.* (2013) found that parents of children with MPS III report similar coping strategies and resiliency factors, and experience similar levels of overall psychological functioning, to parents of children with IDD. As a result, parenting interventions that are effective in an IDD population may also be appropriate for parents of children with MPS III. Accordingly, the aim for the empirical paper was to use a case-series design to trial the effectiveness and acceptability of the Stepping Stones programme for parents of children with MPS III (see Appendix 8 for original protocol). The research protocol was approved by a local NHS Research Ethics Committee and NHS Trust Research and Development [R&D] (Appendix 9).

Challenges to implementation

The logistical issues and practicality of implementing the Stepping Stones intervention were carefully deliberated for some time. It was initially agreed that the intervention would be delivered on a one-to-one basis with parents either over the phone or utilising internet-based video conferencing. This was thought to be a pragmatic way of delivering the programme, given that sessions could be arranged at individual

parent's convenience and would not constrain the geographical location of recruited families. There is evidence for the effectiveness of Triple P delivered using a telephone supported, self-directed format (Cann, Rogers & Worley, 2003). However, there were some concerns in terms of how this may impact on the primary aims of reporting the effectiveness and acceptability of the intervention. Given that the project was essentially a pilot investigation of Stepping Stones for an MPS III population, changing the mode of delivery of the intervention may have significantly influenced outcomes. Additionally, any potential benefits from meeting other parents of children with MPS III would have been lost with a one-to-one delivery format. The advantages and disadvantages of the two different modes of delivery (group vs. telephone format) were weighed up, but this decision was eventually constrained by the Stepping Stones training that was available from Triple P International in the UK at the time. The researcher completed *group* Stepping Stones training, and thus was only formally qualified to deliver the intervention in this format. This also constrained the type of resources which could be ordered from Triple P International to support intervention delivery. Despite attempts to gain additional training to enable one-to-one delivery of the intervention, this was eventually not possible due to financial and logistical constraints. It was subsequently decided to proceed with delivery in a group format. These encountered issues are embedded within the wider context of the juxtaposition of the developing evidence base for Triple P and the commercial body of Triple P International (see Coyne & Kwakkenbos, 2013, Sanders *et al.*, 2013 and Wilson *et al.*, 2012 for a discussion).

Group Stepping Stones consists of nine sessions, with three sessions mid-intervention delivered via one-to-one telephone support. This leaves six group sessions for parents to attend. In recognition of the pressure on families of children with MPS III and the distance some families travelled to the hospital, the content of these six sessions was planned to be condensed into four group sessions (with the three telephone session as normal). This was deemed to still be a realistic evaluation of the effectiveness and acceptability of the intervention, given that previous research has highlighted flexibility in session delivery as long as there is fidelity to the model (Mazzucchelli & Sanders, 2010). The researcher spent time shadowing established Stepping Stones groups in the local area to enhance implementation skills. Other potential adaptations to the programme were considered in relation to the specific behavioural phenotype displayed by children with MPS III (Cross & Hare, 2013) and the need for a sensitive approach to some aims of the Stepping Stones programme which focus on building child skills, given that MPS III involves developmental regression. It was for this reason also that children deemed to be at the end phase of MPS III were excluded.

Recruitment challenges

From the outset, the rarity of MPS III presented a challenge to sample size and recruitment. This was taken into consideration and consequently, the case-series design was deemed appropriate. Previous research has indicated that a sample size of 6 – 8 participants is suitable for a multiple-baseline case series design (Wells *et al.*, 2009) and, after discussion with clinicians at St. Mary's hospital, Manchester, this was considered a realistic target. Recruitment was restricted to families under the care of St Mary's hospital, as the group was planned to run from this location and it was unfeasible for the researcher to travel across the UK to run alternative groups.

There were delays in obtaining NHS R&D approval which impacted on the recruitment period. In total, 29 families were either sent a recruitment letter and information sheet (Appendix 10) or were given the information during a routine clinic appointment. It was crucial to gain support from the clinical team at the hospital in order to maximise recruitment; therefore multiple contacts were made and project aims were presented in the multidisciplinary team meeting. Despite these active efforts and gaining support from the team, uptake was extremely low and only two families contacted the researcher for further information

about the project. As a result, an amendment was submitted to ethics allowing for additional methods of recruitment (Appendix 11). This included further recruitment through clinics at the hospital, a member of the child’s existing care team being able to obtain permission for the researcher to contact families directly over the phone and registering the project with the MPS Society UK. Four families (six parents) subsequently agreed to take part in the research and completed initial questionnaire measures either at the hospital or during a home visit. It seemed that these families tended to agree to participate as they already attended the hospital regularly due to their child’s involvement in an enzyme replacement trial. Reasons for non-participation were obtained from some families and predominantly centred on the feasibility of attending group sessions, with one mother also reporting that the timing of the research was not practical as she was expecting her second child. Most families reported that they would find it beneficial to meet other parents of children with MPS III, but did not feel able to commit to the Stepping Stones group programme.

The decision whether to recruit families of children who were involved in an enzyme replacement trial at St. Mary’s hospital for the project was carefully considered from the outset. After several discussions with medical colleagues, it was initially decided that taking part in the Stepping Stones intervention would not confound results in relation to the outcome of the medical trial and that parents should be given the opportunity to participate in a psychosocial intervention. However, this was a multi-site international trial and at a late stage it was decided by senior investigators that families involved in the enzyme replacement study should be excluded from the Stepping Stones project. At this point, given that this included three out of the four families who had agreed to take part in the study, it was decided to cease recruitment and terminate the project. Table 1 presents a timescale of events and the courses of action for the original project. It was deemed necessary to change the topic of the original literature review to complement the change of project to investigating circadian rhythm functioning in MPS III.

Table 1. Timeline of events for original project

Event or action	Date
Approval from University of Manchester Research Subcommittee	Dec 2011
Completion of Group Stepping Stones Training	Jan 2012
On-going discussions with Triple P International regarding additional training	Feb – June 2012
Shadowing of local Stepping Stones groups	April – May 2012
Decision to proceed with group format	July 2012
Approval from NHS Research Ethics Committee	Sept 2012
Approval from NHS R&D	Nov 2012
Recruitment commenced	Nov 2012
Amendment submitted to ethics regarding recruitment process	Feb 2013
Initial assessments completed with 6 parents	Jan – Feb 2013
Stepping Stones project terminated	March 2013

Personal reflections

The researcher had previously worked in a paediatric psychology service and had developed a strong interest in the impact of childhood illness on attachment and parenting strategies. Thus, evaluating the Triple P parenting programme with an MPS III population was considered an invaluable opportunity. Meeting families of children with MPS III during recruitment for the Stepping Stones intervention was a critical part of understanding their experience of having a child with MPS III. One mother described that she had agreed to take part in the project as she was willing to “try anything” that might be helpful. Another family talked about the importance of meeting other parents of children with MPS III, as their child had only

just received a diagnosis. The researcher was acutely aware of the emotive impact of researching a severely life-limiting condition. It was imperative to balance the role of a researcher and clinician delivering the parenting intervention, whilst maintaining appropriate boundaries in terms of not providing therapeutic intervention in relation to parental wellbeing or adjustment. A distress protocol was developed for this purpose and families were signposted to additional support where necessary, such as the MPS Society or their general practitioner.

Changing projects at a late stage was difficult for the researcher given the time and effort put into the initial project and having met families who had agreed to participate. The researcher was enthusiastic about implementing a potentially beneficial psychosocial intervention in MPS III and it was difficult to have to explain the reasons for termination of the project to families. Almost all parents asked about whether the group would be run in the future. However, with hindsight, these difficulties provided an extremely useful learning experience regarding the challenges of clinical research and the resources needed to implement new clinical interventions. As acknowledged by Cross (2012), it was apparent that clinical psychology could be embedded within the multi-disciplinary teams that currently offer support to families of children with rare genetic conditions. This may allow clinical intervention and research to be effectively combined (Cross, 2012).

There are many potential reasons why uptake of the Stepping Stones intervention was low. The practicality of attending group sessions and perceived 'time consuming' nature of the intervention was discussed by some families who had shown some initial interest in the project. This could be considered an indication of the level of pressure and strain on families caring for children with complex conditions that they felt unable to commit to a potentially beneficial intervention. Other families who did not respond conceivably may have felt that behavioural difficulties were not their primary concern, may have felt that participating in a group would have been a distressing experience or may have been uncomfortable with a group format. Potentially, some parents may have also had a negative or defensive reaction to the description of the intervention as a parenting programme, feeling that their parenting skills per se were not the problem. This was certainly a disadvantage of recruitment via post. Previous research has indicated invasion of privacy, logistical issues and low socio-economic status as barriers to participation in parenting programmes (Heinrichs, Bertram, Kuschel & Hahlweg, 2005).

Dissemination

An individual report from actigraphic data was produced for each child with MPS III by Mahon (2012). It was hoped that this would provide information to parents and aid any subsequent intervention for sleep disturbance (Mahon, 2012). The literature review and empirical paper will both be submitted for publication and abstracts will be submitted for oral presentation at the UK Seattle Club intellectual disability research conference and relevant sleep conferences. Results from the empirical paper have already been presented in poster format at the 'Cerebra Centre Academic Conference, 2013' in Birmingham. Findings will also be disseminated to the genetics department at St. Mary's hospital and the MPS Society UK.

Summary

The overall aim of this thesis was to investigate the relationship between sleep disturbance and behavioural difficulties in IDD populations and examine circadian rhythm functioning in the neurodevelopmental condition, MPS III. It is anticipated that the literature review will provide a valuable overview of the current research into sleep and behavioural problems in IDD for clinicians working in the area. The empirical paper extends evidence of a disruption in circadian rhythm functioning in MPS III, which may be a viable explanation for the high prevalence of sleep disturbance observed in this population. Advancements in the understanding of sleep-wake patterns in MPS III will hopefully allow for the development of effective interventions for individuals and families. Both papers have highlighted the importance of targeting sleep disturbance in children with IDD and have presented a discussion of the clinical implications of findings, alongside avenues for further research. The challenges of conducting research in clinical settings, with a rare genetic condition, have been reflected upon in this paper. Despite these challenges, it has been a privilege and invaluable learning opportunity to complete this project with families of children with MPS III.

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Appendix 1

Author guidelines for Journal of Applied Research in Intellectual Disabilities

Journal of Applied Research in Intellectual Disabilities

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The topics it covers include community living, quality of life, challenging behaviour, communication, sexuality, medication, ageing, supported employment, family issues, mental health, physical health, autism, economic issues, social networks, staff stress, staff training, epidemiology and service provision. Theoretical papers are also considered provided the implications for therapeutic action or enhancing quality of life are clear. Both quantitative and qualitative methodologies are welcomed. All original and review articles continue to undergo a rigorous, peer-refereeing process. Please read the instructions below carefully for details on submission of manuscripts, the journal's requirements and standards as well as information concerning the procedure after a manuscript has been accepted for publication. Authors are encouraged to visit <http://authorservices.wiley.com/bauthor/> for further information on the preparation and submission of articles.

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Acceptance of papers is based on the understanding that authors have treated research participants with respect and dignity throughout. Please see Section 2.2 below.

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It is a requirement that all authors have been accredited as appropriate under submission of the manuscript. Contributors who do not qualify as authors should be mentioned under Acknowledgements.

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-McGill P. & Toogood A. (1993) Organising community placements. In: *Severe Learning Disabilities and Challenging Behaviours: Designing High Quality Services* (Eds E. Emerson, P. McGill & J. Mansell), pp. 232-259. Chapman and Hall, London.

-Qureshi H. & Alborz A. (1992) Epidemiology of challenging behaviour. *Mental Handicap Research* 5, 130-145

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Appendix 2

Quality assessment tool

Adapted quality assessment tool

Question/component	Score		
	0	1	2
1. What is the sample size?*	N < 29 (small)	N = 30 – 99 (medium)	N ≥ 100 (large)
2. Type of sample	Mixed ID/TD (not separated in analysis)	Mixed ID/PDD conditions	Specific ID condition/genetic syndrome
3. Is there a control group?	No	Yes, comparison to TD/ ID/physical health condition sample (not matched)	Yes, comparison to TD/ ID/ physical health condition sample (matched)
4. Assessment of sleep	No validated/ standardised measure or not reported	Validated/ standardised assessment tool or sleep diary	Objective measurement (actigraphy/PSG)
5. Assessment of behaviour	No validated/ standardised measure or not reported	Validated/ standardised assessment tool	Independent observation/time sampling
6. Are the aims/ hypotheses clearly described?	No	Yes	-
7. Do researchers have confirmation of diagnosis?	No independent verification/not reported	Recruited through 3 rd party with syndrome specific association/ specialist provision	Researchers aware of diagnostic evidence/ independent verification
8. Is information on medication provided?	No	Some details	Full details and/or controlled for
9. Is information on comorbidity provided?	No	Some information provided, but not controlled for	Information provided and attempts made to control for
10. Is the recruitment process clearly described?	No	Some detail provided	Full details with information on participation rates (selection bias)
11. Is information provided on previous sleep interventions?	No/Unclear	Yes	-
12. Statistical analysis:			
a) Is it powered (i.e. sample large enough for analysis)?	No/Unclear	Yes	-
b) Has data been assessed for parametric assumptions?	No details provided	Yes (or can be assumed from non-parametric analysis)	-
c) Statistics used	Descriptive statistics only	Group comparisons or correlational analysis	Regression
d) Is effect size/power reported?	No	Yes	-
e) Is the analysis appropriate?	No/Uncertain	Yes, mostly	Yes, definitely
f) Are actual probability values reported (except where $p < 0.001$)?	No	Yes	-

*Based on central limit theorem (Field, 2011)

Total scores

Strong quality = 20 – 28; Moderate quality = 11 – 19; Weak quality = ≤10

Appendix 3

Author guidelines for Journal of Intellectual Disability Research

Journal of Intellectual Disability Research

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1. GENERAL

The Journal of Intellectual Disability Research is devoted exclusively to the scientific study of intellectual disability and publishes papers reporting original observations in this field. The subject matter is broad and includes, but is not restricted to, findings from biological, educational, genetic, medical, psychiatric, psychological and sociological studies, and ethical, philosophical, and legal contributions that increase knowledge on the treatment and prevention of intellectual disability and of associated impairments and disabilities, and/or inform public policy and practice. Such reviews will normally be by invitation. The Journal also publishes Full Reports, Brief Reports, Letters to Editor, and an 'Hypothesis' papers. Submissions for Book Reviews and Announcements are also welcomed.

The Journal of Intellectual Disability Research will feature four Annotation articles each year covering a variety of topics of relevance to the main aims of the journal or topics. Senior researchers, academics and clinicians of recognised standing in their field will be invited to write an Annotation for the journal covering an area that will be negotiated with the Associate Editor, Prof. Chris Oliver, on behalf of the Editorial team. Anyone expert in his/her particular field wishing to submit an uninvited review is advised to seek prior guidance from the Associate Editor.

All papers are assessed by expert referees.

Please read the instructions below carefully for details on the submission of manuscripts, the journal's requirements and standards as well as information concerning the procedure after a manuscript has been accepted for publication in [The Journal of Intellectual Disability Research](#). Authors are encouraged to visit John Wiley & Sons Pte Ltd's [Author Services](#) for further information on the preparation and submission of articles and figures.

2. ETHICAL GUIDELINES

The Journal of Intellectual Disability Research adheres to the ethical guidelines for publication and research summarised below.

2.1. Authorship and Acknowledgements

Authorship: Authors submitting a paper do so on the understanding that the manuscript has been read and approved by all authors and that all authors agree to the submission of the manuscript to the Journal. ALL named authors must have made an active contribution to the conception and design and/or analysis and interpretation of the data and/or the drafting of the paper and ALL must have critically reviewed its content and have approved the final version submitted for publication. Participation solely in the acquisition of funding or the collection of data does not justify authorship and, except in the case of complex large-scale or multi-centre research, the number of authors should not exceed six.

The Journal of Intellectual Disability Research adheres to the definition of authorship set up by The International Committee of Medical Journal Editors (ICMJE). According to the ICMJE authorship criteria should be based on 1) substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content and 3) final approval of the version to be published. Authors should meet conditions 1, 2 and 3.

It is a requirement that all authors have been accredited as appropriate upon submission of the manuscript. Contributors who do not qualify as authors should be mentioned under Acknowledgements.

Acknowledgements: Under Acknowledgements please specify contributors to the article other than the authors accredited. Please also include specifications of the source of funding for the study and any potential conflict of interests if appropriate. Suppliers of materials should be named and their location (town, state/county, country) included.

2.2. Ethical Approvals

Experimental Subjects: experimentation involving human subjects will only be published if such research has been conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version, 2002 www.wma.net/e/policy/b3.htm) and the additional requirements, if any, of the country where the research has been carried out. Manuscripts must be accompanied by a statement that the research was undertaken with the understanding and written consent of each participant and according to the above mentioned principles. A statement regarding the fact that the study has been independently reviewed and approved by an ethical board should also be included. Editors reserve the right to reject papers if there are doubts as to whether appropriate procedures have been used.

All studies using human participants or animal subjects should include an explicit statement in the Material and Methods section identifying the review and ethics committee approval for each study, if applicable. Editors reserve the right to reject papers if there is doubt as to whether appropriate procedures have been used.

Ethics of investigation: Papers not in agreement with the guidelines of the Helsinki Declaration as revised in 1975 will not be accepted for publication.

2.3 Clinical Trials

Clinical trials should be reported using the CONSORT guidelines available at www.consort-statement.org. A CONSORT checklist should also be included in the submission material (http://www.consort-statement.org/mod_product/uploads/CONSORT_2001_checklist.doc).

Manuscripts reporting results from a clinical trial must provide the registration number and name of the clinical trial. Clinical trials can be registered in any of the following free, public clinical trials registries: www.clinicaltrials.gov, clinicaltrials-dev.ifpma.org/, isrctn.org/. The clinical trial registration number and name of the trial register will be published with the paper.

The Journal of Intellectual Disability Research encourages authors submitting manuscripts reporting from a clinical trial to register the trials in any of the following free, public clinical trials registries: www.clinicaltrials.gov, clinicaltrials-dev.ifpma.org/, isrctn.org/. The clinical trial registration number and name of the trial register will then be published with the paper.

2.4 Conflict of Interest and Source of Funding

Conflict of Interest: Authors are required to disclose any possible conflict of interest. These include financial (for example patent, ownership, stock ownership, consultancies, speaker's fee). Author's conflict of interest (or information specifying the absence of conflicts of interest) will be published under a separate heading entitled 'Conflict of Interests'.

The Journal of Intellectual Disability Research requires that sources of institutional, private and corporate financial support for the work within the manuscript must be fully acknowledged, and any potential conflicts of interest noted. As of 1st March 2007, this information will be a requirement for all manuscripts submitted to the Journal and will be published in a highlighted box on the title page of the article. Please include this information under the separate headings of 'Source of Funding' and 'Conflict of Interest' at the end of your manuscript.

If the author does not include a conflict of interest statement in the manuscript then the following statement will be included by default: "No conflicts of interest have been declared".

Source of Funding: Authors are required to specify the source of funding for their research when submitting a paper. Suppliers of materials should be named and their location (town, state/county, country) included. The information will be disclosed in the published article.

2.5 Appeal of Decision

Authors who wish to appeal the decision on their submitted paper may do so by e-mailing the Editorial Office with a detailed explanation for why they find reasons to appeal the decision.

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3. SUBMISSION OF MANUSCRIPTS

Manuscripts should be submitted electronically via the online submission site <http://mc.manuscriptcentral.com/jidr>. The use of an online submission and peer review site enables immediate distribution of manuscripts and consequentially

speeds up the review process. It also allows authors to track the status of their own manuscripts. Complete instructions for submitting a paper are available online and below. Further assistance can be obtained from Ms Sue M Hampton-Matthews at the Editorial Office of JIDR, Second Floor, Douglas House, 18b Trumpington Road, Cambridge, CB2 2AH, UK +44 1223 746 124; e-mail: shm44@medschl.cam.ac.uk.

- Launch your web browser (supported browsers include Internet Explorer 6 or higher, Netscape 7.0, 7.1, or 7.2, Safari 1.2.4, or Firefox 1.0.4) and go to the journal's online Submission Site: <http://mc.manuscriptcentral.com/jidr>
- Log-in or click the 'Create Account' option if you are a first-time user.
- If you are creating a new account.
 - After clicking on 'Create Account', enter your name and e-mail information and click 'Next'. Your e-mail information is very important.
 - Enter your institution and address information as appropriate, and then click 'Next.'
 - Enter a user ID and password of your choice (we recommend using your e-mail address as your user ID), and then select your area of expertise. Click 'Finish'.
- If you have an account, but have forgotten your log in details, go to Password Help on the journals online submission system <http://mcv3support.custhelp.com> and enter your e-mail address. The system will send you an automatic user ID and a new temporary password.
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- After you have logged in, click the 'Submit a Manuscript' link in the menu bar.
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 - When you have selected all files you wish to upload, click the 'Upload Files' button.
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3.3. Manuscript Files Accepted

Manuscripts should be uploaded as Word (.doc) or Rich Text Format (.rft) files (not write-protected) plus separate figure files. GIF, JPEG, PICT or Bitmap files are acceptable for submission, but only high-resolution TIF or EPS files are suitable for printing. The files will be automatically converted to HTML and PDF on upload and will be used for the review process. The text file must contain the entire manuscript including title page, abstract, text, references, tables, and figure legends, but no embedded figures. Figure tags should be included in the file. Manuscripts should be formatted as described in the Author Guidelines below.

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3.4. Blinded Review

All manuscripts submitted to The Journal of Intellectual Disability Research will be reviewed by two experts in the field. The Journal of Intellectual Disability Research uses double-blinded review. The names of the reviewers will thus not be disclosed to the author submitting a paper and the name(s) of the author(s) will not be disclosed to the reviewers.

To allow double-blinded review, please submit (upload) your main manuscript and title page as separate files.

Please upload:

- Your manuscript without title page under the file designation 'main document'
- Figure files under the file designation 'figures'
- The title page, Acknowledgements and Conflict of Interest Statement where applicable, should be uploaded under the file designation 'title page'.

All documents uploaded under the file designation 'title page' will not be viewable in the HTML and PDF format you are asked to review at the end of the submission process. The files viewable in the HTML and PDF format are the files available to the reviewer in the review process.

3.5. Suggest a Reviewer

The Journal of Intellectual Disability Research attempts to keep the review process as short as possible to enable rapid publication of new scientific data. In order to facilitate this process, please suggest the names and current e-mail addresses of 1 potential international reviewer whom you consider capable of reviewing your manuscript. In addition to your choice the journal editor will choose one or two reviewers as well.

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You may suspend a submission at any phase before clicking the 'Submit' button and save it to submit later. The manuscript can then be located under 'Unsubmitted Manuscripts' and you can click on 'Continue Submission' to continue your submission when you choose to.

3.7. E-mail Confirmation of Submission

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Revised manuscripts must be uploaded within 3 months of authors being notified of conditional acceptance pending satisfactory revision. Locate your manuscript under 'Manuscripts with Decisions' and click on 'Submit a Revision' to submit your revised manuscript. Please remember to delete any old files uploaded when you upload your revised manuscript. Please also remember to upload your manuscript document separate from your title page.

4. MANUSCRIPT TYPES ACCEPTED

Original Research Article The main text should proceed through sections of Abstract, Introduction, Methods, Results, and Discussion.

Full Reports of up to 4,500 words are suitable for major studies, integrative reviews and presentation of related research projects or longitudinal enquiry of major theoretical and/or empirical conditions.

Brief Reports of up to 1,500 words are encouraged especially for replication studies, methodological research and technical contributions.

Annotation Articles should be no more than 5,500 words long including tables and figures and should not have been previously published or currently under review with another journal. The normal instructions to authors apply. The date for submission of the article should be negotiated with the Associate Editor. An honorarium of £400 in total shall be paid to the authors(s) when the article is accepted for publication.

Three main types of Annotations will be commissioned: 1. Authoritative reviews of empirical and theoretical literature. 2. Articles proposing a novel or modified theory or model. 3. Articles detailing a critical evaluation and summary of literature pertaining to the treatment of a specific disorder.

A Hypothesis Paper can be up to 2,500 words and no more than twenty key references. It aims to outline a significant advance in thinking that is testable and which challenges previously held concepts and theoretical perspectives.

5. MANUSCRIPT FORMAT AND STRUCTURE

5.1. Format

Language: The language of publication is English. Authors for whom English is a second language must have their manuscript professionally edited by an English speaking person before submission to make sure the English is of high quality. It is preferred that manuscripts are professionally edited. A list of independent suppliers of editing services can be found at http://authorservices.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author and use of one of these services does not guarantee acceptance or preference for publication.

Abbreviations, Symbols and Nomenclature: Spelling should conform to The Concise Oxford Dictionary of Current English and units of measurements, symbols and abbreviations with those in Units, Symbols and Abbreviations (1977) published and supplied by the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. This specifies the use of SI units.

It is important that the term 'intellectual disabilities' is used when preparing manuscripts.

Please note that 'intellectual disability', as used in the Journal, includes those conditions labelled mental deficiency, mental handicap, learning disability and mental retardation in some countries.

5.2. Structure

All manuscripts submitted to *The Journal of Intellectual Disability Research* should include: Title, Keywords, structured Abstract, Main Text (divided by appropriate sub headings) and References.

Title Page: Please remember that **peer-review is double-blind**, so that neither authors nor reviewers know each others' identity. Therefore, **no identifying details of the authors or their institutions must appear in the submitted manuscript; author details should be entered as part of the online submission process.** However, a 'Title Page' must be submitted as part of the submission process as a 'Supplementary File Not for Review'. This should contain the title of the paper, names and qualifications of all authors, their affiliations and full mailing address, including e-mail addresses and fax and telephone numbers.

Keywords: The author should also provide up to six keywords to aid indexing.

Abstracts: For full and brief reports a structured summary should be included at the beginning of each article, incorporating the following headings: Background, Method, Results, and Conclusions. These should outline the questions investigated, the design, essential findings, and the main conclusions of the study.

Optimizing Your Abstract for Search Engines: Many students and researchers looking for information online will use search engines such as Google, Yahoo or similar. By optimizing your article for search engines, you will increase the chance of someone finding it. This in turn will make it more likely to be viewed and/or cited in another work. We have compiled [these guidelines](#) to enable you to maximize the web-friendliness of the most public part of your article.

5.3. References

The Journal follows the Harvard reference style. References in text with more than two authors should be abbreviated to (Brown et al. 1977). Authors are responsible for the accuracy of their references.

The reference list should be in alphabetical order thus:

- Giblett E.R. (1969) Genetic Markers in Human Blood. Blackwell Scientific Publications, Oxford.
- Moss T.J. & Austin G.E. (1980) Preatherosclerotic lesions in Down's syndrome. *Journal of Mental Deficiency Research* **24**, 137- 41.
- Seltzer M. M. & Krauss M.W. (1994) Aging parents with co-resident adult children: the impact of lifelong caregiving. In: *Life Course Perspectives on Adulthood and Old Age* (eds M. M. Seltzer, M.W. Krauss & M. P. Janicki), pp. 3–18. American Association on Mental Retardation, Washington, DC.

Where more than six authors are listed for a reference please use the first six then 'et al.'

The Editor and Publisher recommend that citation of online published papers and other material should be done via a DOI (digital object identifier), which all reputable online published material should have - see www.doi.org/ for more

information. If an author cites anything which does not have a DOI they run the risk of the cited material not being traceable.

We recommend the use of a tool such as EndNote or Reference Manager for reference management and formatting. EndNote reference styles can be searched for here: www.endnote.com/support/enstyles.asp
Reference Manager reference styles can be searched for here: www.refman.com/support/rmstyles.asp

5.4. Tables, Figures

Tables: Tables should include only essential data. Each table must be typewritten on a separate sheet and should be numbered consecutively with Arabic numerals, e.g. Table 1, Table 2, etc., and give a short caption.

Figures: All graphs, drawings and photographs are considered figures and should be numbered in sequence with Arabic numerals. All symbols and abbreviations should be clearly explained.

Tables and figures should be referred to in the text together with an indication of their approximate position recorded in the text margin.

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Although low quality images are adequate for review purposes, print publication requires high quality images to prevent the final product being blurred or fuzzy. Submit EPS (line art) or TIFF (halftone/photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Do not use pixel-oriented programmes. Scans (TIFF only) should have a resolution of at least 300 dpi (halftone) or 600 to 1200 dpi (line drawings) in relation to the reproduction size (see below). Please submit the data for figures in black and white or submit a Colour Work Agreement Form (see Colour Charges below). EPS files should be saved with fonts embedded (and with a TIFF preview if possible).

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Appendix 4

Recruitment letter

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 & Dr Brain Biggar. 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 07961842244, or email us at Sanfilippo@listserve.manchester.ac.uk, and a Researcher will contact you. We will also be providing packs of information at the forthcoming MPS Society conference. 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 5

Participant information sheets

(Parents of children with MPS III, parents of control group, control group children aged 11-15 years)

Participant Information Sheet

Study Title: An Investigation of Sleep and Circadian Rhythms 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. 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 up to 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.
- 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. 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. It will also inform the development and implementation of innovative treatments for MPS III such as gene therapy.

1.7 Expenses

Any 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.

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).

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 at the university 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, 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.

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

1.5 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.

1.6 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.

1.7 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 6

Consent and assent forms

(Parents of children with MPS III, parents of control group, consent form for control group aged 14-15 years, assent form for control group aged 6-13 years)

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 childwho 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 _____

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 participate 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 Consenting 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 _____

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: _____

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 7

Evidence of project approval

(NHS Research Ethics committee and NHS R&D)



National Research Ethics Service
North West 12 Research Ethics Committee – Lancaster

Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

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.

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>.

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:

<i>Document</i>	<i>Version</i>	<i>Date</i>
GP/Consultant Information Sheets	01	28 January 2011
Participant Information Sheet: For parents of MPS iii children - questionnaire compnants olny	01	28 January 2011
Letter from Sponsor		07 February 2011
CV for Sheena Aspil		09 February 2011
CV for Maria Canal		28 January 2011
Participant Information Sheet: For parents of MPS iii children - all componants	01	28 January 2011
Participant Consent Form: Informed assent for mainstream controls	01	28 January 2011
Letter from Professor Wraith		10 September 2010
Letter from funder		15 September 2010
Template for intial contact letter -MPS III families	01	28 January 2011
Investigator CV		
Participant Information Sheet: For parents of neurotypical contols - mainstream	01	28 January 2011
Participant Information Sheet: For parents of intellectual disability controls	01	28 January 2011
Participant Information Sheet: For mainstream neurotypical control children aged 6-10	01	28 January 2011
Participant Information Sheet: For neurotypical mainstream children aged 11 - 15	01	28 January 2011
Participant Consent Form: Circadian rhythm and sleep MPS III	01	28 January 2011
Participant Consent Form: Behaviour and family functioning MPS iii	01	28 January 2011
Protocol	1	28 January 2011
CV for James Wraith		17 December 2010
Evidence of insurance or indemnity		07 February 2011
Evidence of insurance or indemnity		21 June 2010
Participant Consent Form: Behaviour and family functioning controls ID	01	28 January 2011
Participant Consent Form: Circadian rhythm and sleep controls mainstream	01	28 January 2011
Questionnaire: Learning disability casemix scale		
Questionnaire: Resilience scale for adults		
Questionnaire: Sanfilippo behaviour rating scale		
Questionnaire: Eyberg child behaviou inventory		
Questionnaire: Vineland - II		
Questionnaire: Multimensional scale of perceived support		
Questionnaire: Aberrant behaviour checklist		
Questionnaire: Paediatric inventory for parents		
Questionnaire: Developmental behaviour checklist		
REC application	3.0	10 February 2011
CV for Louise Mahon		06 December 2010
CV for Brian Bigger		
Template for intial contact letter - ID group	01	28 January 2011
Protocol for risk issues that become apparent through data collected	01	28 January 2011

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.

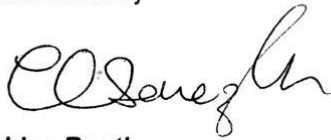
We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/NW/0068

Please quote this number on all correspondence

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

Yours sincerely



pp. **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*

Central Manchester University Hospitals 
NHS Foundation Trust

Research & Development
1st Floor Post Graduate Centre
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL
Tel: 0161-276-4125
Fax: 0161-276-5766

Lynne.Webster@cmft.nhs.uk
<http://efronet.xmhc.nhs.uk/directorates/cephand>

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

Ref: R01593-LI: 2-WRAITH

Dear Professor Wraith

PIN: R01593 (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

Dr Lynne Webster
Head of Research Office

Date: 08/06/2011

Encs (Internal Authorisations)

cc. Miss Elaine Cross
Sarah Leo
Dr Dougal Hare

Documents Acknowledged/Approved

Document	Version Number / Reference	Date
NRES Approval	11/NW/0068	10 March 2011
NHS SSF	Version 3.0	
NHS REC Form	Version 3.0	
NRES Confirmation Conditions Met	11/NW/0068	11 March 2011
Participant Information Sheet: Parents of MPS III Children - Questionnaire Components Only	Version 01	28 th January 2011
Participant Information Sheet: Parents of MPS III Children - All Components	Version 01	28 th January 2011
Participant Information Sheet: Parents of ID Controls	Version 01	28 th January 2011
Participant Information Sheet: Neurotypical Controls - Age 6-10	Version 01	28 th January 2011
Participant Information Sheet: Neurotypical Controls - Age 11-15	Version 01	28 th January 2011
Participant Information Sheet: Parents of Neurotypical Controls	Version 01	28 th January 2011
Consent Form: Behaviour and Family Functioning Controls	Version 01	28 th January 2011
Consent Form: Informed Assent for Mainstream Controls	Version 01	28 th January 2011
Consent Form: Circadian Rhythm and Sleep MPS III	Version 01	28 th January 2011
Consent Form: Circadian Rhythm and Sleep Controls Mainstream	Version 01	28 th January 2011
Consent Form: Behaviour and Family Function MPS III	Version 01	28 th January 2011
Protocol	Version 1	28 th January 2011
Protocol: Risk Issues that Become Apparent Through Data Collected for Research Purposes	Version 1	28 th January 2011
Protocol: Adult Participants Who are in Emotional Distress	Version 1	28 th January 2011
Protocol: Child Participants Who are in Emotional Distress	Version 1	28 th January 2011
GP Letter	Version 01	28 th January 2011
Template for Initial Contact Letter - ID Group	Version 01	28 th January 2011

Version 1.1 - 17:08:09

Letter 2 - RD approval with conditions Aug 2009 MASTER

Template for Initial Contact Letter – Mainstream	Version 01	28 th January 2011
Template for Initial Contact Letter – MPS III Families	Version 01	28 th January 2011
Questionnaire: Eyberg Child Behaviour Inventory		
Questionnaire: Vineland-II Adaptive Behaviour Scales	Second Edition	
Questionnaire: Developmental Behaviour Checklist (DBC-P)		
Questionnaire: General Health Questionnaire		
Questionnaire: General Resilience Scale for Adults		
Questionnaire: Brief COPE		
Questionnaire: Multidimensional Scale of Perceived Social Support		
Questionnaire: Pediatric Inventory for Parents		
Questionnaire: Children's Sleep Habits Rating Scale	Version 1.0	9 th June 2010
Questionnaire: Sanfilippo Behaviour Rating Scale		

Appendix 8

Original project protocol

**Implementing the 'Stepping Stones' Triple-P Intervention with parents of children with
MPS III: effectiveness and acceptability**

*(Short title: Supporting parents of children with MPS III: evaluating the Stepping Stones parenting
programme)*

Research proposal submitted with ethics application to Lancaster REC
September 2012

Rachel Mumford, Dr Dougal Hare, Dr Penny Bunton & Dr Heather Adams

1. Introduction

MPS III (Sanfilippo syndrome) is a rare genetic condition from a group of lysosomal storage disorders; estimates suggest approximately 132 people (aged 3-18 years) live in the UK with MPS III. There are four recognised subtypes of MPS III caused by mutations in one of four different gene locations, each resulting in a different enzymatic defect. (Ruijter *et al.*, 2008). The presentation of MPS III can be divided into three phases. The first phase is characterised by a slowing of development; the third 'end' phase is characterised by immobility, dysphagia and significant medical needs. The second 'active' phase of MPS III initially presents between 2-6 years old and is characterised by a significant decline in cognitive skills, language loss and behavioural problems, including destructiveness, restlessness/agitation, aggression and severe sleep disturbance (Valstar *et al.*, 2008; Bax & Colville, 1995). There has been little research into the functioning of families that support a child with MPS III. Bax & Colville (1995) examined behaviour and family functioning across MPS conditions. They found high rates of behavioural problems across families and concluded that parents received no or little support with behavioural difficulties. Empirical evidence supports this, with the current focus predominantly on medical intervention/management.

The Triple-P positive parenting programme is an evidence-based, multi-level intervention designed to enhance parent's knowledge, skills and confidence. Triple-P has been shown to produce significant reductions in child problematic behaviour (Thomas & Zimmer-Gembeck, 2007). High levels of parental acceptance and satisfaction with the programme have been reported (Sanders, 1999). Stepping Stones Triple-P (SSTP) has been developed specifically for parents of children with a range of developmental disabilities and has demonstrated significant treatment effects in an ASD population and with parents of a child with mild-moderate developmental delay (Plant & Sanders, 2007; Roberts *et al.*, 2006). There have been no studies to date investigating the use of SSTP with conditions involving cognitive/developmental regression.

This study forms part of a substantial research project at the University of Manchester examining various aspects of MPS III. Currently, one aspect of this research is the investigation of family functioning in MPS III, with a view to informing appropriate clinical interventions. The present study therefore aims to evaluate whether Stepping Stones Triple P is an effective and acceptable intervention with an MPS III population. We plan to deliver the manualised SSTP intervention in a group format over a 10-week period. As per the Stepping Stones protocol, this will also include 3 weeks of individual telephone sessions with parents. The study has wider implications for the support and intervention which could be offered to families, alongside medical management of MPS conditions.

2. Aims and objectives

The principal aims of this study are:

1. To evaluate the effectiveness of the Stepping Stones Triple P programme (SSTP) delivered in a group format with parents/primary caregivers of children with MPS III.
2. To assess the impact of SSTP on reported child behaviour and parental variables (inc. family functioning/wellbeing, coping and parental satisfaction/competence).
3. To explore the acceptability of SSTP delivered via a group format and parental satisfaction with the intervention.
4. To evaluate long-term behavioural and parental wellbeing outcomes at 3 and 6 month follow up.

3. Design

As this study is fundamentally a pilot of the effectiveness and acceptability of the Stepping Stones programme with this population, a multiple baseline case series design will be employed. This will involve a 2-4 week baseline period, 10 week intervention and follow up phases. Individual session data will be examined, and outcomes will be compared from pre- to post-intervention and at 3 month and 6 month follow up.

The multiple baseline method controls for potential confounds including maturation, exposure to the clinical situation, repeated testing and regression to the mean; thus increasing the confidence with which any observable changes can be attributed to the intervention. The case series approach is most appropriate given the early stages of this research paradigm. It will involve a small number of participants but detailed multiple measures of psychological wellbeing and child behaviour.

In total, a sample of 8-10 participants will be recruited into the study. As a feasibility study employing a multiple baseline case series design, a sample size of 8 is an acceptable number of participants required (Wells *et al.*, 2009). A formal power calculation is not required as statistics will involve graphical analysis of the data, which does not look for significant differences between groups.

4. Measures

A range of standardized psychosocial measures (listed below) will be utilised. In addition, information on child medical history and participant demographics will also be gathered. These measures will predominantly be obtained from the child's medical records. Parents/legal guardians will be asked for permission to access their child's medical records.

Medical/demographic information will include:

- Child & parent age
- Time point of diagnosis
- Child medical history (inc. treatment to date, significant events/illness, comorbidities)
- Ethnicity
- Socioeconomic information (based on CENSUS data published in relation to participant's postcode)

Standardised measures will comprise of:

1. Eyberg Child Behaviour Inventory (ECBI; Eyberg, 1999): 36 items; assesses intensity and frequency of difficult behaviours and the degree to which parent finds them problematic.
2. Paediatric Quality of Life Inventory (PedsQL; Varni *et al.*, 1999): evaluates child quality of life.
3. PedsQL Family Impact Module (Varni *et al.*, 2004): parents rate the impact of their child's condition on their own well being and family functioning.
4. Brief COPE Inventory (Carver *et al.*, 1989): 28 items assessing parent coping strategies.
5. Being a Parent Scale (Johnston & Mash, 1989): 16 items assessing parenting confidence.
6. Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; Tennant *et al.*, 2007): 14 items assessing positive mental health and wellbeing.
7. Child Adjustment and Parent Efficacy Scale – Developmental Disability (CAPES-DD; Morawska & Sanders, 2010): 30 items assessing frequency of problematic behaviour and parenting confidence.
8. Aberrant Behaviour Checklist (Aman *et al.*, 1986): 58 items assessing difficult behaviours and the degree to which parents find them problematic

Parents/caregivers will be asked to complete all measures at an initial baseline assessment, post-intervention and follow-up (3 and 6 months). Parents/caregivers will then be randomly assigned to either 2, 3 or 4 weeks of weekly no-treatment baseline assessments. During baseline assessments participants will be asked to complete only the Eyberg Child Behaviour Inventory (ECBI), Warwick-Edinburgh Mental Wellbeing Scale and CAPES-DD. The Stepping Stones group intervention will commence following the end of baseline period. All baseline assessment measures will be conducted over the phone with the researcher, Rachel Mumford.

Parents/caregivers will then be asked to complete the ECBI, Warwick-Edinburgh Mental Wellbeing Scale and CAPES-DD prior to every group intervention session.

Participants will complete all measures post-intervention and at 3 and 6 month follow up. Questionnaires will be sent out via post and parents will be provided with a pre-paid, addressed envelope for their return. A standard Triple P satisfaction measure (Client Satisfaction Questionnaire) will be completed post-intervention and at follow up. This will consist of Likert scales to rate satisfaction with the Stepping Stones programme. Additional open-ended questions regarding the acceptability of the programme will also be incorporated to obtain qualitative data.

5. Participants

The aim is to recruit 8-10 parents of children with MPS III who are under the care of St Mary's Hospital, Central Manchester and Manchester Children's University Hospitals NHS Trust. This recruitment target was set in accordance with previous literature utilising a case series design. All parents of children aged 3-10 years will be invited to take part. This specific age range has been chosen as it generally coincides with the 'active' phase of MPSIII in which behavioural difficulties are predominant.

Inclusion criteria:

- Parents/primary caregivers of a child aged 3-10 with a diagnosis of MPS III
- Sufficient English skills to understand Stepping Stones material

Exclusion criteria:

- Child <3 years or >10yrs old or deemed by medical staff to be at end stage of MPS III
- Parent/caregiver has participated in another formal parenting programme within the last 6 months

6. Procedure

6.1 Recruitment and consent (see Figure 1)

Potential participants will be made aware of the project by a general letter and participant information sheet sent to families from the administration of St Mary's Hospital, Central Manchester and Manchester Children's University Hospitals NHS Trust. Parents may also be made aware of the project by a member of their child's existing care team at St Mary's hospital during regular hospital clinics. The letter will briefly outline the study and families will be asked to make contact with the research team (via phone, email or post) or to inform a member of their child's existing care team if they would like to take part. A phone call will then be arranged with interested families to allow the researcher to explain the study in more detail and provide the opportunity for parents to ask any questions about the study. Parents will be given time to consider their participation if needed and, if they want to take part, either a home visit or meeting at hospital clinic will be arranged in order to complete consent forms and the initial assessment measures. At this point consent will also be sought from parents/primary caregivers to access their child's medical records in order to obtain medical and demographic data. This is to reduce the amount of information requested from parents in questionnaire format. We will also ask a nurse practitioner independent from the research team to be available to families should they want to discuss the project.

Recruited families will have an allocated baseline period of between 2 to 4 weeks before starting the intervention. During this time they will complete the ECBI, Warwick-Edinburgh Mental Wellbeing Scale and CAPES-DD weekly to establish a stable baseline score. Due to time constraints, the first two participants recruited will have a 4 week baseline, the second two will have a 3 week baseline, the third two will have a 3 week baseline and the fourth two will have a 2 week baseline. Once a stable baseline is established, all participants will be invited to attend the first group Stepping Stones session and intervention sessions will commence. At the first session parents will be provided with the group Stepping Stones resources.

6.2 Intervention

Following the baseline period, parents will take part in 10 sessions of the manualised Stepping Stones Triple P intervention delivered in a group format with other parents of a child with MPS III (see Appendix A for an outline of session content). Sessions will be facilitated by Rachel Mumford (Trainee Clinical Psychologist)

supervised by Dr Penny Bunton (Clinical Psychologist). 25 'core strategies' for managing behaviour will be outlined, as well as a specific session on parenting well-being. The intervention will be delivered over a 10 week period and groups will take place at Royal Manchester Children's Hospital. As per the Stepping Stones protocol, within the 10 week period 3 of the weeks will involve individual telephone sessions with parents (rather than attending a group session) to focus on and provide support for their specific concerns. Given the flexibility of the mode of delivery of the intervention sessions, parents will be consulted regarding their preferences for the time of the group. This will include considering whether for the group sessions parents prefer:

- a) weekly 2 hour groups or
- b) fortnightly/monthly 4 hour groups.

Parents will be asked to complete the ECBI, CAPES-DD and Warwick-Edinburgh Mental Wellbeing Scale prior to each group session. During the 3 weeks of individual telephone sessions, parents will complete these measures over the phone with the researcher. Post-intervention measures will be collected one week after the final intervention session.

7. Data analysis

Collated data will be entered onto a password protected database, encrypted via the University of Manchester. All data will be collected and stored in accordance with the Data Protection Act 1998.

This is a pilot case series study and so formal statistics will not be calculated. Based on previous published multiple baseline case series (Fisher & Wells, 2008; Wells *et al.*, 2009), graphical representation and descriptive statistics will be the predominant form of analyses to determine intervention effect. Individual data will be plotted to allow for visual inspection of any changes in scores over the baseline, treatment and follow up phases. Effect sizes and clinical significance of changes will be calculated where possible and, depending on normality of distribution, correlated t-tests could be used to supplement visual analysis of data. Data regarding participant satisfaction with the intervention will also be subject to quantitative and qualitative analyses.

8. Ethical issues

8.1 Consent

Parents/caregivers will receive a detailed information sheet that outlines the nature of the study and the implications for participants. Participants will be given an adequate amount of time to consider their decision to participate in the study or not. It will be made particularly clear to participants that their decision regarding participation will not affect their child's medical care in any way. This issue will be highlighted in the participant information leaflet and also reiterated verbally when parents/caregivers initially contact the research team. Furthermore, parents/caregivers will be made aware that they can drop out of the study at any time and that this will not affect their child's medical care.

8.2 Confidentiality and anonymity

Participant information will be kept strictly confidential at all times. Identifying participant information (e.g. their names) will be given a confidential ID number and only members of the research team will have the corresponding participant details to this identifier. All researchers will act in accordance with NHS policies and guidelines at all times. In the case of possible risk to self and others information will be shared as necessary (see Appendix B for risk protocol). Participants will be made aware of this at the start of their initial assessment with the research team.

8.3 Participant burden and distress

Some parents/caregivers may find completing the questionnaires or participating in the intervention distressing at times. As a trainee clinical psychologist, the researcher delivering the intervention has experience in working with and minimising any such distress. They will also be able to contact their supervisor, where necessary, for advice in such situation. In some cases, it may be that a response on questionnaires or discussion during intervention sessions highlights significant emotional distress and the

need for further psychological support. A distress protocol (Appendix C) has been developed for this situation.

As much as possible, the timing of the parent group sessions will be arranged to suit families. The researchers are consulting with all parents interested in taking part regarding their preferences about the time of the group. There is also flexibility as to whether parents would prefer i) weekly 2-hour group sessions or ii) fortnightly 4-hour group sessions. The number of questionnaires parents/caregivers have been asked to complete has been carefully considered in order to minimise burden, whilst still obtaining sufficient data for a baseline design and analysis.

8.4 Standard care

Parents/caregivers taking part in the study will not affect the standard medical care that is available to their child. Participants are free to withdraw from the study at anytime and this also will not affect the standard care available to their child. However, parents/caregivers will not be able to participate in another parenting intervention at the same time as receiving the Stepping Stones intervention. Engaging in two interventions is likely to lead to confusion for both the client and the researchers and would confound results regarding the effectiveness of the Stepping Stones intervention.

8.5 Dissemination of findings

Feedback and dissemination of all results will be offered to all parents/caregivers and to the wider MPS III population via the MPS III society and presentation at the annual MPS conference, which many parents attend. These findings will also add to the evidence base, through submission to an appropriate journal.

9. Key references

Bax, M, & Colville, G.A. (1995). Behaviour in mucopolysaccharide disorders. *Archives of Disease in Childhood*, 73, 77-81.

Plant K, Sanders M. (2007). Reducing problem behavior during care-giving in families of preschool-aged children with developmental disabilities. *Research in Developmental Disabilities*.;28:362-384.

Roberts C, Mazzucchelli T, Studman L, *et al.* . (2006). Behavioral family intervention for children with developmental disabilities and behavioral problems. *Journal of Clinical Child & Adolescent Psychology*. 35(2):180-193.

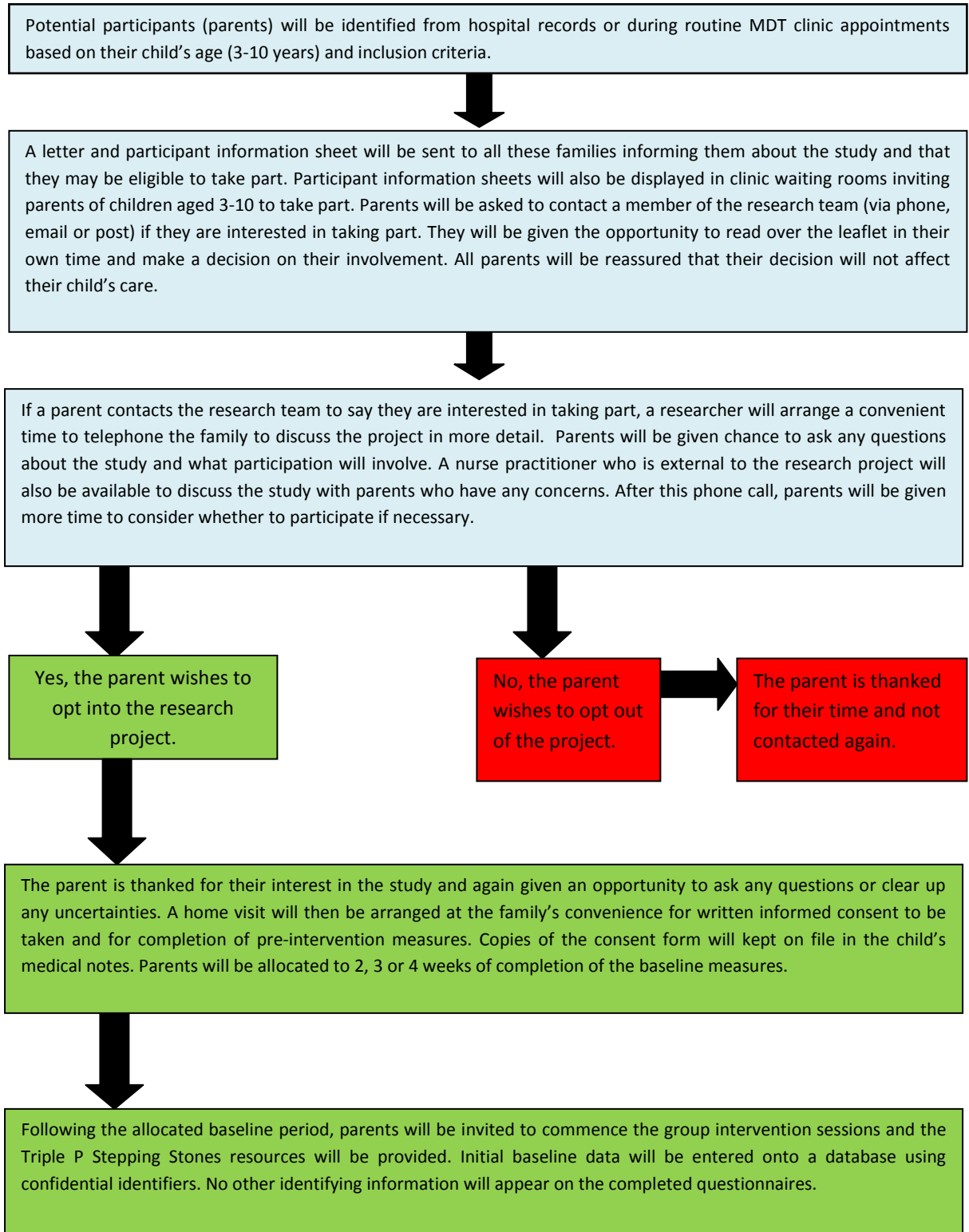
Rutter, G.J.G., Valstar, M.J., Van de Kamp, J.M., Van der Helm, R.M., Wevers, R.A., Poorthuis, B.J.H.M., Van Diggelen, O.P., Pshezhetsky, A.V., Wiiburg, F.A. (2007). Clinical course and molecular analysis of 29 Dutch patients with Sanfilippo type C (MPSIIIC) disease. *Journal of Inherited Metabolic Disease*, 30, 99-99.

Sanders, M. R. (1999). Triple P- positive parenting program: Towards an empirically validated multilevel parenting and family support strategy for the prevention of behaviour and emotional problems in children. *Clinical Child and Family Psychology Review*, 2, 71–90.

Thomas, R. & Zimmer-Gembeck, M.J. (2007). Behavioral Outcomes of Parent-Child Interaction Therapy and Triple P—Positive Parenting Program: A Review and Meta-Analysis. *J Abnorm Child Psychol*, 35, 475–495.

Whittingham, K., sofronoff, K., Sheffield, J. & Sanders, M.R. (2009). Stepping Stones Triple P: An RCT of a parenting programme with parents of a child diagnosed with an autism spectrum disorder. *J Abnorm Child Psychol*, 37, 469-480.

Figure 1: Flow chart of recruitment process



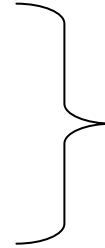
Appendix A: Outline of session content

Session 1 (group format)

*Meet other parents
'Get to know you' exercises
Sharing experiences*

Session 2 (group format)

Introduction to Triple P and Positive Parenting ideas



To be combined into
1x4 hour session

Session 3 (group format)

Promoting children's development

Session 4 (group format)

Teaching new skills and behaviours



To be combined into
1x4 hour session

Session 5 (group format)

Managing difficult behaviour and parenting routines

Session 6 (group format)

*Planning ahead for individual sessions
Parental wellbeing*



To be combined into
1x4 hour session

Sessions 7– 9 (individual telephone format)

*Implementing parenting routines
Focus on specific concerns of parents*

Session 10 (group format)

*Programme close
Summary of session content*

Appendix B: Risk protocol

Supporting parents of children with MPS III: evaluating the Stepping Stones parenting programme

Protocol for identified risk issues

(risk is deemed to include potential harm to self or others)

Preventative strategy

Parents will be made aware of the limits of confidentiality on the participant information sheet.

Intervention

Although the research includes an intervention component, the researcher (Trainee Clinical Psychologist) will not provide any direct therapeutic input beyond the scope of the manualised Stepping Stones intervention if a significant risk arises.

Reactive strategy – action to be taken

If a potential risk issue is identified then immediate consultation will be sought with academic supervisors, Dr Dougal Hare or Dr Penny Bunton, who are both Clinical Psychologists with extensive experience of working with families. Depending on the outcome of this consultation, the family involved may be contacted and asked to contact their GP for additional support. In addition, we will send a brief letter to their GP highlighting the issue of concern, which the family will also receive a copy of. If there is deemed to be imminent risk of harm to self or others, immediate contact will be made with social services or community mental health team as appropriate.

As the project involves a parenting intervention, identified risks may relate to child protection issues. In this instance, we would undertake our legal obligation to report this to social services or the safeguarding team at Central Manchester and Manchester Children's University Hospitals NHS Trust. Participating parents would be informed of the actions we had taken, but may not necessarily receive a copy of all correspondence.

Appendix C: Distress protocol

Supporting parents of children with MPS III: evaluating the Stepping Stones parenting programme

Protocol for participants who are in emotional distress

(distress will be deemed to include major acute distress and long-term psychological distress)

Preventative strategy

At the outset all parents will be provided with a list of agencies to contact for additional information and support following the active intervention stage. The likelihood of participant distress is also mitigated by the use of an evidence-based manualised intervention, which has been found to be acceptable to parents in previous research studies. Parents will also be prepared for the likely content of sessions beforehand and, as a Trainee Clinical Psychologist, the researcher will be able to use their clinical skills to approach any difficult topics in a sensitive manner.

Intervention

As the research includes an intervention component, the researcher (a Trainee Clinical Psychologist) may provide direct input if emotional distress is identified (for example, using supportive empathic statements, problem-solving strategies and drawing on the content of Stepping Stones session 5 on 'parental wellbeing'). If parents become upset during session, they will be offered the opportunity to stop the session and reschedule or to take a break from the session. Episodes of parental distress will be monitored and discussed in supervision where necessary.

Reactive strategy – action to be taken

Participating parents, who are deemed to show continued **significant** emotional distress during sessions, or where concerns arise in relation to parental mental health, will be encouraged to contact their GP and will be helped to do so if they wish. The decision to access help will remain with the parent. The researcher will ensure that the parent has a GP before commencing intervention. If it is out of hours and the emotional distress is deemed to be significant, the parent will be directed to the emergency GP 'out of hours' service. Again they will be assisted with this if necessary.

If the parent shows a level of emotional distress deemed by the researcher to put them at risk of imminent harm to self or others, then an appropriate contact will be made with their GP, social services or community mental health team. Parents will be made aware of this on the participant information sheet.

Appendix 9

Evidence of approval for original project
(NHS Research Ethics committee and NHS R&D)



Health Research Authority
National Research Ethics Service

NRES Committee North West - Lancaster
HRA NRES Centre - Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7818
Facsimile: 0161 625 7299

26 September 2012

Miss Rachel Mumford
Trainee Clinical Psychologist
Manchester Mental Health and Social Care Trust
Division of Clinical Psychology
Zochonis Building, 2nd Floor
Oxford Road, Manchester
M13 9PL

Dear Miss Mumford

Full title of study: Implementing the 'Stepping Stones' Triple-P Intervention with parents of children with MPS III: effectiveness and acceptability.

REC reference number: 12/NW/0653

IRAS reference: 98709

Thank you for your letter of 26 September 2012. I can confirm the REC has received the documents listed below as evidence of compliance with the approval conditions detailed in our letter dated 13 September 2012. Please note these documents are for information only and have not been reviewed by the committee.

Documents received

The documents received were as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Letter of invitation to participant	2	26 September 2012
Participant Consent Form	2	26 September 2012

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.

12/NW/0653

Please quote this number on all correspondence

Yours sincerely

A handwritten signature in black ink, appearing to read 'C Ebenezer', written in a cursive style.

Mrs Carol Ebenezer
Committee Co-ordinator

E-mail: nrescommittee.northwest-preston@nhs.net

Copy to: *Ms Lynne Macrae,*
Ms Alison Robinson, R&D Central Manchester University Hospitals NHS
Foundation Trust

Research Office
1st Floor Post Graduate Centre
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL
Tel: 0161-276-3565
Fax: 0161-276-5766

Dr Simon Jones
Consultant in Paediatric Metabolic Diseases
Genetic Medicine
6th Floor
St. Mary's Hospital
Oxford Road
Manchester
M13 9WL

Ref: R03040-Ltr 2-JONES

Dear Dr Jones

PIN: R03040 (Please quote this number in all future correspondence)

REC Reference: 12/NW/0653

Research Study: Implementing the 'Stepping Stones' Triple-P Intervention with parents of children with MPS III: effectiveness and acceptability

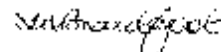
Thank you for submitting the above study for NHS R&D permission. The University of Manchester is the Sponsor for this study which is not on the NIHR portfolio.

I am pleased to confirm that the Research Office has now received all necessary documentation, and the appropriate governance checks have been undertaken. This letter is issued subject to the research team complying with the attached conditions, Trust SOPs, the DH Research Governance Framework, and any other applicable regulatory requirements. This approval is in relation to the documentation listed.

This study is classed by the DH as a clinical trial and as such CMFT are required to report whether the research was initiated within 70 days or provide valid reasons for not doing so. The approval has been subject to delays so recruitment of the first patient should be by 19th December 2012 in order to meet the 70 day recruitment target or 23rd December 2012 if this is not possible. Please notify Sophia Lockwood the date when the first patient was recruited.

I would like to take this opportunity to wish you well with your research.

Yours sincerely



Lorraine Broadfoot
Research Operations Manager

Date: 23rd November 2012

Appendix 10

Recruitment letter and participant information sheet for original project

Department of Clinical Genetics
6th Floor, St Mary's Hospital
Oxford Road
Manchester
M13 9WL

Dear >insert parent name<,

[Supporting parents of children with MPS III: evaluating the Stepping Stones parenting programme](#)

We are writing to you to inform you about the above named research study involving parents of children with a diagnosis of MPS III that is being conducted in conjunction with the University of Manchester. We are writing to you specifically as you are eligible to take part because your child is aged between 3-10 years old.

Our aim is to find new ways of supporting parents of children with MPS III. We understand that having a child with MPS III can be a stressful experience and we know that some children can display behaviour that can be difficult to manage at times. We want to see if the 'Triple P Stepping Stones' parenting programme, which has been specifically developed for parents of a child with a developmental disability, can be helpful for families of a child with MPS III. This would involve taking part in a group with other parents of children with MPS III over a 10-week period to complete the Stepping Stones programme with a trained practitioner. As we know that families often have lots of appointments to attend, we will make the time of the group sessions as flexible as possible. The group will be run at Royal Manchester Children's Hospital.

Please find enclosed a participant information sheet which explains the proposed project in more detail. If you are interested in taking part, please take the time to read over this information leaflet and consider your decision.

We are asking that **you make initial contact** with the research team to let them know that you might be interested in taking part. You can contact us by phone (...), email (rachel.mumford-2@postgrad.manchester.ac.uk) or post (The University of Manchester, 2nd Floor Zochonis Building, Brunswick Street, Manchester, M13 9PL). Alternatively, you can also let a member of your child's existing medical team at St Mary's Hospital know that you are interested in taking part and then we will get in touch with you.

We will arrange to telephone you at a convenient time to discuss the project in more detail and answer any questions that you have.

Thank you for taking the time to read this letter and we look forward to hearing from you,

Yours sincerely,

Rachel Mumford
Trainee Clinical Psychologist
University of Manchester

Supporting parents of children with MPS III: evaluating the Stepping Stones parenting programme

INFORMATION FOR PARTICIPANTS

Thank you for taking the time to read this leaflet. You are invited to take part in a research study for parents of children with MPS III. It is important for you to understand why the research is being done and what it will involve. To help you decide whether or not to take part, this leaflet outlines why the research is being done and what it would involve for you. Please take your time to read this leaflet carefully and discuss it with others if you wish. Feel free to ask us if there is anything that is not clear, or if you would like more information. Contact details are provided at the end of this leaflet.

What is the purpose of the study?

We understand that having a child with MPS III can be a stressful experience at times. We know that some children can display behaviour that can be difficult to manage. This study aims to find new ways of supporting parents of children with MPS III.

The Positive Parenting Programme (Triple P) is designed to help parents manage a wide range of parenting concerns, like difficult behaviours and sleep problems. There is lots of research across the world that supports the Triple P approach. A version of Triple P, called Stepping Stones, has been developed to specifically help parents of children with a developmental disability. We want to see if running a Stepping Stones parent group can be helpful for parents of a child with MPS III.

Why have I been invited to take part?

We are asking all parents/guardians of children aged 3-10 years with a diagnosis of MPS III who are under the care of St Mary's Hospital in Manchester to take part.

Do I have to take part?

No. Entry to the study is entirely voluntary. It is your decision whether or not to take part. You should not feel under any pressure to make a decision. If you do decide to take part you will be asked to sign a consent form to indicate your agreement. Even after signing you can change your mind at any time without giving a reason. This will not affect the care that your child receives now or in the future in any way.

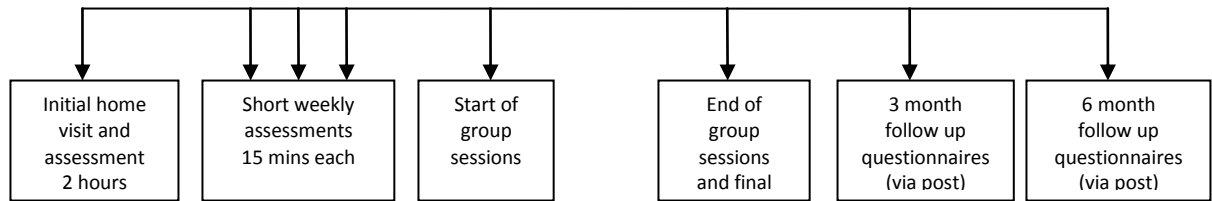
If you do initially decide to take part and then withdraw from the study, it would be useful for us to use any information received from you up to the point of withdrawal. We will ask for your permission to do this, but we will not use your information without your consent.

What happens if I think I want to take part?

Making initial contact

Firstly, we ask that you contact the research team to let them know you are interested in taking part. We will then arrange to speak to you over the phone to discuss the study in more detail and give you the opportunity to ask any questions.

Study timeline



Home visit and assessments

If you agree to take part, we will then arrange a home visit at your convenience so we can meet you in person, answer any additional questions about the study and complete some initial assessment questionnaires. This home visit may last approximately 2 hours. At this time we will also ask you to sign a consent form and will ask for your permission to access relevant sections of your child's medical records to obtain medical history and demographic information. If you prefer we will ask you for this information instead.

Short weekly assessments

After this initial visit, we will ask you to complete a series of shorter weekly assessments over the phone with the main researcher, Rachel Mumford. You will be allocated a set number of weeks (between 2-4 weeks) for completing these short assessments. This will involve completing three of the same questionnaires from the initial home visit and should only take approximately 15 minutes. We will arrange the phone call at your convenience. These short assessments are necessary as they provide us with detailed information about your family's experiences before starting the Triple P Stepping Stones group. This information will help us identify if the Stepping Stones programme we are offering is useful to parents.

Start of Stepping Stones parent group

After your last short assessment, you will be invited to come to the first session of the Stepping Stones parent group. The group will be run at Royal Manchester Children's Hospital. We anticipate that there will be 8-10 parents all starting the group at the same time. At this point we will also provide a number of Stepping Stones resources for you to use during the group. The group will be lead by Rachel Mumford (Trainee Clinical Psychologist) and will focus on the main difficulties that parents are experiencing at that time and helping them to develop new ways of managing difficult behaviour and situations. We plan to run the parent group over a 10 week period. Within the 10 week period, 3 of the weeks will involve individual telephone sessions with parents (rather than attending a group session) to focus on and provide support for your specific concerns. We know that families often have lots of appointments to attend; therefore we will consult with all parents who plan to take part in the group and ask for their preferences about the time of the group sessions. This will include considering whether you would prefer:

- a) a weekly 2 hour group or
- b) a fortnightly 4 hour group.

Before that start of each parent group session we will ask you to complete the same three questionnaires as in the short assessments, taking about 15 minutes.

Assessment & evaluation after the group

At the end of the 10-week programme, we will ask you to complete the same questionnaires as in the initial assessment. This will help us to find out whether the Stepping Stones programme has been helpful. We will also ask you to complete an additional questionnaire about your satisfaction with the Stepping Stones parenting programme. For your convenience, we will ask that you complete these questionnaires in your own time and return them via post. We will provide a stamped addressed envelope for their return. However, if you would prefer then a home visit with the researcher can be arranged to complete the questionnaires. Following this, we will write to you again at 3 and 6 months after the end of the programme

and ask you to complete the same questionnaire measures again via post. We will provide a stamped addressed envelope for their return. This will help us find out about the effects of the Stepping Stones programme over a longer period of time.

What are the possible benefits of taking part?

The Stepping Stones parenting programme has previously been shown to reduce difficult child behaviour and parent stress levels, alongside increasing parenting confidence. It is hoped that taking part in the intervention will help parents to develop new strategies for dealing with difficult behaviour/situations and to feel supported in doing so. We hope that the study will help services to develop a better understanding of the experiences and feelings of parents of children with MPS III.

In the longer-term, the results of the study will help with the development of 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.

What are the possible disadvantages of taking part?

Parents must make the time to complete the assessments and attend the parent group sessions. We will make this as convenient as possible, by visiting you at home for the initial assessment and being as flexible as possible for parents when organising the time of the group.

Some people may find it upsetting to fill in questionnaires in relation to their child's behaviour or their own wellbeing. The research team are specifically trained to help people deal with distress and will be available to talk to. A list of agencies will be provided who can offer additional information/support after the intervention is finished.

Will my taking part be confidential?

Yes. All the information collected during the course of the research will be kept strictly confidential; no one outside of the study team will see your information. All your data from the study will be identifiable by a personalised number only and will be kept in a securely locked filing cabinet on the University of Manchester premises.

Data will be entered onto a computer database that will be password protected and encrypted. Each participant will be assigned a number and therefore no names will 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 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 always speak to you first about this.

What will happen to the results of the research study?

The results of the study will be published in scientific and clinical journals. Presentations may also be given at scientific conferences. All data will be anonymous and no names or any other information that might identify individual participants will be published. If you wish to know the outcome of our research, we will be happy to discuss this with you and/or supply a copy of the article should you wish.

Who is organising the research?

This research is being conducted by Rachel Mumford, Trainee Clinical Psychologist, as part of the Doctorate in Clinical Psychology at the University of Manchester. It will be carried out under the guidance of Dr Dougal Hare and Dr Penny Bunton (Academic Supervisors at the University of Manchester) and Dr Simon Jones and Professor Ed Wraith (Clinical Supervisors at St Mary's Hospital). Dr Heather Adams, a psychologist at the University of Rochester Medical Center (USA) is also a co-investigator with the research team. Any data shared with Dr Adams will be completely anonymous and will be identifiable by a confidential number only.

Who has reviewed the study?

All research in the NHS is reviewed 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 approved by the Ethics Committee.

What if there is a problem?

If you have concerns or complaints about any aspect of this study, you can ask to speak to one of the researchers who will do their best to answer your questions.

Alternatively, if you remain unhappy and wish to complain formally, you can do this through the University of Manchester complaints procedure (research-governance@manchester.ac.uk; 0161 275 8093) or by contacting the Patient Advice and Liaison Service (PALS) at Central Manchester Foundation Hospitals NHS Trust by phone (0161 276 8686) or email (pals@cmft.nhs.uk).

Further information

If you have any questions, concerns or would like further information about the study at any point you can also contact a member of our research team by the following means: by phone (07534 384954), email (rachel.mumford-2@postgrad.manchester.ac.uk) or post (The University of Manchester, 2nd Floor Zochonis Building, Brunswick Street, Manchester, M13 9PL).

Please keep this information sheet. Thank you for taking the time to read it.

Appendix 11

Evidence of approval for ethics amendment



Health Research Authority
National Research Ethics Service

NRES Committee North West - Lancaster

HRA NRES Centre - Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Tel: 0161 625 7818
Fax: 0161 625 7299

13 February 2013

Miss Rachel Mumford
Trainee Clinical Psychologist
Manchester Mental Health and Social Care Trust
Division of Clinical Psychology
Zochonis Building, 2nd Floor
Oxford Road, Manchester
M13 9PL

Dear Miss Mumford

Study title: Implementing the 'Stepping Stones' Triple-P Intervention with parents of children with MPS III: effectiveness and acceptability.
REC reference: 12/NW/0653
Amendment number: 1
Amendment date: 06 February 2013
IRAS project ID: 98709

Firstly, with regards to the recruitment process (section A27.1), it is requested that a member of the child's existing care team at St. Mary's Hospital (e.g. Clinical nurse specialist) is able to make contact with families to ask their permission to be contacted over the phone by a member of the research team about the research. Secondly, it is requested that an additional interview aspect be added to the research project for parents who have decided not to take part in the group if there is minimal uptake of the group.

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

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:

Document	Version	Date
Participant Consent Form: interview	1	06 February 2013
Participant Information Sheet	2	06 February 2013
Protocol	2	06 February 2013
Notice of Substantial Amendment (non-CTIMPs)	1	06 February 2013

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.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

12/NW/0653:	Please quote this number on all correspondence
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Yours sincerely



pp.
Dr Lisa Booth
Chair

E-mail: nrescommittee.northwest-lancaster@nhs.net

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

Copy to: *Ms Alison Robinson, R&D Central Manchester University Hospitals
NHS Foundation Trust
Ms Lynne Macrae*