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Sleep in children with Smith-Magenis syndrome; a case-control actigraphy study

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Abstract

Study Objectives:1) To compare both actigraphy and questionnaire assessed sleep quality and timing in children with Smith-Magenis syndrome (SMS) to a chronologically age-matched typically developing (TD) group. 2) To explore associations between age, nocturnal and diurnal sleep quality and daytime behaviour.

Methods: Seven nights of actigraphy data were collected from 20 children with SMS (mean age 8.70; SD 2.70) and 20 TD children. Daily parent/teacher ratings of behaviour and sleepiness were obtained. Mixed linear modelling was used to explore associations between total sleep time and daytime naps and behaviour.

Results: Sleep in children with SMS was characterised by shorter total sleep time (TST), extended night waking, shorter sleep onset, more daytime naps and earlier morning waking compared to the TD group. Considerable inter-daily and inter-individual variability in sleep quality was found in the SMS group, so caution in generalising results is required. An expected inverse association between age and TST was found in the TD group, but no significant association was found for the SMS group. No between group differences in sleep hygiene practices were identified. A bidirectional negative association between TST and nap duration was found for the SMS group. In the SMS group increased afternoon sleepiness was associated with increased irritability ($p=.007$) and overactivity ($p=.005$).

Conclusion: These findings evidence poor sleep quality in SMS and the need to implement evidence-based interventions in this population.

Keywords: Smith-Magenis syndrome, actigraphy, sleep, intellectual disability, behaviour

Statement of significance: Smith-Magenis syndrome (SMS) is characterised by circadian rhythm abnormalities, however research investigating the impact of circadian rhythm disturbance on children's sleep is limited. Children with SMS experience both daytime sleepiness and behavioural difficulties, but their relationship has not been studied. We described actigraphy data which contrasts sleep of children with SMS to that of age-matched typically developing children. Using temporal analysis, we identified a relationship between behavioural difficulties and daytime sleepiness and a hypothesised homeostatic relationship between nocturnal and diurnal sleep in SMS. Implications for intervention include individualised assessment of sleep for children with SMS given variation in sleep quality between children and a combination of behavioural (e.g. nap restriction) and pharmacological approaches to improve sleep quality.

Introduction:

Smith-Magenis syndrome (SMS) is a rare genetic syndrome, associated with near universal sleep disturbance[1]. Genetic specificity of pathways for sleep disturbance in SMS have been proposed as the *RAI1* gene on chromosome 17p 11.2, which is haploinsufficient in SMS, is implicated in the transcription of the circadian locomotor output cycles kaput (*CLOCK* gene), which regulates the expression of genes responsible for the regulation of the circadian rhythm [2] . Understanding the profile, impact and cause of sleep disturbance in this genetically homogenous group has the potential to further our understanding of aspects of more general sleep physiology, in addition to improving our ability to intervene effectively to improve sleep in SMS.

SMS occurs in 1/25000 live births [3]. Notable features of SMS include a mild to moderate intellectual disability, midface hyperplasia, infantile hypertonia, retinal, cardiac, renal and limb anomalies and sleep disturbance [4,5] . Typically developing children exhibit low levels of melatonin during the daytime and then the levels increase significantly from about 1900hr reaching maximal levels by 0300hr. These peak overnight melatonin levels are highest between the ages of 1-3 years (329.5 ± 42.0 pg/mL) [6] and then start to decline during puberty [7] (67.1± 13.4 pg/mL by the end of puberty). Children with SMS are reported to have an inversion of their circadian rhythm, with four studies describing melatonin synthesis in SMS peaking during the daytime [8-11]. The 24-h melatonin profiles of individuals with SMS show significant interindividual variations [8,11] but in most studies are described as 'inverted',[8 10] with melatonin levels rising from low night-time levels around 0600 hr, reaching a maximal level by 1200 hr and falling again to low levels by 2000 hr [8]. Therefore, the melatonin levels in most children with SMS exhibit a circadian rhythm with elevated levels during the daytime and very low levels during the night-time [8,9].

In keeping with the melatonin profiles parent reports suggest that the sleep schedule in SMS is advanced; bedtimes for children aged 4-17 years range between 8pm-9pm and morning waking from 4am to 6.30 am (mean 5.30 am), with increased early morning waking relative to typically developing (TD) children and children with other neurodevelopmental disorders [8,12] . There have been limited objective studies of sleep in children with SMS.

Total sleep duration in children with SMS has been assessed using actigraphy in two studies, including eight and 12 children with SMS, which both found reduced total sleep time compared to age-matched controls [5,8] . A polysomnography study of 28 children and adults with SMS, demonstrated that the total sleep time for 43% of the sample was less than seven

hours and that 89% of individuals had more than 10 spontaneous awakenings throughout the night [10].

In existing studies there is inconsistency in the reporting of sleep parameters, and timing of the sleep period and the proportion of the night spent awake are often not reported. The present study uses actigraphy to provide a detailed description of sleep disturbance in children with SMS compared to TD children. Actigraphy and parental diaries are ideal methodologies to assess nocturnal and diurnal sleep in children with SMS, as they are less invasive and more ecologically valid than polysomnography and can capture sleep/wake cycles over a longer period of time [5]. A recent review concluded that actigraphy is 'currently the most appropriate measure available to objectively record general sleep patterns in the non-laboratory setting as an alternative to polysomnography' [13] (Van de Water et al., p. 198).

Whilst children with SMS clearly demonstrate reduced total sleep time compared to their TD peers, authors in one study argue that SMS children compensate for part of their reduced total sleep time by napping during the daytime [5]. Given the reported early afternoon melatonin peak, children's propensity to nap could result from either "sleep debt", a build-up of "sleep pressure" according to the homeostatic process underlying sleep-wake cycles or as a result of circadian influence, the daytime melatonin peak, or a combination of both (two-process model [14]). In TD toddlers, there is a homeostatic relationship between diurnal napping and nocturnal sleep quality, as sleep efficiency was significantly improved following diurnal nap restriction [15].

Existing actigraphy studies have used siblings as controls for children with SMS, which compares children in a matched environment [16] .However, the inclusion of community-recruited controls elucidates on what might be considered typical sleep for an age-matched

child. As sleep has a developmental trajectory it is important that groups are age-matched. Using multi-level modelling to account for variance across assessment days and participants, the present study will explore the relationships between sleep and behaviour in SMS. This is important given the call for interventions to improve behaviour in SMS to address underlying sleep disturbance [17], therefore more research between sleep disturbance and behaviour in this group is required. The present study will address the limitations of existing literature by reporting actigraphy assessed sleep quality, timing and variability from one of the largest age-matched case-control samples of children with SMS to date.

Aims of this study

1. To compare actigraphy-assessed sleep quality parameters (onset latency, sleep onset and offset time, sleep duration, duration of night waking and sleep efficiency) between children with SMS and TD children.

2. To compare the variability in children's sleep quality across the assessment period in the SMS and TD groups.

3. To explore the bidirectional relationship between nocturnal and diurnal sleep duration to elucidate on the hypothesised role of sleep homeostasis in SMS.

4. To compare sleep hygiene practices and prevalence of excessive daytime sleepiness between the SMS and TD groups.

5. To contrast the relationships between sleep quality and sleep timing with age between children with SMS and TD children.

6. To explore the relationship between daytime sleepiness and overactivity and impulsivity and irritability in SMS.

Method

Study design and population

Children with SMS aged 4-15 years (N=26) were recruited to the study. Six children were unable to tolerate the Actiwatch for four or more nights, so this manuscript refers to data from 20 participants. The mean age of the SMS group was 8.70 (SD 2.70). All children attended school or nursery for at least three half days in the week, and were confirmed to have difficulty with sleep and an SMS confirmed deletion according to parent/carer report [a]. Children with SMS were matched on age and gender with TD children (see Table 1; TD mean age 9.06, SD 3.32). Children with SMS were recruited through an existing database of families who had provided consent to be contacted about research studies and through the Smith-Magenis syndrome Foundation UK. TD children were recruited through families and friends of researchers at the Cerebra Centre for Neurodevelopmental disorders. Children were recruited with the intention of representing sleep quality in the TD population, and consequently the following exclusion criterion was applied to the TD group: having a statement of special educational needs considered by a clinical psychologist to impact upon sleep quality, e.g. hemiplegia and ADHD. None of the children in the TD group scored above the cut-off for autism spectrum disorder on the social communication questionnaire [18]. Actigraphy and questionnaire data for 45 TD children were collected and subsequently 20 children closest in age, followed by gender were matched to the children with SMS following the SMS group data collection. This study was approved by the University of Birmingham. Informed consent was obtained from parents. For ethical reasons, participants were not asked to discontinue any medications in order to participate in this observational study.

Measures

[a] Interpretation of difficulty with sleep was left to the discretion of parents

A background questionnaire was completed by parents to collect information about children's medication use and family income. Daily timing of melatonin administration was not collected, however, average bedtime was the time inferred for melatonin administration. These data are presented in Table S2.

Adaptive abilities in the SMS group were assessed using the Vineland Adaptive Behavior-2 Interview (VABS [19]; Sparrow, 2011) to include receptive, expressive and written communication, personal, domestic, community, interpersonal relationships, play and leisure, coping skills and gross and fine motor skills. An overall developmental age score was derived by averaging these 11 scores, adapting the method used previously [20] . No measure of ability was used in the TD group; chronological age was assumed to be commensurate with developmental age as no statements of additional learning needs were indicated.

Sleep disturbance and sleep hygiene questionnaires

Severe sleep disturbance was assessed using the Modified Simonds and Parraga sleep questionnaire (MSPSQ [21,22]) which has been validated for use with individuals aged 2 to 16 with an autism spectrum disorder [22]. The presence of severe night waking, settling problems and early morning wakings were derived from this questionnaire based on the frequency (many times a week or daily) and intensity of the problems (e.g. night waking- takes over a few minutes to fall back to sleep; settling- takes over an hour to fall asleep).

Excessive daytime sleepiness was assessed using the modified Epworth Sleepiness Scale (MESS [23]). Parents/carers rate the likelihood of their child falling asleep in eight different situations (0 to 3), with high scores indicating a greater likelihood of falling asleep. The questionnaire is based on the Epworth Sleepiness Scale (ESS) for adults. The ESS has good reliability and validity [24]. The MESS has been used previously with children with intellectual

disabilities and neurodevelopmental disorders[23]. As a proportion of children with neurodevelopmental disorders are nonverbal, the question referring to 'sitting quietly and talking to someone' was modified by the authors to include 'sitting quietly and talking to or interacting with someone'. Wording for each question is presented in Table S1. Seven out of the eight questions used in the MESS in the present study are similar to those used in a validation study of the Epworth Sleepiness Scale for Children and Adolescents with individuals aged 12-18 years, which showed strong test-retest reliability and high internal reliability[25]. In the present study a cut off score of >10 was used to identify children at risk of excessive daytime sleepiness.

Sleep hygiene was assessed using the Family Inventory of Sleep Habits (FISH [26]) developed from a sample of children with autism spectrum disorder. Items were scored on a five-point Likert scale, with higher scores indicating better sleep habits. The test-retest reliability of the measure with children with ASD is .83, and in the TD population is .59. The FISH also has good external validity with measures of childhood sleep [25].

Actigraphy

Sleep quality was assessed using the Actiwatch 2, manufactured by Philips Respironics. This accelerometer's sampling rate is 32Hz and 30-second epochs were used. Sleep onset and offset were defined as the clock times at the start of the first of ten minutes scored as sleep (after lights out time) and the end of the last ten minutes scored as sleep respectively. 24-hour total sleep time was computed from: mean actigraphy derived total sleep time + daytime nap duration (sum of all naps in the day, averaged across assessment period). Wake After Sleep Onset (WASO) was detected according to the device's medium sensitivity (40 counts per epoch). All other parameters were calculated according to default Actiware version 6.0.7's

settings, as these settings were found to have the greatest concordance with polysomnography [27]. Compared to polysomnography, these settings have high sensitivity to detect sleep (.94) and specificity to detect waking (.69) in school-aged children[27] [b] (see Figure 1 for example actigrams for a TD child and a child with SMS).

<<INSERT FIGURE 1a-b ABOUT HERE>>

Sleep diary

As an ajunct to actigraphy data, parents completed a paper sleep diary on behalf of their child to include bedtime (time child got into bed), time lights turned off, whether the event marker used to indicate bedtime and wake time was pressed at the correct time in the evening and morning, estimated time taken to fall asleep, wake up time in the morning and time got out of bed. Other important data for actigraphy cleaning were collected, to include the timings and nature of any sedentary periods of activity after 6pm, timings of any daytime naps, and the timings of periods when the Actiwatch was removed.

Lights out time was used to define the start of the rest period, the intention for the child to fall asleep [c] according to a data cleaning protocol using both the event marker, sleep diary and the automatically calculated rest period on the actigram to avoid relying solely on the software automatically calculated sleep intervals, which have poorer concordance with polysomnography [28].

Parental reporting of early morning final wake time may be inaccurate; therefore, sleep offset used the end of the autoscored rest interval. Additional daytime rest intervals calculated automatically due to artefact were removed, as were intervals during which the Actiwatch was

[b] Meltzer et al. (2012) used 1 min epochs in comparison with polysomnography.
[c] Two children with SMS fell asleep on the sofa prior to being put into bed. For parity, the time parents indicated for lights out time was still used in these cases.

removed. Intervals were extended to capture the entire sleep period if an additional 20 minutes after the end of the autoscored rest period but before the sleep diary indicated wake up time were coded as sleep by the software. Inter-rater reliability data for lights out time using a two-way mixed analysis which assessed the consistency of rating for 20% of the data (all nights for four children) for the SMS group was excellent [29]: intra-class coefficient .99 (CI:.98-1.0). The intra-class coefficient for the TD group was good: .61 (CI: .29-.81).

Daily behaviour ratings

Parents and teachers were asked to indicate the severity of overactivity/impulsivity, irritability and daytime sleepiness on a five-point Likert scale from 1 (not at all severe) to 5 (very severe) for the following segments of the day: before school, during the morning at school, the afternoon at school and after school. At the weekend parents completed this measure in the morning and afternoon. Overactivity/impulsivity ratings were based upon the following observations: "finding it difficult to wait, acting as if driven by a motor, wanting things immediately and finding it difficult to hold still". These items were taken from The Activity Questionnaire [30].

Observations referring to irritability were taken from the Affective Reactivity Index [31] "is easily annoyed by others, often and easily loses his/her temper, stays angry for a long time, gets angry frequently and overall irritability causes him/her problems". The severity of daytime sleepiness was rated according to the following objective measures: yawning, rubbing eyes, dazed/daydreaming, resting head on desk/lying down and eyes closed [32] (Owens, 2009 p. 417).

Procedure

Parents were advised that children could wear the Actiwatch on either their wrist or ankle, with wrist placement preferable. Nineteen children with SMS wore the watch on their wrist, one on their ankle. Alternative ankle placement was permitted given the sensory and behavioural difficulties experienced by children with SMS. All TD children wore the Actiwatch on their wrist. A researcher visited the parents of children with SMS to explain how to complete the sleep diaries and the procedure for pressing the event marker button on the Actiwatch. A training video was sent to parents of TD children to detail this procedure. Parents were advised that the Actiwatch was waterproof and should be worn continuously as far as possible. All actigraphy data were collected during school term time to maintain consistency.

Analysis

To compare actigraphy assessed parameters of sleep quality between children with SMS and TD children, Mann Whitney U tests were conducted on the data as some of the variables were not normally distributed. An ANCOVA was used to adjust for the administration of melatonin to aid sleep to compare differences between the SMS and TD groups in actigraphy parameters. Participant characteristics are presented in Table 1. For between group comparisons the alpha value was set at <.01 to minimise risk of Type I error. Descriptive data in Table 2 refer to the group median of the assessment period means for each individual child, as opposed to daily means. The group median or mean will hereafter be referred to as the grand median/mean. The degree of variability in total sleep time and WASO for children with SMS

and TD children was compared by calculating a coefficient of variance for each group [33].This index was calculated as grand SD of total sleep time/ grand Mean of total sleep time.[d]

To assess the degree of inter-daily stability of individual children's total sleep time across the assessment period, the coefficient of variance was calculated for each child using the following formula: SD of total sleep time / Mean of total sleep time.

Mann-Whitney U tests were used to compare the questionnaire total scores for the FISH measure of sleep hygiene and the MESS for the SMS and TD groups. The proportion of children meeting the cut off scores on the MESS, for sleep disordered breathing problems and for severe sleep problems on the MSPSQ in both groups was compared using Chi squared tests.

The contribution of age to total sleep time in children with SMS and TD children and between age and 24-hour total sleep time for children with SMS was assessed using linear regressions. Individual datum points for all children were plotted on a scatterplot with a fitted regression line. These statistical analyses were conducted using SPSS.

The fifth and sixth aims of the study were addressed using linear mixed modelling in the R language using lme4 [34] and matrix packages. The relationships between total sleep time for each child on each night and daily nap duration and total sleep time and afternoon sleepiness ratings were modelled bidirectionally. The predictive ability of afternoon sleepiness ratings to affect overactivity/impulsivity and irritability ratings was only modelled in this one direction. As these data may contain random effects at the level of the individual participant and for each day of replication of measurement, the null hypothesis was modelled with random

[d] Total Sleep Time and WASO were normally distributed

intercepts for day and participant (e.g., Dependent variable=1+ (1|day) + (1|participant)[e]. The significance of the random effects was assessed by using the chi-squared test to compare the effect for the complete null model to the effect for the model with one or other of the random effects removed. If both day and participant were demonstrated to be significant random effects or neither effect significantly contributed to the model they were therefore included in the null effect model. The theoretical model: (Dependent variable = 1 + independent variable + final null model) was compared to the final null effect model using a Chi-squared test (Maximum Likelihood). If a significant difference between these two models was found, the independent variable was considered to predict the dependent variable. Mean Behaviour ratings on days with and without a nap were compared using a Wilcoxon signed rank test.

Results

The data in Table 1 show the close matching of children with SMS to TD children on both age and gender. No significant differences were found for level of family income between the SMS and TD groups when assessed using a demographic questionnaire (χ^2= 4.05, p=.669). Exogenous melatonin dosage ranged from 1mg to 10mg (see Table S2 for details). There were no significant differences on any of the actigraphy assessed sleep quality parameters between children who used melatonin compared with children who did not (see Table S3 for inferential statistics).

<<INSERT TABLE 1 ABOUT HERE>>

[e] The null hypothesis was also modelled using the intercept and slope model for each dependent variable. As no significant difference between the intercept only and the intercept and slope model was found for the majority of dependent variables, the intercept(s) only (most parsimonious model) was chosen to model the random effect(s). For overactivity and irritability, both the intercept and slope model significantly contributed to the random effects model.

Actigraphy assessment of sleep quality in children with SMS and TD children

<<INSERT TABLE 2 ABOUT HERE>>

The data in Table 2 revealed significantly earlier morning wake times, shorter sleep onset latencies and longer night waking periods for the SMS group. Children with SMS had significantly shorter total sleep time compared to TD children. There was a trend towards earlier lights out times in children with SMS compared to TD children. At least one diurnal nap during the assessment period was recorded for 95% (n=19) of children with SMS[f] compared with only 15% (n=3) TD children. The three TD children who napped ranged in age from 5.63 years to 15.75 years.

Comparing inter-child variability in total sleep time and night waking across both groups and inter-daily stability of these parameters and nap duration for individual children

No difference in the ratio of weekend nights to weeknights was found between the groups (see Table 2). The coefficient of variance revealed more disparity in total sleep time and WASO for children with SMS versus TD children (see Table 3). Total sleep time and WASO varied more between nights for the individual child with SMS across the assessment period than it did for the TD child. Nap duration varied by a mean of 90% across the assessment period for individual children with SMS.

<<INSERT TABLE 3 ABOUT HERE>>

Sleep hygiene, snoring and excessive daytime sleepiness in children with SMS and TD children

No significant differences in sleep hygiene scores were found between the two groups (see Table 4). A significantly greater proportion of children with SMS had scores indicative

[f] No valid actigraphy data for the diurnal nap pairing was available for one child with SMS so subsequent analyses including nap data refer to n=18.

of excessive daytime sleepiness (13 children, 76.5%) versus TD children (0 children), (X^2= 23.58 (1), p<.001, phi: .80; large effect size).

<<INSERT TABLE 4 ABOUT HERE>>

Comparing the cross-sectional developmental trajectory of sleep duration of children with SMS and TD children

The data in Figure 2a demonstrate that total sleep time decreased significantly with age in TD children, R^2= .59, F (1,18) = 25.65, p<.001 (Beta: -.767), whereas no association between age and total sleep time was found for children with SMS R^2<.01, F (1,18)=.068, p=.798 (Beta: -.061).

<<INSERT FIGURE 2a-c ABOUT HERE>>

No significant association between age and total 24-hour sleep time (to include daytime naps) was found R^2= .02, F (1,18) = .38, p=.546 (Beta: -.144). See Figure 2b.

Lights out time became later with age in both the TD R^2= .58, F (1,18) = .24.96, p<.001 (Beta: .762) and the SMS groups R^2= .28, F (1,18)= 6.95, p=.017 (Beta:.528). See Figure 2c.

Modelling the relationships between total sleep time, daytime naps and daytime sleepiness

A significant negative relationship between nap duration and total sleep time was found (see Table 5). To account for variation in these variables between nights and also individual variability between participants, multilevel modelling was used to assess the temporal relationship between daytime naps in the afternoon and total sleep time that night, i.e. the variance in total sleep time explained by nap duration. The inverse relationship was

investigated between the duration of total sleep time at night and nap duration the following day, to explore the variance in nap duration explained by the duration of total sleep time. The relationship between afternoon sleepiness rating and total sleep time was also modelled in both directions. As significant positive relationships between daytime sleepiness ratings and overactivity and impulsivity and irritability were found using a correlation, multilevel modelling was also used to explore the degree of variance in total sleep time explained by afternoon daytime sleepiness ratings and the degree of variance in afternoon daytime sleepiness ratings explained by total sleep time. The variance in afternoon overactivity and impulsivity and irritability ratings associated with afternoon daytime rating was modelled in this direction only. The results from this analysis are detailed in Table 6. Irritability ratings were significantly lower on days when children did nap compared to days when child did not nap. There was no significant difference in overactivity scores on days where children did and did not nap (see Table 7).

<<INSERT TABLE 5 ABOUT HERE>>

<<INSERT TABLE 6 ABOUT HERE>>

<<INSERT TABLE 7 ABOUT HERE>>

In summary, these results show that: a) longer daytime nap duration predicted shorter total sleep time that night, b) shorter total sleep time that night predicted longer nap duration the next day, c) afternoon sleepiness rating that afternoon did not predict total sleep time that night and d) that total sleep time did not predict next day afternoon sleepiness rating, e) longer daily nap duration predicted higher sleepiness ratings in the afternoon, f) higher afternoon sleepiness rating significantly predicted higher overactivity/impulsivity and g)

afternoon sleepiness rating significantly predicted higher irritability rating for that same afternoon (see Figure 3).

INSERT FIGURE 3 ABOUT HERE

Discussion

This study shows children with SMS have a significantly shorter sleep duration (over 1.5 hrs) than TD controls, and experience worse sleep quality through earlier morning waking and longer wake after sleep onset periods. Sleep schedule data derived from actigraphy and sleep diary data provide further evidence of abnormal circadian rhythms in SMS with a trend towards significantly earlier bedtimes and close to a two-hour earlier morning wake time as well as more daytime naps.

Despite the limited sample size and high degree of variability for some measures, the strengths of our design include (1) actigraphy assessed sleep quality in children with SMS with parent-reported sleep disturbance enhanced by contrast with control TD children, (2) the use of an objective assessment of sleep capturing night waking and total sleep, (3) the first study to use an analysis strategy to account for heterogeneity in behaviour ratings to model the error variance from between participants, and (4) the first to use temporal analysis to investigate the direction of causality between daytime sleepiness and difficult behaviours.

This study provides further evidence of substantial interpersonal variability of sleep quality, night waking and total sleep time between individuals with SMS, which may occur downstream from variation in circadian rhythmicity in individuals with SMS [11] . The variation in night waking both between children and between assessment nights highlight the importance of longer term sleep assessments, between four and seven nights as opposed to relying on one night assessments of sleep quality [34]. Further research is needed to elucidate

causal mechanisms of night waking variability and should be considered as part of a comprehensive sleep assessment prior to intervention planning. Interpersonal variability in volume of melatonin secretion, which may be associated with age and gender in individuals with SMS [35], could be manifest in the variability in sleep quality between individuals found in this study. Of the 90% of children with SMS who napped during the assessment period with both actigraphy and nap data, nap duration varied by 90%, or by 15 minutes (standard deviation) over the course of the assessment period. This variation relative to the mean is explained by the lack of nap on five days on average during the assessment period. These data differ from DeLeersnyder et al.'s (2001) findings, whereby all children slept for at least 30 minutes per day according to parent report. This variation is an important consideration in the role of homeostatic versus circadian mechanism of daytime naps in children with SMS. Due to their inconsistency, it is hypothesised that a reliable peak in daytime melatonin synthesis does not fully explain diurnal napping in SMS. In addition, under constant conditions, the peak, or the midpoint between dim light melatonin onset and dim light melatonin offset in healthy adults is only moderately correlated with nocturnal sleep onset [36]. Therefore, assumptions about the relationship between diurnal sleep and melatonin phase in children with SMS, whose melatonin rhythm has not been compared to sleep timing, require further research. Future research should consider the role of day-to-day variation in total sleep time and sleep schedules and behaviour in children with SMS, as evidence from typically developing populations has identified variation in bedtime as a risk factor for hyperactivity [37].

Nap duration was associated with total sleep time, and using multi-linear modelling, daytime nap duration was shown to be predicted by total sleep time the previous night, and total sleep time that night was predicted by nap duration that day. A negative relationship between nap duration and total sleep time suggests that either children's propensity to fall asleep during the

day or the availability of a nap period, e.g. letting the child sleep in their bed or not disturbing them, was predicted by shorter total sleep time, and longer nap duration predicted shorter total sleep time. This suggests that homeostatic processes may underpin daytime naps in children with SMS. However, there was no relationship between parent/teacher ratings sleepiness that day and total sleep time that night, or between total sleep time the previous night and sleepiness in the afternoon the following day. The hypothesised role of circadian processes in the diurnal and nocturnal sleep quality of children with SMS is summarised in Figure 4.

<<INSERT FIGURE 4 ABOUT HERE>>

The afternoon sleepiness rating was chosen as the variable to be included in the analysis as research has proposed that in individuals with SMS who have a distinctive peak in melatonin levels, this is most likely to occur between 1200hr to 2000hr [8,10]. However, over half of the participants in Chik et al.'s study did not have a peak in melatonin between 8000h and 18hr, therefore it is possible that sleepiness should be assessed throughout the day [9]. The timing of children's nap in the current study, which occurred on average at 2pm, did provide support for selecting the afternoon session to reflect the peak in children's sleepiness. Children with SMS do clearly have a heightened propensity to fall asleep during the day according to the modified Epworth Sleepiness Scale, which is distinct from behavioural indicators of sleepiness. Therefore, caution should be used when observations of daytime sleepiness are used as a proxy for sleep debt. There is a need to stress the importance of evidencing the relationship between increased daytime sleepiness and overactivity and impulsivity, as any interventions designed to reduce diurnal propensity to fall asleep may also reduce challenging behaviour (See Figure 4). Lower irritability scores on days with a nap compared to days

without a nap suggest that reducing daytime sleepiness may be effective in reducing difficulty behaviour, however, these data only refer to a small number of children so caution is needed when drawing conclusions from these data. Despite homeostatic processes potentially underlying daytime nap duration, 24-hour sleep duration in children with SMS does not equate to the total nocturnal sleep time of TD children. On the assumption that children with SMS require the same duration of sleep as TD children, diurnal naps do not fully compensate for the sleep debt accrued due to reduced nocturnal sleep time. This supports the findings of Gropman et al. (2006) [5]. To further the practical application of these findings, additional research could evaluate the opportunity for daytime naps provided to children, versus the proportion of naps that occur spontaneously, described at 'sleep attacks' [8] (DeLeersnyder et al., 2001, p 113). Parents and teachers could capitalise on the homeostatic drive to maximise sleep efficiency during the night by restricting nap duration to consolidate sleep during the night, as evidenced in TD toddlers [15].

In addition to divergent sleep timing from TD children, a cross-sectional trajectory analysis of total night time sleep time and total 24-hour sleep revealed that neither total sleep time nor 24-hour total sleep time decreased with age, unlike the trajectory shown by TD children. However, total sleep time varied significantly more among children with SMS than TD children, which may have accounted for more variance than age. It is possible that the high interpersonal variance in total sleep time may have masked age differences, therefore a longitudinal study is needed to assess the developmental trajectory of total sleep time in children with SMS. Due to the small sample and age range these findings need to be considered with caution. The findings from the current study support those of a polysomnography study of a smaller sample of children and adults [10], but not those of Gropman et al. (2006) [5]. As in the present study so few TD children napped during the day, 24-hour total sleep time was not compared to that of children with SMS. However, data in

Gropman's [5] study referred to children from age one to seven years, whereas the present study did not extend to children younger than four, which could account for this difference in findings.

The poorer sleep quality in SMS was not accounted for by differences in sleep hygiene between the SMS and the TD group. This has important implications for treatment of sleep disturbance in this group, as whilst it is important to assess sleep hygiene on a case by case basis, poor sleep hygiene was not related to the poorer sleep quality experienced by children with SMS. Therefore, specific interventions for sleep disturbance for children with SMS need to assess and target other causes of sleep disturbance, such as differences in circadian rhythms which may underpin early morning waking and maximise homeostatic drive by nap restriction.

Limitations included (1) the small sample size of this study relative to other actigraphy studies, however it is one the largest age-matched case-control studies of sleep in SMS and is the first to highlight the variability in sleep quality between children with SMS (2) This was a pragmatic study thus we did not exclude children with SMS who were on medications intended to improve nocturnal and reduce daytime sleep, we did not collect daily timing of administration of melatonin. It is possible that these medications altered our sleep parameters in the SMS group. However, our data shows that no child was on medication that was 'normalising' sleep. In fact, our data suggest that children with SMS did not respond to the administration of exogenous melatonin. (3) The MESS cut-off score has not been validated in a paediatric population, but the Epworth Sleepiness Scale and various modifications of the scale are widely used in research literature. Further work is needed to validate the optimum cut-off score to identify excessive daytime sleepiness in children. We did not include a comprehensive assessment of sleep-disordered breathing, but did identify that children with SMS were more likely to have heavy or loud breathing compared to TD children, but were

not more likely to snore. Given a range of anatomical reasons why this population are predisposed to sleep disordered breathing [38], the potential impact of sleep disordered breathing on daytime behaviours, and a possible underlying genetic explanation [39], we suggest routine objective screening, perhaps with oximetry and ambulatory cardiorespiratory studies. (4) We did not use melatonin assays to assess circadian processes in this sample. Previous studies in SMS have collected plasma or urine samples in a hospital environment. It was therefore beyond the scope of this study of sleep in the child's usual home environment to include collection of plasma or urine samples by parents. However, there is a need to develop a protocol for home-based collection of urine samples to study patterns of melatonin synthesis in children with intellectual disability at risk of circadian rhythm disorders.

Conclusions

Circadian and homeostatic process are hypothesised to underpin the sleep timing and sleep quality observed in children with SMS with parent reported sleep disturbance. Variable sleep quality comprising short sleep duration, extended night waking and daytime naps in children with SMS evidence the need for comprehensive multi-night assessments of sleep quality. Our other recommendation is assessment of sleep hygiene before suggesting sleep hygiene adjustments as first line intervention and to acknowledge the specific sleep disturbances: night waking and early morning waking which affect children with SMS.

The drive to sleep during the daytime is influenced by the duration of nocturnal sleep time and conversely nocturnal sleep time is also influenced by daytime sleep quality. This finding provides an opportunity for intervention to maximise homeostatic drive to optimise nocturnal sleep. We suggest there is an opportunity to combine such approaches with the pharmacological strategies of reducing daytime melatonin production with morning beta-blockers and consolidating nocturnal sleep with evening melatonin.

Taken together, these findings provide preliminary evidence for a theoretical model of the mechanism of sleep quality and timing in SMS and present opportunities to improve sleep quality in children with SMS, which may reduce difficult behaviours, therefore enhancing the quality of life of children with SMS and their caregivers.

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Figure captions:

Figure 1a: Actigram of a typically developing 4 year old child

Figure 2b: Actigram of a child with Smith-Magenis syndrome aged 4 years.

Figure 1

Actigrams of TD children and children with SMS

Figure 2a. Relationships between total sleep time and age in typically developing TD children and children with Smith-Magenis Syndrome (SMS)

Figure 2b. Relationship between 24-hour total sleep time and age in children with Smith-Magenis syndrome (SMS)

Figure 2c. Relationships between lights out time and age in typically developing (TD) children and children with Smith-Magenis syndrome (SMS)

Figure 2

Cross sectional trajectories of the relationship between total sleep time (Figure 2a), 24 hour total sleep time (Figure 2b) and lights out time (Figure 2c) and age in children with SMS and TD children with fitted regression lines

Figure 3

Mixed linear models of the relationships between total sleep time, daytime sleepiness, total sleep time, daytime nap duration and between daytime sleepiness and overactivity, impulsivity and irritability

Figure 4

Model of relationships sleep timing, sleep quality and diurnal sleep and behaviour and hypothesised role of homeostatic and circadian processes in Smith-Magenis syndrome

Supplementary material captions:

Table S1: Modified Epworth Sleepiness Scale

Table S2: Medications administered to children with SMS

Table S3: Actigraphy parameters between children who did and did not take medication to aid their sleep

Table 1 *Demographic characteristics of children with SMS and TD children*

		SMS (n=20)	TD (n=20)	T score/ χ^2, p value
Mean age (SD)		8.70 (2.70)	9.06 (3.32)	.374, p=.710
Males (%)		9 (45)	10 (50)	.1, p=.752
Family income	Less than £15,000	1 (5.6)	0	4.05, p=.669
	£15,001 to £25,000	1 (5.6)	3 (16.7)	
	£25,001 to £35,000	4 (22.2)	4 (22.2)	
	£35,001 to £45,000	1 (5.6)	1 (5.6)	
	£45,001 to £55,000	4 (22.2)	5 (27.8)	
	£55,001 to £65,000	4 (22.2)	1 (5.6)	
	£65,001 or more	3 (16.7)	4 (22.2)	
Regularly taking melatonin for sleep (%)[a]		12 (67)	0	19.49, p<.001
Sleep medication helpful (% of children taking medication)		12 (100)	-	
Developmental age [b]		48 months	-	
Mean nights of actigraphy (SD)		6.65 (1.46)	6.85 (.87)	.525, p=.603
Mean ratio of weekend nights to weeknights (SD)		.25 (.08)	.29 (.05)	1.59, p=.120

[a] Due to two missing questionnaire packs, medication data are only presented for 19 children with SMS, 1 child: "melatonin as and when required", excluded from total (n=18).

[b] Due to two missing Vineland Adaptive Behavior Scale interview, data only refer to 18 children. Four children had one missing subscale score (expressive language, fine or gross motor skills). There scores were averaged over 10 subscales.

Table 2

Grand median and interquartile ranges of actigraphy parameters across the assessment period and average duration and timing of daytime naps according to sleep diary in children with SMS and TD children

	SMS	**TD**	**Between group comparisons**			
			Mann Whitney U/χ^2	*P*	Adjusted p value [b]	Cohen's R
Lights out time (hh:mm) Median (IQR)	20:14 (19:20-20:38)	20:41 (20:19-21:26)	113.5	.019	.01	-0.37
Sleep offset (hh:mm) Median (IQR)	5:12 (4:24-5:50)	7:02 (6:53-7:23)	15.5	<.001*	<.001*	-0.79
Sleep onset latency in mins Median (IQR)	7.09 (1.90-17.50)	20.48 (12.47-71.65)	75.0	<.001*	.159	-0.54
Wake After Sleep Onset in mins Median (IQR)	71.35 (56.84-102.47)	52.65 (35.30-57.62)	82.0	.001*	.001*	-0.50
Sleep efficiency (%) Median (IQR)	79.43 (75.04-84.57)	83.17 (80.19-85.62)	136.0	.083	.017	-0.27
Total sleep time in mins Median (IQR)	416.5 (402.5-484.8)	513.0 (489.8-537.5)	64.0	<.001*	.001*	-0.58
Average duration of daily diurnal nap across assessment period [a] Mean (SD)	16.43 (14.74)	8.69 (5.11)	-	-		-
Timing of diurnal nap in mins Mean (SD)	13:59 (2.02)	17:26 (2:42)	-	-		-

* Significant at p level <.01 [a] Excludes children with no reported diurnal nap with pairing of valid actigraphy data (SMS n= 2, TD, n=17). See footnote f

[b] Adjusted for medication use to aid sleep.

Table 3 *Coefficient of variance statistics for total sleep time and wake after sleep onset between children and within an individual child's assessment period in children with SMS and TD children*

	SMS	TD
Coefficient of variance nap duration with assessment period (%)[a]	90	-
Coefficient of variance TST between children (%)	14	9
Coefficient of variance WASO between children (%)	48	32
Coefficient of variance TST within assessment period (%)	14	10
Coefficient of variance WASO within assessment period (%)	37	24

[a] Data refer to 18 children with SMS with valid nap/actigraphy data pairing

Table 4 *Scores on questionnaire measures of sleep hygiene, sleepiness, and sleep problems*

	n	SMS (n=18)	n	TD (n=20)	U statistic/ χ^2	P value	Effect size Cohen r/ Phi
Median sleep hygiene score on FISH† (IQR)	16	48.50 (45.50-52.50)	19	48.0 (48.0-53.0)	142.50	.751	.05
Median modified Epworth sleepiness scale score † (IQR)	17	14.0 (10.5-17.0)	20	2.0 (2.0-3.75)	1.50	<.001 *	.85
Number (%) of children with severe settling problems	19	0	20	0	-	-	-
Number (%) of children with severe night waking problems	19	14 (73.7)	20	1 (5.0)	19.42	<.001 *	.71
Number (%) of children with severe early morning waking	19	12	20	1	14.83	<.001 *	.62

problems		(63.2)		(5.0)			
Always snores N (%)	18	0 (88.9)[a]	20	0 (100)	2.35	.126	.25
Snores more than half the time N (%)	18	4 (22.2)[a]	20	2 (10.0)	3.77	.152	.32
Snores loudly N (%)	17	2 (11.8)[b]	20	1 (5.0)	1.86	.395	.22
Has heavy or loud breathing N (%)	18	12 (66.7)	20	4 (20)	8.46	.004*	-.47
Has trouble breathing or struggles to breathe N (%)	17	1 (5.9) [b]	20	0 (0)	2.49	.288	.26

* Significant at p level <.01 [a] Two parents reported 'don't know' [b] One parent reported 'don't know

Table 5

Spearman's correlations between nap duration, afternoon sleepiness, irritability and overactivity ratings and total sleep time that night

		Total Sleep Time	Nap duration	Sleepiness ratings	Irritability ratings	Overactivity ratings
Total Sleep Time	r_s	-				
Nap duration	r_s	-.25**	-			
Sleepiness ratings	r_s	-.19	.27*	-		
Irritability ratings	r_s	-.04	-.04	.32**	-	
Overactivity ratings	r_s	-.03	-.02	.29*	.70**	-

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

Table 6.

Modelling relationships between nap duration, TST, daytime sleepiness and behaviour using mixed linear modelling.

	Random effects	Fixed effects	Estimate	Standard Error	t value	Statistical difference between null and theoretical model
Relationship between duration of nap that day on duration of TST that night (n=131)	Between participant variation	Intercept	436.57	13.81	31.61	X^2 = (1) 6.14, p=.013*
		Duration of nap	-.48	.19	-2.49	
Relationship between duration of TST that night on nap duration the following day (n=111)	Between participant variation	Intercept	51.08	18.44	2.77	X^2 = (1) 3.92, p=.048*
		Duration of TST	-.08	.04	-2.02	
Impact of duration of TST that night on sleepiness score the	Between participant variation	Intercept	2.25	1.05	2.13	X^2 (1) 0.03, p=.875

following day (n=77)		Duration of TST	<.01	<.01	0.21	
Impact of afternoon sleepiness rating on duration of TST that night (n=80)	Variation between participants	Intercept	421.51	23.58	17.88	X^2 (1) .09, p=.761
		Afternoon sleepiness rating	-1.65	5.71	-.29	
Relationship between impact of nap duration on afternoon sleepiness rating (n=80)	Variation between participants	Intercept	2.22	0.23	9.60	X^2 (1) 4.85, p=.028*
		Nap duration	0.08	<0.01	2.21	
Relationship between impact of afternoon sleepiness rating on afternoon overactivity rating (n=76)	Between participant variation and variation between assessment days (Intercept and slope model)	Intercept	1.71	0.30	5.66	X^2 = (1) 7.75, p=.005**
		Afternoon sleepiness rating	0.32	0.11	2.94	

Relationship between impact of afternoon sleepiness rating on afternoon irritability rating (n=76)	Between participant variation and variation between assessment days (Intercept and slope model)	Intercept	1.48	0.29	5.09	X^2= (1) 7.41, p=.007*
		Afternoon sleepiness rating	0.30	0.11	2.81	

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

Table 7

Irritability and overactivity ratings on days with and without a nap

Afternoon behaviour ratings	n	Median day with nap (Interquartile range)	Median day without nap (Interquartile range)	Z	P value
Irritability	11	2.0 (1.0-2.33)	2.50 (2.25-3.30)	-2.20	.028
Overactivity	13	2.0 (1.5-3.0)	2.50 (2.13-3.67)	.512	.609