Title: A cross-syndrome comparison of sleep-dependent learning on a cognitive procedural task

Short title: Sleep-dependent learning in DS and WS

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Abstract

Sleep plays a key role in the consolidation of newly acquired information and skills into long term memory. Children with Down syndrome (DS) and Williams syndrome (WS) frequently experience sleep problems, abnormal sleep architecture and difficulties with learning; thus, we predicted that children from these clinical populations would demonstrate impairments in sleep-dependent memory consolidation relative to children with typical development (TD) on a cognitive procedural task: The Tower of Hanoi.

Children with DS (n = 17), WS (n = 22) and TD (n = 34) completed the Tower of Hanoi task. They were trained on the task either in the morning or evening, then completed it again following counterbalanced retention intervals of daytime wake and night time sleep. Children with TD and with WS benefitted from sleep for enhanced memory consolidation and improved their performance on the task by reducing the number of moves taken to completion, and by making fewer rule violations. We did not find any large effects of sleep on learning in children with DS, suggesting that these children are not only delayed, but atypical in their learning strategies.

Importantly, our findings have implications for educational strategies for all children, specifically considering circadian influences on new learning and the role of children's night time sleep as an aid to learning.

Abbreviations: typical development (TD), Down syndrome (DS), Williams syndrome (WS), rapid eye movement (REM), slow wave sleep (SWS)

Key words: paediatric sleep, Down syndrome, Williams syndrome, sleep-dependent learning, memory
Highlights

- The present study was the first to use the Tower of Hanoi task to assess cognitive procedural sleep-dependent learning in children with Down Syndrome (DS) and Williams Syndrome (WS).

- Children with typical development and with WS showed enhanced performance on the task in relation to sleep.

- We did not find evidence of sleep-dependent learning in children with DS, suggesting that these children are not only delayed, but atypical in their learning strategies.

- Circadian influences ought to be considered when examining children's learning and developing new educational strategies.
Substantial evidence suggests that sleep plays an active role in consolidating newly learnt information and skills into memory. In both adults and children, sleep-dependent learning occurs for explicit material (Davis, Di Betta, Macdonald, & Gaskell, 2009; Henderson, Weighall, Brown, & Gaskell, 2012), which appears to benefit from slow wave sleep (SWS; the deepest stage of sleep) for reactivation of new memories, strengthening of neural pathways and transfer from the hippocampus to cortical regions for long term storage (Born, Rasch, & Gais, 2006). Conversely, learning of implicit or procedural information shows a sleep-related advantage in adults but not always in children (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2014; Wilhelm, Metzkow-Meszaros, Knapp, & Born, 2012) and may benefit most from rapid eye movement sleep (REM; the stage normally associated with dreaming) (Maquet et al., 2000; Smith, Nixon, & Nader, 2004). In addition, the level of performance prior to sleep appears to be positively associated with the degree to which consolidation during sleep occurs (Wilhelm et al., 2012).

Children with neurodevelopmental disorders experience problems with learning and sleep. This study focuses on children with Down syndrome (DS) and Williams syndrome (WS); two disorders associated with mild to moderate intellectual disability, but with contrasting patterns of cognitive strengths and weaknesses. In addition, sleep problems are common in both clinical groups.

**Down syndrome**

DS is the most common sporadic chromosomal cause of intellectual disability, affecting around 1 in 1000 live births worldwide and usually caused by an additional copy of chromosome 21 (trisomy 21) (Roizen & Patterson, 2003). It is characterised by atypical physical characteristics and a particular language weakness, but with relative strengths in visual and spatial processing (Jarrold & Baddeley, 2001; Roizen & Patterson, 2003).

Sleep problems are common in DS, with up to 80% of children thought to be affected by obstructive sleep apnoea syndrome (OSAS); where the upper airway becomes blocked and causes difficulty breathing during sleep. Events in children are most likely to occur during
REM sleep (Tauman & Gozal, 2011) and include apnoeas (airway occlusion) and hypopnoeas (partial occlusion) which may be associated with oxygen desaturation (hypoxia), increased blood carbon dioxide (hypercarbia), and highly fragmented sleep (Austeng et al., 2014; Hill et al., 2016). Individuals with DS experience multiple risk factors for OSAS, including obesity, hypertrophy of tonsils and adenoids, macroglossia, relatively small upper airway, underdeveloped midface, generalised hypotonia, and frequent upper respiratory tract infections (Churchill, Kieckhefer, Landis, & Ward, 2012). OSAS and fragmented sleep are independently associated with poorer cognitive functioning (Breslin et al., 2014; Sadeh, Gruber, & Raviv, 2002; Tauman & Gozal, 2011).

In addition to OSAS, difficulties initiating and maintaining sleep, early morning waking, restlessness and daytime sleepiness are frequently reported (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2013; Breslin, Edgin, Bootzin, Goodwin, & Nadel, 2011; Richdale, Francis, Gavidia-Payne, & Cotton, 2000; Tietze et al., 2012). An increased amount of SWS and reduced REM sleep have also been reported, with the REM sleep reduction being associated with greater cognitive impairment (Diomedi et al., 1999; Harvey & Kennedy, 2002; Miano et al., 2008; Nisbet, Phillips, Hoban, & O’Brien, 2015).

**Williams Syndrome**

WS is a rare neurodevelopmental disorder affecting around 1 in 20,000 births and caused by a deletion of around 28 genes at 7q11.23. Individuals with WS have a distinctive physical appearance, as well as a characteristic cognitive profile comprising hyper-sociability contrasting with anxiety for new or unexpected situations, relatively good language abilities and poor visuospatial abilities (Donnai & Karmiloff-Smith, 2000). Sleep problems have recently received attention, with objective measures and parent reports showing that children with WS commonly experience long sleep onset latencies, and increased night wakings (Annaz, Hill, Ashworth, Holley, & Karmiloff-Smith, 2011; Ashworth et al., 2013; Mason et al., 2011) and abnormal secretion of cortisol and melatonin (Sniecinska-Cooper et al., 2015). Parents also report bedwetting, sleep anxiety, body pain,
and snoring to be common (Annaz et al., 2011; Ashworth et al., 2013; Sarimski, 1996; Udwin, Yule, & Martin, 1987). Differences in sleep architecture have also been reported; specifically, a decrease in REM sleep and an increase in SWS (Gombos, Bódizs, & Kovács, 2011; Mason et al., 2011).

**Sleep-dependent learning in DS and WS**

Few studies have investigated sleep-dependent learning in DS or WS. We previously reported comparisons between DS, WS and TD on a declarative task (Animal Names), whereby children learnt pseudo-words as the names of ten animals (e.g., Jaala the Pig and Orin the Horse) and were requested to recall these names after training and following intervals of night-time sleep and daytime wake (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2017). Children with TD benefited from sleep for enhanced memory consolidation, demonstrated by improved recall following sleep compared to wake, whereas the task showed differential effects for children with DS and WS. Children with DS who learnt the names in the morning consolidated more information across the three test sessions, whilst children who trained in the evening showed a trend to forget the names that they had learnt. Children with WS consolidated more information between training and the first retest, regardless of whether the retention interval contained sleep or wake. The findings in our DS group have been replicated by Spanò et al. (Under review) in preschoolers with DS, who learnt pseudo-words as object labels and were tested four hours later, following wake or sleep. Children demonstrated enhanced retention over the wake period compared to the sleep period.

In 14 school-aged children with WS (discrete from the current sample), we previously demonstrated that performance on a motor sequence learning task (the finger tapping task) actually showed a non-significant decrease across a period of sleep. In comparison, 14 control children with TD showed a significant improvement on the task following sleep but no change after wake (Dimitriou, Karmiloff-Smith, Ashworth, & Hill, 2013).
These studies comprise the only known publications on sleep-dependent learning in children with DS and WS but have important implications for children’s learning and education plans. The current study investigated sleep-dependent learning on a cognitive procedural task; the Tower of Hanoi. Following pilot studies of three tasks (a fine motor control task, a perceptual contour integration task, and the Tower of Hanoi) the Tower of Hanoi was selected as it showed evidence of sleep-dependent learning in ten children aged 3 to 14 years, and was appropriate for children with intellectual disabilities as task difficulty could be adjusted. The task also shows evidence of sleep-dependent learning in adults. Smith et al. (2004) trained 18 healthy adults on the Tower of Hanoi task and monitored sleep using polysomnography (PSG). The number of REMs (not REM periods) and REM density increased on the post-learning night, whereas time spent in REM sleep and % of REM sleep did not change from baseline. They also found that the 6 individuals with the highest IQ, and therefore assumed to have the greatest learning potential, showed the greatest increase in REMs and REM density from baseline, which correlated significantly with improvement on the task. This suggests a strong, possibly two-way, interaction between cognition and sleep architecture. In addition, selective deprivation of REM sleep is known to disrupt sleep-dependent gains on this task (Smith, 1995). We previously reported that children with TD show sleep-dependent learning on the Tower of Hanoi task (Ashworth et al., 2014). This task has not previously been used to assess sleep-dependent learning in children with neurodevelopmental disorders; thus, here we extend our TD data by providing a comparison with children with DS and WS. We hypothesise that 1) given the known reduction of REM sleep in both DS and WS, these groups will show reduced sleep-dependent memory consolidation on the Tower of Hanoi task, whilst children with TD will benefit from sleep and demonstrate an improvement on the task; 2) children who are high performers at baseline will show the greatest sleep-dependent gains; 3) mental age will be positively associated with sleep-dependent gains on the task.
Method

Participants

Twenty-two children with DS (11 male), 22 children with WS (10 male) and 34 with TD (17 male) aged 6-12 years took part in the study. The majority of children were white. Children from the TD group were recruited through local primary schools in London. Parents of children with DS were contacted through local parent and child groups, and special needs schools. Parents responded either to the school/group or directly to the researcher if they wished to take part in the study. Williams Syndrome Foundation UK, assisted with recruitment of children with WS. Parents were contacted initially by telephone by the researcher and were later given full information in writing. In the TD and DS groups respectively 71% (34/48) and 52% (22/42) of initial responders finally took part in the study. Reasons for non-participation included that the family changed their mind, child illness, not meeting inclusion criteria, or that the researcher was unable to visit all recruited families. Ninety-two percent (22/24) of WS families who initially agreed to participate finally took part in the study. Non-participation in these cases was due to child illness. Parents confirmed that all children with DS had tested positively for chromosome 21 trisomy and children with WS had microdeletion of genes at the elastin locus (7q11.22-23) diagnosed by the fluorescence in situ hybridisation test. To avoid introducing confounding factors which may affect children’s sleep and/or cognitive skills exclusion criteria included co-morbid disorders such as attention deficit hyperactivity disorder or autism spectrum disorder, psychiatric conditions, use of hypnotic medication, or current treatment for OSAS. Determination of exclusion criteria were based on parent report. The Research Ethics Committee at Institute of Education, London granted ethical approval for the project entitled “Sleep and cognition in children with Down syndrome and Williams syndrome”, and the study was supported by Down Syndrome Education International and The Williams Syndrome Foundation, UK. Prior to participation, parents gave written informed consent and, where able, the children gave their verbal assent and testing was stopped if the child
became upset by the task or they were unable to complete it. Thus, data were removed for five of the youngest children with DS and one with WS who were unable to complete the task. Details of the final sample are shown in Table 1. Analysis of Variance (ANOVA) and Chi-square tests respectively yielded no significant chronological age ($F(2,69)=1.48, p=.23, \eta_p^2=.04$) or sex differences ($\chi^2(2,72)=.05, p=.98, \phi=.03$) between the three groups. Non-verbal mental age, based on Raven’s Coloured Progressive Matrices (RCPM) (Raven, Raven, & Court, 1998) was comparable between the DS and WS groups and was significantly higher for the TD group ($F(2,42.71)=76.76, p<.001, \eta_p^2=.70$). Variances for the RCPM scores were non-homogeneous so degrees of freedom and the $F$ statistic were adjusted according to the welch test.

Table 1.

**Participant details**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Male/female</th>
<th>Age in years $(M \text{ (SD)})$</th>
<th>Age range (years)</th>
<th>RCPM Raw Score $(M \text{ (SD)})$</th>
<th>RCPM Mental Age Equivalent (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>34</td>
<td>17 / 17</td>
<td>9.22 (1.58)</td>
<td>6.19 – 12.02</td>
<td>26.88 (5.21)</td>
<td>10.75</td>
</tr>
<tr>
<td>DS</td>
<td>17</td>
<td>8 / 9</td>
<td>10.11 (1.68)</td>
<td>7.19 – 12.23</td>
<td>13.24 (3.29)</td>
<td>Under 5</td>
</tr>
<tr>
<td>WS</td>
<td>21</td>
<td>10 / 11</td>
<td>9.39 (2.05)</td>
<td>6.16 – 12.58</td>
<td>14.71 (3.07)</td>
<td>6.25</td>
</tr>
</tbody>
</table>

**Materials and Method**

The Tower of Hanoi is a mathematical puzzle invented by Eduardo Lucas in 1883 (see Figure 1). It consists of three pegs and a number of stackable disks of different diameters that can be slid onto any peg. It starts with the disks stacked in ascending order on the leftmost peg. The task objective is to move the entire stack of disks to the rightmost peg in as few moves as possible whilst following a strict set of rules: only one disk may be moved
at a time and no disk may be placed on top of a smaller disk. The fewest possible number of moves is $2^n - 1$ where $n$ is the number of disks.

The experimenter explained the rules to the child and ensured they understood by demonstrating legal and illegal moves and asking if each move was allowed, until the child was sure of the rules. Children were told that they should plan their moves carefully and try to complete the puzzle in as few moves as possible.

Children’s moves and rule violations were counted. If a child lifted the disk from a peg and placed it back on the same peg, it was counted as one move. If they touched or lifted a disk but it remained on the peg, it was not counted as a move.

Pilot data were used to determine an appropriate level of difficulty; thus, children with TD completed the task with five disks whereas children with DS and WS used four disks. All children completed the task five times during the training session, taking around 30 minutes. They were retested following retention intervals of wake and sleep, where they completed the task twice during each test session. Retests took around 10 to 15 minutes each. The rules were reiterated at the start of each test session. This procedure was designed to allow children to become familiar with the task during the first session and then not have too much practice in the following sessions so that improvement could not be due to rehearsal. Scores were the mean of the final two trials of the training session, and
of both trials at each retest. Improvement or decline in performance was determined where the child had a change in score of at least one point.

To control for possible time-of-day effects on learning whereby we may expect children to perform better if they are trained in the morning on a task as opposed to the evening (Schmidt, Collette, Cajochen, & Peigneux, 2007), a counterbalanced design was used. Children were randomly allocated to two Circadian Conditions: half of the children were trained and tested (Test 1) in the morning (Wake-sleep condition), and the other half in the evening (Sleep-wake condition). They were then retested twice at approximately 12 (Test 2) and 24 (Test 3) hours post-training following intervals of wake and sleep (Figure 2). T-tests and Chi-square respectively showed no significant age or sex differences between the Sleep-wake and Wake-sleep conditions (all p values >.05).

Evening sessions took place at the child’s home, with start times ranging from 17:45 to 20:45 (M = 19:11, SD = 00:39) depending on habitual bedtime as reported by parents. Morning sessions were usually at the child’s school and occurred between 07:40 and 10:30 (M = 08:55, SD = 00:24). Therefore, the average wake time interval was 10:13 hours (range: 8:30 to 11:45 hours), and the sleep time interval was 13:30 hours (range: 12:05 to 15:15 hours). Between groups ANOVAs showed a significant difference between the three groups for length of the sleep interval ($F(2,69)=5.28, p=.007, \eta_p^2=.13$), driven by children with DS having a 37-minute longer sleep interval relative to the TD group. There was no significant difference between groups for the wake interval duration ($F(2,69)=3.14, p=.05$ (ns), $\eta_p^2=.08$). Ideally the interval would be 12 hours between each test, however these time differences were unavoidable due to variations in school start times and the need to minimise disruption to normal routines and bedtimes.

Children were tested individually, seated at a table in a quiet room, without other distractions. For children with DS and WS, their learning assistant was usually also present. To minimise the interference effects that may occur from wake periods during the sleep retention interval, children were tested as close to bedtime as possible and as early in the
morning as possible, usually as soon as they arrived at school or immediately after registration. They were also asked to avoid any cognitively demanding activities, such as music practice or school work, between the evening and following morning test sessions. Children completed the RCPM during the morning retest session after they had completed the Tower of Hanoi.

Children's sleep was monitored at the time of testing for seven days and nights using actigraphy (movement monitoring) with an Actiwatch Mini (CamNTech) worn on the non-dominant wrist. Data were analysed using Sleep Analysis 7 (CamNTech, Cambridge, UK) at the default ‘medium’ sensitivity level. Actigraphy confirmed that all children slept on the night of the study.

<table>
<thead>
<tr>
<th>Time</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>M'nt</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wake-Sleep condition</td>
<td>Train &amp; Test 1 (30m)</td>
<td>Test 2 (10m)</td>
<td>Sleep</td>
<td>Test 3 &amp; RCPM (15m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-Wake condition</td>
<td>Train &amp; Test 1 (30m)</td>
<td>Sleep</td>
<td>Test 2 &amp; RCPM (15m)</td>
<td>Test 3 (10m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Testing schedule for Wake-Sleep and Sleep-Wake circadian conditions.

**Results**

**Sleep**

Table 2 shows actigraphy data for core sleep characteristics along with ANOVA results comparing groups on these variables. Post-hoc tests using the Bonferroni correction showed that children with TD had later bedtimes than both other groups, whilst children with DS had the most disturbed sleep, evidenced by increased number of night wakings.
and lower sleep efficiency (% sleep from sleep onset to sleep offset). Despite this, the total sleep time for the three groups was remarkably similar. Further sleep data for these groups are reported in Ashworth et al. (2013).

Importantly, actigraphy data corroborated parent reports that all children slept on the night of the study.

Table 2.

* Actigraphy data and ANOVA results comparing the three child groups (TD, DS, WS)

<table>
<thead>
<tr>
<th></th>
<th>TD (n=34)</th>
<th>DS (n=17)</th>
<th>WS (n=21)</th>
<th>F</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed time (hh:mm)</td>
<td>21:26 (0:39)</td>
<td>20:35 (0:31)</td>
<td>20:48 (0:39)</td>
<td>12.39</td>
<td>&lt;.001</td>
<td>.26</td>
</tr>
<tr>
<td>Actual sleep time (h:mm)</td>
<td>8:16 (0:38)</td>
<td>8:18 (0:52)</td>
<td>8:16 (0:55)</td>
<td>0.02</td>
<td>.98</td>
<td>.001</td>
</tr>
<tr>
<td>Sleep efficiency*</td>
<td>87.74 (3.75)</td>
<td>82.53 (5.97)</td>
<td>88.59 (3.23)</td>
<td>11.33</td>
<td>&lt;.001</td>
<td>.25</td>
</tr>
<tr>
<td>Number of night wakings</td>
<td>31.00 (7.91)</td>
<td>39.98 (9.57)</td>
<td>28.22 (6.16)</td>
<td>11.34</td>
<td>&lt;.001</td>
<td>.25</td>
</tr>
</tbody>
</table>

* % sleep from sleep onset to sleep offset

Significant differences in **bold**

**Tower of Hanoi**

Due to test differences between the TD and clinical groups on the Tower of Hanoi, firstly scores were transformed to be comparable between groups. The TD group completed the task with five disks hence the minimum possible number of moves was 31. For the DS and WS groups completing the four-disk task, the minimum possible number of moves was 15. The constant here is 2.067 (calculated as 31/15) meaning that the five-disk task takes 2.067 times more moves than the four-disk task. The scores of the DS and WS groups were therefore multiplied by 2.067 to make them comparable to the TD group. All mention of
scores hereafter refers to the transformed scores. Rule violations were also counted and were not transformed.

Data were analysed using IBM SPSS v.24 and screened for outliers using Cooks distances. No outlying scores were found.

Firstly, we assessed that the DS and WS groups were well-matched by conducting an ANOVA to compare scores at Test 1. There was no significant difference between the three groups ($F(2,69)=0.54$, $p=.59$, $\eta^2=.02$). T-tests showed that, within each group, there was no significant difference between baseline scores from the two Circadian Conditions (all $p$ values > .05), indicating no significant circadian effects of morning or evening training.

Next, group differences on the task were investigated using repeated measures ANOVAs with the within-subjects factor of Test Session (three levels: Test 1, Test 2, Test 3) and two between-subjects factors: Child Group (TD, DS, WS) and Circadian Condition (Sleep-wake, Wake-sleep). Interactions were investigated further by conducting repeated measures ANOVAs for each Child Group and Circadian Condition. Separate analyses were conducted for the two dependent variables: moves to completion and rule violations. The Bonferroni correction was applied to post hoc tests. Where sphericity was violated, the Greenhouse-Geisser estimate was used to adjust degrees of freedom and the $F$ statistic, and multivariate statistics with Wilks’ Lambda are reported.

**Group differences for number of moves taken on the Tower of Hanoi.**

Table 3 and Figure 3 show the number of moves taken at each Test Session by each Child Group and Circadian Condition. Note that fewer moves indicates better performance.
Table 3. Number of moves taken (Mean (SD)) at each Test Session by Child Group (TD, DS, WS) and Circadian Condition (Sleep-wake, Wake-sleep) on the Tower of Hanoi task

<table>
<thead>
<tr>
<th>Condition Group</th>
<th>n</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-wake</td>
<td></td>
<td>PM</td>
<td>AM</td>
<td>PM</td>
</tr>
<tr>
<td>TD</td>
<td>17</td>
<td>57.91 (14.29)</td>
<td>49.38 (15.53)</td>
<td>46.06 (9.11)</td>
</tr>
<tr>
<td>DS</td>
<td>8</td>
<td>66.66 (33.49)</td>
<td>54.65 (13.26)</td>
<td>59.68 (28.17)</td>
</tr>
<tr>
<td>WS</td>
<td>10</td>
<td>54.05 (9.30)</td>
<td>51.68 (8.76)</td>
<td>59.94 (19.23)</td>
</tr>
<tr>
<td>Wake-sleep</td>
<td></td>
<td>AM</td>
<td>PM</td>
<td>AM</td>
</tr>
<tr>
<td>TD</td>
<td>17</td>
<td>66.94 (19.30)</td>
<td>69.09 (18.20)</td>
<td>50.62 (15.23)</td>
</tr>
<tr>
<td>DS</td>
<td>9</td>
<td>61.44 (25.86)</td>
<td>59.37 (14.75)</td>
<td>56.04 (16.24)</td>
</tr>
<tr>
<td>WS</td>
<td>11</td>
<td>60.22 (27.38)</td>
<td>67.18 (18.80)</td>
<td>50.74 (10.56)</td>
</tr>
</tbody>
</table>

Figure 3. Number of moves taken across three sessions on the Tower of Hanoi task for each Child Group (TD, DS, WS) and Circadian Condition (Sleep-wake, Wake-sleep). Note that fewer moves indicates better performance. Minimum possible moves is 31.

There was a significant main effect of Test Session ($F(2,132)=4.91, p=.01, \eta^2_p = .07$), driven by an overall improvement of scores from Session 1 to Session 3. As expected, the main
effects of Child Group ($F(2,66)=.26, p=.78, \eta^2=.01$) and Circadian Condition ($F(1,66)=1.77, p=.19, \eta^2=.03$) were not significant, indicating that the TD, DS and WS groups and the Sleep-wake and Wake-sleep Conditions were well-matched after transforming scores.

There was a significant interaction effect between Circadian Condition and Test Session ($F(2,132)=5.82, p=.004, \eta^2=.08$) but not between Child Group and Test Session ($F(4,132)=2.06, p=.09, \eta^2=.06$), indicating that the pattern of scores between Test Sessions differed by Circadian Condition but not by Child Group. The Child Group by Circadian Condition by Test Session interaction was also not significant ($F(4,132)=0.61, p=.65, \eta^2=.02$), meaning that the pattern of scores between Test Sessions for each Child Group was not dependent on the Circadian Condition.

These interactions were investigated in further detail by conducting repeated measures ANOVAs for each Child Group with the between-subjects factor of Circadian Condition.

In the TD group but not the DS or WS groups there was a main effect of Test Session (TD: $F(2,64)=8.25, p=.001, \eta^2=.21$; DS: $F(2,30)=1.66, p=.21, \eta^2=.10$; WS: Wilks' Lambda=.89, $F(1.55,29.35)=0.58, p=.34, \eta^2=.11$). The interaction between Test Session and Circadian Condition was significant only in the WS group (TD: $F(2,64)=2.29, p=.11, \eta^2=.07$; DS: $F(2,30)=.80, p=.45, \eta^2=.05$; WS: Wilks' Lambda=.48, $F(1.55,29.35)=5.38, p=.001, \eta^2=.52$), indicating differences in performance across Test Sessions between the two Circadian Conditions for children with WS.

Finally, to determine performance changes between each Test Session, repeated measures ANOVAs were conducted for each Child Group and Circadian Condition. The TD group in both Circadian Conditions showed a significant improvement on the task following the sleep retention interval but no significant change after wake. Children with DS showed no significant change in scores after wake or sleep. Children with WS in the Wake-sleep condition significantly improved on the task following sleep but not wake. Performance of children with WS in the Sleep-wake condition did not significantly change following sleep or wake, however the decline in performance following wake approached significance.
(\(p=.08\)). The change in number of moves and ANOVA results for repeated measures are presented in Table 4.

Table 4.

Changes in number of moves and repeated-measures ANOVA results for each Child Group (TD, DS, WS) and Circadian Condition (Sleep-wake, Wake-sleep) on the Tower of Hanoi task.

<table>
<thead>
<tr>
<th>Group</th>
<th>Condition</th>
<th>n</th>
<th>Retention interval</th>
<th>Change in number of moves</th>
<th>(F)</th>
<th>(p)</th>
<th>(\eta^2_p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>Sleep-wake</td>
<td>17</td>
<td>Sleep</td>
<td>-8.53</td>
<td>9.35</td>
<td>.01</td>
<td>.37</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>-3.32</td>
<td>.59</td>
<td>.45</td>
<td>.04</td>
</tr>
<tr>
<td>Wake-sleep</td>
<td>17</td>
<td>Sleep</td>
<td>-18.47</td>
<td>12.55</td>
<td>.003</td>
<td>.44</td>
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<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>2.15</td>
<td>.09</td>
<td>.77</td>
<td>.01</td>
</tr>
<tr>
<td>DS</td>
<td>Sleep-wake</td>
<td>8</td>
<td>Sleep</td>
<td>-12.01</td>
<td>2.23</td>
<td>.18</td>
<td>.24</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Wake</td>
<td>5.04</td>
<td>.50</td>
<td>.50</td>
<td>.07</td>
</tr>
<tr>
<td>Wake-sleep</td>
<td>9</td>
<td>Sleep</td>
<td>-3.33</td>
<td>1.41</td>
<td>.27</td>
<td>.15</td>
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<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>-2.07</td>
<td>.10</td>
<td>.76</td>
<td>.01</td>
</tr>
<tr>
<td>WS</td>
<td>Sleep-wake</td>
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<td>Sleep</td>
<td>-2.38</td>
<td>.33</td>
<td>.58</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>8.27</td>
<td>3.83</td>
<td>.08</td>
<td>.30</td>
</tr>
<tr>
<td>Wake-sleep</td>
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<td>Sleep</td>
<td>-16.44</td>
<td>18.40</td>
<td>.002</td>
<td>.65</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>6.95</td>
<td>1.37</td>
<td>.27</td>
<td>.12</td>
</tr>
</tbody>
</table>

Significant differences in **bold**

**Group differences for rule violations on the Tower of Hanoi.**

Using an identical analysis approach, rule violations on the Tower of Hanoi task were explored using a series of repeated-measures ANOVAs. Fourteen children with TD who did not commit any rule violations were not included in the analysis as they already performed
at ceiling level. Exclusion of these children did not affect the significance of the findings. All children with DS and WS made rule violations. The mean number of rule violations at each test session are shown in Table 5 and Figure 4.

Table 5. Number of rule violations made at each Test Session by Child Group (TD, DS, WS) and Circadian Condition (Sleep-wake, Wake-sleep) on the Tower of Hanoi task

<table>
<thead>
<tr>
<th>Condition Group</th>
<th>n</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
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<tbody>
<tr>
<td>Sleep-wake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TD</td>
<td>10</td>
<td>.85 (.97)</td>
<td>.05 (.16)</td>
<td>.25 (.63)</td>
</tr>
<tr>
<td>DS</td>
<td>8</td>
<td>5.31 (1.60)</td>
<td>3.50 (1.77)</td>
<td>4.56 (2.77)</td>
</tr>
<tr>
<td>WS</td>
<td>10</td>
<td>7.60 (2.83)</td>
<td>4.25 (2.78)</td>
<td>4.10 (2.27)</td>
</tr>
<tr>
<td>Wake-sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TD</td>
<td>10</td>
<td>.80 (.42)</td>
<td>.40 (.81)</td>
<td>.05 (.16)</td>
</tr>
<tr>
<td>DS</td>
<td>9</td>
<td>8.17 (3.00)</td>
<td>7.22 (3.31)</td>
<td>5.94 (3.57)</td>
</tr>
<tr>
<td>WS</td>
<td>11</td>
<td>7.82 (3.78)</td>
<td>8.14 (3.46)</td>
<td>4.59 (2.51)</td>
</tr>
</tbody>
</table>

Figure 4. Number of rule violations made across three sessions on the Tower of Hanoi task for each Child Group (TD, DS, WS) and Circadian Condition (Sleep-wake, Wake-sleep).
A repeated measures ANOVA with the within-subjects factor of Test Session (three levels: Test 1, Test 2, Test 3) and two between-subjects factors: Child Group (TD, DS, WS) and Circadian Condition (Sleep-wake, Wake-sleep) showed a significant main effect of Test Session ($F(2,104)=27.09, p<.001, \eta_{p}^2=.34$). There was also a significant main effect of Child Group ($F(2,52)=45.19, p<.001, \eta_{p}^2=.64$) whereby the TD group committed significantly fewer rule violations than children with DS and WS, who performed similarly. The effect of Circadian Condition was significant ($F(1.52)=6.35, p=.02, \eta_{p}^2=.11$), with fewer rule violations made overall by children in the Sleep-wake than the Wake-sleep condition.

There was a significant interaction effect between Circadian Condition and Test Session ($F(2,104)=9.50, p<.001, \eta_{p}^2=.15$) and between Child Group and Test Session ($F(4,104)=5.84, p<.001, \eta_{p}^2=.18$). The Child Group by Circadian Condition by Test Session interaction was also significant ($F(4,104)=2.73, p=.03, \eta_{p}^2=.10$).

These interactions were investigated in further detail by conducting repeated measures ANOVAs for each Child Group with the between-subjects factor of Circadian Condition. The main effect of Test Session was significant for all groups (TD: Wilks’ Lambda=.30, $F(1.43,25.66)=11.99, p<.001, \eta_{p}^2=.70$; DS: $F(2,30)=3.98, p=.03, \eta_{p}^2=.31$; WS: $F(2,38)=23.69, p<.001, \eta_{p}^2=.56$). The interaction effect between Test Session and Circadian Condition was significant only in the WS group (TD: Wilks’ Lambda=.80, $F(1.43,25.66)=1.77, p=.15, \eta_{p}^2=.20$; DS: $F(2,30)=2.03, p=.15, \eta_{p}^2=.12$; WS: $F(2,38)=8.71, p=.001, \eta_{p}^2=.32$), indicating differences in performance across Test Sessions between the two Circadian Conditions for children with WS.

Finally, to determine performance changes between each Test Session, repeated measures ANOVAs were conducted for each Child Group and Circadian Condition. The TD Sleep-wake condition showed a significant improvement on the task following the sleep retention interval, indicated by a reduction in the number of rule violations, but no significant change after wake. The TD Wake-sleep condition showed no significant change in number of rule violations after either sleep or wake. Children with DS showed no significant change in
scores after wake or sleep. Children with WS in both Circadian Conditions had significantly reduced number of rule violations following sleep, but not wake. The change in number of rule violations and ANOVA results for repeated measures are presented in Table 6.

### Table 6.
Changes in number of rule violations and repeated-measures ANOVA results for each Child Group (TD, DS, WS) and Circadian Condition (Sleep-wake, Wake-sleep) on the Tower of Hanoi task

<table>
<thead>
<tr>
<th>Group</th>
<th>Condition</th>
<th>n</th>
<th>Retention interval</th>
<th>Change in number of rule violations</th>
<th>F</th>
<th>p</th>
<th>ηp²</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>Sleep-wake</td>
<td>10</td>
<td>Sleep</td>
<td>-.80</td>
<td>9.44</td>
<td>.01</td>
<td>.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>.20</td>
<td>1.71</td>
<td>.22</td>
<td>.16</td>
</tr>
<tr>
<td></td>
<td>Wake-sleep</td>
<td>10</td>
<td>Sleep</td>
<td>-.35</td>
<td>2.00</td>
<td>.19</td>
<td>.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>-.40</td>
<td>2.09</td>
<td>.18</td>
<td>.19</td>
</tr>
<tr>
<td>DS</td>
<td>Sleep-wake</td>
<td>8</td>
<td>Sleep</td>
<td>-1.81</td>
<td>4.33</td>
<td>.08</td>
<td>.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>1.06</td>
<td>2.72</td>
<td>.14</td>
<td>.28</td>
</tr>
<tr>
<td></td>
<td>Wake-sleep</td>
<td>9</td>
<td>Sleep</td>
<td>-1.28</td>
<td>2.47</td>
<td>.16</td>
<td>.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>-.94</td>
<td>1.08</td>
<td>.33</td>
<td>.12</td>
</tr>
<tr>
<td>WS</td>
<td>Sleep-wake</td>
<td>10</td>
<td>Sleep</td>
<td>-3.35</td>
<td>30.13</td>
<td>&lt;.001</td>
<td>.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>-.15</td>
<td>.12</td>
<td>.73</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>Wake-sleep</td>
<td>11</td>
<td>Sleep</td>
<td>-3.55</td>
<td>29.59</td>
<td>&lt;.001</td>
<td>.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wake</td>
<td>.32</td>
<td>.21</td>
<td>.66</td>
<td>.02</td>
</tr>
</tbody>
</table>

Significant differences in **bold**

**Association Between Baseline Performance and Sleep-Dependent Learning**

To explore our one-tailed hypothesis that children who were high performers at baseline would show the greatest sleep-dependent gains, partial correlations for each Child Group were used to control for age and correlate score at Test 1 with sleep-related change in score
(calculated as score before sleep minus score after sleep). There was a significant negative correlation for children with DS ($r=-.63$, $p=.005$, one-tailed), and the negative correlation for children with WS approached significance ($r=-.38$, $p=.051$, one-tailed), indicating that, contrary to our hypothesis, for these two groups children with better baseline performance showed the least increase in sleep-related gains. There was no significant association for the TD group ($r=-.07$, $p=.34$, one-tailed).

There were no significant correlations between baseline performance and sleep-related change in score for rule violations after controlling for age in any group (all $p$ values <.05, one-tailed).

A median split was performed on each group to categorise participants as high or low performers based on scores at Test 1. Chi-square was then used to assess whether performance at Test 1 (high, low) was associated with an improvement, decline, or no change in sleep-related change in score. This showed that only for the DS group was there a significant effect, driven by low performers at baseline showing the most sleep-related improvement (TD: $\chi^2(1,34)=0.00$, $p=.67$ one-tailed, phi=.00; DS: $\chi^2(2,17)=6.42$, $p=.02$ one-tailed, exact $p$ not available due to low cell counts, phi=.61; WS: $\chi^2(1,21)=0.10$, $p=.59$ one-tailed, phi=.07) (see Table 7).

Identical analyses were performed to investigate rule violations. Chi-square showed no significant association between baseline performance and sleep-related improvement on the task for any group (all $p$ values<.05, one-tailed).
Table 7.
Number of children whose performance on the Tower of Hanoi task improved, reduced or did not change following sleep. Split by Child Group (TD, DS, WS) and high and low performance at Test 1

<table>
<thead>
<tr>
<th></th>
<th>Improvement</th>
<th>Reduction</th>
<th>No change</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High performance</td>
<td>14</td>
<td>3</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Low performance</td>
<td>14</td>
<td>3</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>6</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>DS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High performance</td>
<td>2</td>
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<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Low performance</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>WS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High performance</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Low performance</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>12</td>
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<tr>
<td>Total</td>
<td>17</td>
<td>4</td>
<td>0</td>
<td>21</td>
</tr>
</tbody>
</table>

Association Between MA and Sleep-Dependent Learning
To test our third hypothesis, Pearson’s correlations were used to assess the association between non-verbal mental age and sleep-related changes in score, and number of rule violations. There was no significant association between mental age and number of moves taken (all \( p \) values>.05). For rule violations, children in the TD group showed a reduction in sleep-related gains with increasing mental age, whilst children with WS showed
increased sleep-related gains with increasing mental age (TD: $r=.61, p=.002$ one-tailed; DS: $r=.04, p=.44$ one-tailed; WS: $r=-.49, p=.01$ one-tailed).

**Discussion**

The present study was the first to use the Tower of Hanoi task to assess cognitive procedural sleep-dependent learning in children (Ashworth et al., 2014) and the first to provide a cross-syndrome comparison in children with DS and WS. It benefitted from a counterbalanced design, giving confidence that the findings were not due to circadian effects on learning or simply improved performance due to increased number of sessions. In general, all groups showed a trend towards greater improvement following sleep. Performance often declined over the wake interval, possibly due to fatigue in the evening test session, albeit this effect did not reach statistical significance. Both TD Circadian Conditions showed a significant reduction in the number of moves taken to complete the task, and the TD Sleepwake condition also showed a reduction in rule violations following sleep. That the TD Wake-sleep condition did not reduce their rule violations significantly following sleep probably reflects the near ceiling effect in this group, thus there was little scope for improvement.

Children in the DS Sleep-wake condition reduced their mean score by 12 moves (after adjustment) following sleep. In comparison to the significant sleep-dependent improvement of 8.53 moves in the TD Sleep-wake condition, this seems a considerable improvement, yet it is not significant, likely due to greater variability in performance and only having eight participants in the DS Sleep-wake condition which limited power to detect moderate to modest effects. Similarly, for children with DS there was no significant change in the number of rule violations made following sleep or wake, though the reduction following sleep for the Sleep-wake condition approached significance ($p=.08$). It is possible that sleep abnormalities in this group interfere with their ability to consolidate memories during sleep, or that children with DS have reduced resources available to devote to offline
consolidation so sleep preferentially consolidates more recent or more salient aspects of the day. Conversely, although the findings did not reach statistical significance, mean scores indicate that children with DS in the Wake-sleep condition reduced their moves taken and rule violations following both wake and sleep retention intervals. This echoes our previously reported findings for sleep-dependent declarative memory consolidation, whereby children with DS remembered novel words better and for longer when they were taught in the morning as opposed to the evening (Ashworth et al., 2017). This may reflect the accumulation of sleep pressure throughout the day due to poor night-time sleep; thus, hindering consolidation from evening learning. Differing possible explanations for findings in our DS group warrant further research.

For children with WS, significant interactions between Test Session and Circadian Condition indicated an overall improvement in performance following sleep and a decline after the wake retention interval for the number of moves, and number of rule violations made on the task. Further investigation showed that only children in the Wake-sleep condition reduced their number of moves following sleep but not wake; and children with WS in both Circadian Conditions reduced their rule violations following sleep. This contrasts with performance on a declarative task, where we previously reported that children with WS preferentially consolidate memories between learning and the first retest, regardless of whether or not sleep occurs during the retention interval (Ashworth et al., 2017). This pattern of findings suggests time-dependent consolidation for declarative memories and sleep-dependent consolidation for procedural memories for children with WS. Further research will be necessary to extend findings as they have important implications for educational practices; specifically, teaching children with DS the most difficult or important information during morning lessons when they are better able to consolidate new information, and for all children, using their natural sleep as an aid to learning by revisiting newly learnt material the following day. Developing educational strategies that factor in children’s sleep and circadian influences on learning are hugely
important, in particular for children with developmental disorders and intellectual
disabilities as learning in the classroom may be extended to learning life skills and self-care,
which will affect their later ability to live independently and quality of life.

Our findings suggest that children with TD and WS benefit from sleep for the consolidation
of new cognitive procedural skills and task rules, whereas children with DS appear to have
an atypical learning strategy in terms of sleep-dependent learning. Learning on the Tower
of Hanoi task has been shown to be dependent upon REM sleep in healthy adults (Smith,
1995; Smith et al., 2004). Individuals with DS are known to have reduced REM sleep (Nisbet
et al., 2015), which may be responsible for their lack of sleep-dependent gains on the task.
Nonetheless, individuals with WS also have reduced REM sleep (Gombos et al., 2011), but
did show a sleep-dependent improvement. Indeed, differences in the role that REM sleep
plays in neurobehavioural function for children with developmental psychiatric disorders
relative to TD have recently been reported (Kirov, Brand, Banaschewski, & Rothenberger,
2017). This warrants further investigation in children with DS and WS, including how
sleep-dependent changes at a neural level translate to behavioural outcomes. In addition,
sleep problems such as OSAS, which is common in DS, should be investigated alongside
sleep-dependent learning, since OSAS is known to affect neurobehavioural functioning,
commonly occurs during REM sleep, and could exacerbate the effects of reduced REM sleep
(Breslin et al., 2014; Tauman & Gozal, 2011). Given previous research suggesting that
children's pre-sleep level of performance affects their subsequent memory consolidation
(Wilhelm et al., 2012), we predicted that high baseline performers would show the greatest
sleep-dependent gains. Our hypothesis was not supported. In fact, we found an unexpected
negative association between baseline task performance and sleep-related gains for
children with DS, and approaching significance for WS. We hypothesise that this finding is
explained by the finite level of improvement that can be achieved on this task (i.e.,
completing it in the fewest possible moves), hence children with the poorest performance
had the most scope for improvement.
Smith et al. (2004) found that improvement on the Tower of Hanoi task was associated with IQ; adults with the highest IQs showed greater improvement on the task and also a greater increase in REMs and REM density from baseline on the post-learning night, compared to adults with the lowest IQs. Thus, we predicted that children with a higher MA, as a proxy measure of IQ, would show the greatest sleep-related improvements on the task. Our hypothesis was supported in the WS group, who showed increased sleep-related improvement by making fewer rule violations on the task with increasing MA; however, children with TD actually showed fewer sleep-related gains with increasing age for rule violations. Since there were very few rule violations made by the TD group, we expect that this is a spurious finding. Further research is needed to assess whether the association between learning, REM sleep and IQ in adults could be generalised to children with TD and, further, to children with DS and WS. Indeed, in a sample of eight young adults with DS, Diomedi et al. (1999) found that lower IQ was related to reduced REMs and REM percentage. They propose that this reflects a reduction in neural plasticity and the ability to consolidate new information during REM sleep, although they did not research sleep-dependent learning directly. Thus, it is likely that the sleep-dependent learning deficit in individuals with DS could extend beyond the present task and generalise to their difficulties in other areas. Importantly, it suggests that we cannot assume that children with developmental disorders are simply delayed: they are atypical in their learning, which is possibly related to differences in sleep-dependent memory consolidation.

Limitations

The current study was limited by the number of participants and would benefit from including a group of children who were tested at 24 hours post-learning, enabling investigation of time-of-day effects on memory consolidation and overcoming the necessary drawback in the current study of unequal retention intervals. Increasing participant numbers would result in greater power to detect significant findings with moderate to modest effects. For greater generalisability, future studies should use a
larger sample size and recruit from more diverse socioeconomic and ethnic groups. Socioeconomic status should be ascertained using reliable measures. Detailed descriptive background data for participants, which were not collected in the current study, would allow for analysis of potential subgroup differences in a larger sample.

Between-group differences in recruitment strategy meant that almost all families of children with WS who were approached finally took part in the study, whilst only around half of initial contact with DS families led to participation (see Footnote 1). A limitation here is that data are not available on the number of families in the DS and TD groups who were approached with study information but who did not respond.

Whilst we used actigraphy to measure sleep, and thus benefited from a study of sleep in the child’s natural environment that was tolerated by children with intellectual disability, further research would benefit from more detailed sleep studies using polysomnography to determine the finer characteristics of sleep (e.g., REMs and sleep architecture) which may provide firmer associations with sleep-dependent learning.

Conclusions

Generally, children with TD and with WS took fewer moves to complete the Tower of Hanoi task and made fewer rule violations after a night of sleep. Thus, it appears that both groups benefitted from sleep for the consolidation of cognitive procedural memories and declarative rules of the task. This is the first study to compare cognitive procedural sleep-dependent learning in children with DS and WS. Our data should be replicated and extended with detailed measures of sleep quality and sleep architecture to determine the extent to which poor sleep impacts the learning potential of these children.
References


1. The higher percentage of WS families taking part was because these families were already members of the Williams Syndrome Foundation who had agreed to take part in research studies, whilst no such database was available for the DS or TD groups.