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PAPER

A cross-syndrome study of the differential effects of sleep on declarative memory consolidation in children with neurodevelopmental disorders

Anna Ashworth,[1] Catherine M. Hill,[2] Annette Karmiloff-Smith[3] and Dagmara Dimitriou[4]

1. *Centre for Research in Psychology, Behaviour and Achievement, Coventry University, UK*
2. *Clinical Experimental Sciences, Faculty of Medicine, University of Southampton, UK*
3. *Centre for Brain and Cognitive Development, Birkbeck, University of London, UK*
4. *Lifespan Learning and Sleep Laboratory, UCL, Institute of Education, UK*

Abstract

*Sleep plays an active role in memory consolidation. Because children with Down syndrome (DS) and Williams syndrome (WS) experience significant problems with sleep and also with learning, we predicted that sleep-dependent memory consolidation would be impaired in these children when compared to typically developing (TD) children. This is the first study to provide a cross-syndrome comparison of sleep-dependent learning in school-aged children. Children with DS (*n *= 20) and WS (*n *= 22) and TD children (*n *= 33) were trained on the novel Animal Names task where they were taught pseudo-words as the personal names of ten farm and domestic animals, e.g. Basco the cat, with the aid of animal picture flashcards. They were retested following counterbalanced retention intervals of wake and sleep. Overall, TD children remembered significantly more words than both the DS and WS groups. In addition, their performance improved following night-time sleep, whereas performance over the wake retention interval remained stable, indicating an active role of sleep for memory consolidation. Task performance of children with DS did not significantly change following wake or sleep periods. However, children with DS who were initially trained in the morning continued to improve on the task at the following retests, so that performance on the final test was greater for children who had initially trained in the morning than those who trained in the evening. Children with WS improved on the task between training and the first retest, regardless of whether sleep or wake occurred during the retention interval. This suggests time-dependent rather than sleep-dependent learning in children with WS, or tiredness at the end of the first session and better performance once refreshed at the start of the second session, irrespective of the time of day. Contrary to expectations, sleep-dependent learning was not related to baseline level of performance. The findings have significant implications for educational strategies, and suggest that children with DS should be taught more important or difficult information in the morning when they are better able to learn, whilst children with WS should be allowed a time delay between learning phases to allow for time-dependent memory consolidation, and frequent breaks from learning so that they are refreshed and able to perform at their best.*

Research highlights

- This is a novel study investigating sleep-dependent learning in children with Down syndrome and Williams syndrome.
- For children with Down syndrome, sleep-dependent memory gains only approached significance when learning took place in the morning, rather than the evening.
- Memory consolidation in children with Williams syndrome appears to be time-dependent, rather than sleep-dependent.
- Syndrome-specific educational strategies should be developed to integrate sleep, time-course and time of day to optimize children's learning.

Address for correspondence: Anna Joyce (née Ashworth), Centre for Research in Psychology, Behaviour and Achievement, Coventry University, Priory Street, Coventry CV1 5FB, UK; e-mail: anna.joyce@coventry.ac.uk

Introduction

There is compelling evidence that sleep plays a key role in the ability to form and retrieve certain types of memories. Children with neurodevelopmental disorders experience considerable problems with sleep and also with learning (Dyken, Lin-Dyken, Poulton, Zimmerman & Sedars, 2003; Roizen & Patterson, 2003); yet scarcely any studies have investigated this relationship. The present study focuses on sleep-dependent learning of explicit information in two groups: Down syndrome (DS) and Williams syndrome (WS).

Sleep is characterized by reduced consciousness and responsiveness to external stimuli. Despite the apparent bodily quiescence associated with sleep, this state is associated with discrete patterns of brain activation supporting important physiological functions. Broadly, there are two distinct types of sleep: non-rapid eye movement (NREM) and rapid eye movement (REM). NREM is further divided into stages I, II and III, which correspond with deeper stages of sleep and a slowing of electroencephalogram (EEG) activity. Stage III, the deepest stage, is also known as slow wave sleep (SWS). REM is the stage normally associated with memorable dreaming and is characterized by low amplitude mixed frequency EEG similar to wake. These four stages repeat throughout the night in a distinct cyclical pattern (Kahn, Dan, Groswasser, Franco & Sottiaux, 1996; Ohayon, Carskadon, Guilleminault & Vitiello, 2004).

In both adults and children, sleep aids the consolidation of explicit or declarative memory traces; that is memory for facts or events that can be explicitly recalled or 'declared'. This leads to improved retention following sleep compared to wake, even without further practice (Wilhelm, Diekelmann & Born, 2008; Walker, Brakefield, Morgan, Hobson & Stickgold, 2002). This differs from implicit or procedural learning, which shows sleep-dependent consolidation in adults but not always in children (Ashworth, Hill, Karmiloff-Smith & Dimitriou, 2014; Wilhelm *et al.*, 2008). Sleep-dependent declarative learning is often assessed using a task involving novel learning of paired words, with recall of the second word of each pair when prompted with the first. One of the first such studies in children found that 9- to 12-year-olds recalled more concrete noun pairs following a retention interval of sleep than an equivalent period of wake (Backhaus, Hoeckesfeld, Born, Hohagen & Junghanns, 2008). Retention of word pairs correlated positively and significantly with percentage of time spent in NREM sleep, and negatively with percentage of REM sleep. Similarly, in adults, declarative memory consolidation preferentially occurs during NREM sleep (Plihal & Born, 1997). This is thought to occur by offline reactivation of neural pathways involved in learning, thereby transferring new, unstable memory representations from the hippocampus to neocortical networks for long-term storage and hippocampal independence (Born & Wilhelm, 2012). These consolidation mechanisms may replay most efficiently during SWS when there is little other interfering background electrical activity in the brain and low levels of acetylcholine in the hippocampus, a neurotransmitter known to be involved in memory (Gais & Born, 2004). Sleep-dependent declarative learning appears to occur throughout development. Children, adolescents and adults are able to remember more word pairs following sleep than following an equivalent period of wake, regardless of whether initial training takes place in the morning or evening (Plihal & Born, 1997; Potkin & Bunney, 2012; Wilhelm *et al.*, 2008). Sleep also aids consolidation of novel non-words in both adults (Davis, Di Betta, Macdonald & Gaskell, 2009; De Koninck, Lorrain, Christ, Proulx & Coulombe, 1989) and children (Ashworth *et al.*, 2014; Henderson, Weighall, Brown & Gaskell, 2012).

Although evidence is mixed (see Diekelmann, Wilhelm & Born, 2009, for a review), the pre-sleep level of performance appears to influence the degree of sleep-dependent learning that occurs on the post-learning night. For example, Tucker and Fishbein (2008) demonstrated that sleep-dependent gains on three declarative memory tasks (maze learning, word pairs and complex figures) only occurred for adult participants who were high performers, as opposed to low performers, at baseline. In TD children it has been evidenced that sleep-dependent learning on a procedural task requires a certain pre-sleep level of skill (Wilhelm, Metzkow-Mészàros, Knapp & Born, 2012). Conversely, Drosopoulos, Schulze, Fischer and Born (2007) found that word pairs were more likely to be consolidated during sleep when encoding strength was manipulated to be weaker. These apparently conflicting findings may be explained on an individual level; sleep may be more beneficial for consolidating weakly than strongly associated memories, but may be generally less effective in low-performing individuals. This is supported by evidence that on the Tower of Hanoi problem solving task, where individuals with the highest IQ, and therefore assumed to have the greatest learning potential, showed the greatest changes in sleep architecture (increase in REMs and REM density) from baseline, which correlated significantly with improvement on the task (Smith, Nixon & Nader, 2004). This suggests a strong, possibly two-way, relationship between intelligence and sleep architecture.

Childhood is characterized by rapid acquisition of knowledge and skills; thus optimum means of integrating new information to long-term storage are essential for greater educational attainment and life opportunities. It is important that memory consolidation occurs on a daily basis, and it is now clear that sleep plays an active role in this process. Developmental differences in sleep architecture may reflect the intense degree of learning that occurs during childhood, necessitating considerably more NREM sleep for the consolidation of newly learnt declarative material.

Down syndrome

DS is the most common sporadic chromosomal anomaly, affecting around 1 in 1000 live births and usually associated with the occurrence of an additional copy of chromosome 21 (trisomy 21) (Roizen & Patterson, 2003). Although there is wide variability in phenotype, individuals with DS tend to have distinctive physical characteristics and learning difficulties, with an average IQ usually around 50 points (range 30 to 70). The cognitive profile comprises a distinct pattern, with relative strengths in visual and spatial domains along with weaknesses in verbal abilities, including verbal memory (Glasson, Sullivan, Hussain, Petterson, Montgomery *et al*., 2002; Jarrold & Baddeley, 2001, 2002; Roizen & Patterson, 2003).

Sleep problems, especially breathing difficulties during sleep, are common in DS. Obstructive sleep apnoea syndrome (OSAS) occurs when the upper airway becomes occluded, causing difficulty in breathing during sleep. Associated apnoeas (cessation of breathing) and hypopnoeas (abnormally shallow breathing) lead to reduced oxyhaemoglobin, increased circulation of carbon dioxide and, thus, increased night wakings and fragmented sleep. OSAS is thought to affect up to 80% of individuals with DS (Dyken *et al*., 2003; Ng, Hui, Chan, Kwok, Chow *et al*., 2006) due to clinical features such as craniofacial and upper airway abnormalities, obesity, tonsil and adenoid encroachment, and generalized hypotonia (Churchill, Kieckhefer, Landis & Ward, 2011). The majority of sleep data in DS come from parent report studies which report daytime sleepiness (indicating inadequate night time sleep), as well as problems with settling, sleep maintenance and early morning waking (Ashworth, Hill, Karmiloff-Smith & Dimitriou, 2013; Breslin, Edgin, Bootzin, Goodwin & Nadel, 2011; Carter, McCaughey, Annaz & Hill, 2009; Stores, Stores, Fellows & Buckley, 1998). Sleep problems, including OSAS (Andreou, Galanopoulou, Gourgoulianis, Karapetsas & Molyvdas, 2002; Breslin, Spanò, Bootzin, Anand, Nadel *et al*., 2014) and a reduction in REM sleep (Diomedi, Curatolo, Scalise, Placidi, Caretto *et al*., 1999), have been linked to poorer cognitive abilities and IQ in individuals with DS. To our knowledge, no studies have hitherto investigated sleep-dependent learning in DS.

Williams syndrome

WS is a rare sporadic genetic condition affecting around 1 in 20,000 live births. It is caused by a deletion of around 28 genes on the long arm of one copy of chromosome 7 at q11.23, which includes at its centromere the elastin locus. WS is characterized by distinctive physical features including cardiovascular and musculoskeletal abnormalities, hyper-sociability and relatively high performance on some language tasks, such as verbal memory and vocabulary knowledge, despite an average IQ of 56 (range 50 to 70) (see Donnai & Karmiloff-Smith, 2000, for an overview).

Very few studies have investigated sleep problems in WS. Objective measures and parent-report studies have found long sleep latencies and increased night wakings (Annaz, Hill, Ashworth, Holley & Karmiloff-Smith, 2011; Ashworth *et al*., 2013; Mason, Arens, Sharman, Bintliff-Janisak, Schultz *et al*., 2011), whilst parents also report settling problems at bedtime, bed wetting, getting up for the bathroom, body pain and sleep anxiety (Annaz *et al*., 2011; Ashworth *et al*., 2013; Sarimski, 1996; Udwin, Yule & Martin, 1987). Objective studies have also shown that periodic limb movements during sleep (PLMS) may be common (Arens, Wright, Elliott, Zhao, Wang *et al*., 1998; Goldman, Malow, Newman, Roof & Dykens, 2009) alongside differences in sleep architecture including decreased rapid eye movement and increased slow wave sleep (Gombos, Bódizs & Kovács, 2011; Mason *et al*., 2011). In addition, children with WS have been shown to have abnormal evening levels of sleep-related hormones melatonin and cortisol, which could adversely affect sleep (Sniecinska-Cooper, Iles, Butler, Jones, Bayford *et al*., 2015).

Parentally reported shorter sleep duration in toddlers with WS has been linked to delayed language development relative to children with longer sleep duration (Axelsson, Hill, Sadeh & Dimitriou, 2013). To our knowledge, only one study has hitherto investigated sleep-dependent learning in WS (Dimitriou, Karmiloff-Smith, Ashworth & Hill, 2013). Twelve children with WS and 15 TD children (age range 6 to 12 years, $M = 8.6$) completed a motor memory task: the finger tapping task. Children were trained on the task in the evening and retested the following morning and afternoon. Following sleep, the TD group significantly improved in speed and accuracy but there was no evidence of sleep-related

learning in WS. This lack of improvement in the WS group could either be attributed to sleep problems or to possible difficulties with fine motor movements that are needed to perform the finger-tapping task.

Despite clear evidence that children with DS and WS have problems with sleep and also with learning, to our knowledge no studies have hitherto investigated sleep-dependent declarative learning in these groups. The present study is therefore the first to assess this relationship in school-aged children with DS and WS and does so using a novel explicit learning task. These make interesting comparison groups due to having similar levels of intellectual disability alongside contrasting strengths and weaknesses. They also experience different types of sleep problems, which could have differing effects on cognitive abilities, for example, increased SWS in WS could mean preserved sleep-dependent learning, whilst increased OSAS-related disturbance in DS could lead to greater problems with general cognition, including memory consolidation.

Based on previous findings that children with DS and WS experience significant sleep and learning problems relative to TD, we predict that (i) children with DS and WS will be impaired on the learning task relative to TD children; (ii) due to the language basis of the learning task and their relative strength in this area, children with WS will be less impaired on the learning task than children with DS; (iii) TD children will show sleep-related improvements on the learning task; (iv) sleep-dependent learning will be impaired in children with DS; (v) children with WS may show evidence of sleep-dependent learning on the task; and (vi) sleep-dependent gains in performance will be related to better baseline performance on the task.

Methods

Participants

Twenty-two children with DS (11 male), 22 children with WS (10 male) and 34 TD children (17 male) took part in the study. The majority of children were from middle-class socioeconomic backgrounds and were predominantly Caucasian. Data were removed for two boys with DS (aged 7 and 8 years) who were unable to complete the learning task, and from one 9-year-old TD girl who performed at ceiling. Details of the final sample are shown in Table 1. Analysis of Variance (ANOVA) and chi-square tests, respectively, yielded no significant chronological age ($F(2, 72) = .27$, $p = .76$, $\eta_p^2 = .01$) or sex differences (χ^2 $(2, 75) = .29$, $p = .86$, phi = .06) 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 ($F(2, 72) = 98.65$, $p < .001$, $\eta_p^2 = .73$) (see Table 1).

TD children were recruited through local primary schools in London, England. Parents of children with DS were contacted through local support groups, special needs schools and parental groups. Parents responded either to the school/group or directly to the researcher if they wished to take part in the study. Children with WS were recruited through the Williams Syndrome Foundation, UK. Parents were contacted initially by telephone and were later given full information in writing. 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 hybridization* test. Children were excluded from the study if they had co-morbid disorders such as attention deficit hyperactivity disorder or autism, psychiatric conditions, or if they were taking any hypnotic medication. The Institute of Education, University of London Research Ethics Committee granted ethical approval 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.

Animal Names task

The Animal Names task was developed to improve upon the commonly used word pairs task, employing a concept that was more interesting and engaging for

Table 1 *Participant details*

Group	*N*	Male/female	Age in years (*M* (*SD*))	Age range (years)	RCPM Raw score (*M* (*SD*))	Mental age equivalent
TD	33	17/16	9.22 (1.60)	6.19–12.90	27.68 (5.35)	11
DS	20	9/11	9.59 (2.00)	6.09–12.23	12.60 (3.53)	Under 5
WS	22	10/12	9.24 (2.13)	6.08–12.58	14.64 (3.02)	6

participants as well as being easy to understand. The development of the final procedure was assisted by several pilot studies, which showed that this modification was necessary for testing children with DS and WS. This also determined that the task should not be computerized, since the flashcard method allowed the researcher ultimate control of ensuring that the participant was engaged with the task and the ability to allow for distractions.

Children were told that they would be learning the personal names of 10 animals. Farm and domestic animals therefore became the anchor for learning 10 pseudo-words as realistic-sounding names obeying the phonotactics of English. These were Basco the Cat, Razz the Chicken, Artoo the Cow, Kobi the Dog, Spyro the goat, Orin the Horse, Galba the Mouse, Jaala the Pig, Dax the Rabbit and Eagus the Sheep (see Figure 1 for example images).

Ten A6-sized flashcards were printed and laminated with attractive coloured images of each animal. Prior to learning the names it was ensured that all children recognized the animal images. Stimuli were then presented one at a time in random order; the child was told each name and asked to repeat it aloud. For example, the researcher would say 'This is Basco the cat. Can you say it?' The child would say 'Basco the cat' and the researcher responded 'Yes, Basco the cat'. If the child was incorrect, the researcher said 'No, Basco the cat. Can you say it?' After approximately 3 seconds' pause, the next animal was presented. This procedure was conducted for each card. Cards were then shuffled to randomize the order and to avoid primacy or recency effects. The child was again shown each animal and asked if they could remember the name. The researcher then either repeated the name, 'Well done, Basco the cat', or told them the name again, 'This is Basco the cat'. Once complete for all animals, the cards were shuffled and presented a further three times, so that each child was told the names five times in total. The learning phase took around 15 minutes to complete.

Each child then spent around half an hour completing a non-verbal cognitive puzzle (the Tower of Hanoi) to assess sleep-dependent learning on an implicit task. Similar results for the TD group on the Animal Names and Tower of Hanoi tasks have previously been published (Ashworth *et al.*, 2014). Finally, children were tested on the animal names by being shown the cards in random order and asked if they could remember the name (Test 1). This time, to avoid further learning, they were given no feedback. Two points were awarded for a correct answer and one point for an almost correct answer if one phoneme was incorrect, for example 'Pax the rabbit' (instead of Dax). Where children were unable to correctly enunciate the name even during the learning phases, their best effort during training was taken as correct. Points were not awarded if a child gave a correct name for the wrong animal. Children were retested following retention intervals of wake and sleep (Tests 2 and 3). Again, they were not given feedback.

Possible circadian effects on learning (Kuriyama, Stickgold & Walker, 2004) were controlled for by training half of the children in the morning (Wake-Sleep group), and the other half in the evening (Sleep-Wake group). They were then tested twice at approximately 12 (Test 2) and 24 (Test 3) hours post-training following intervals of wake and sleep (Figure 2). At Test 3, children were told the animals' names once more. They then completed the Tower of Hanoi task again for around 10 minutes before being tested on the names for a final time (Test 4). Test 4 allowed the possibility of an in-session memory test to ensure that children had not already reached their maximum ability. *T*-tests and chi-square, respectively, showed no significant age or sex differences between the Sleep-Wake and Wake-Sleep groups (all p values $> .05$).

Evening sessions took place at the child's home, with time ranging from 17:45 to 20:45 (mean 19:10) depending on bedtime. Morning sessions were usually at the child's school and occurred between 07:25 and 10:30 (mean 08:54). This gave an average time interval of

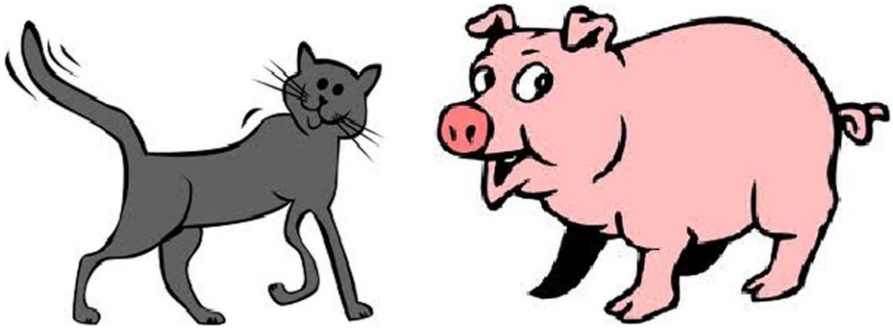

Figure 1 *Example of Animal Names flashcard images: Basco the cat and Jaala the pig.*

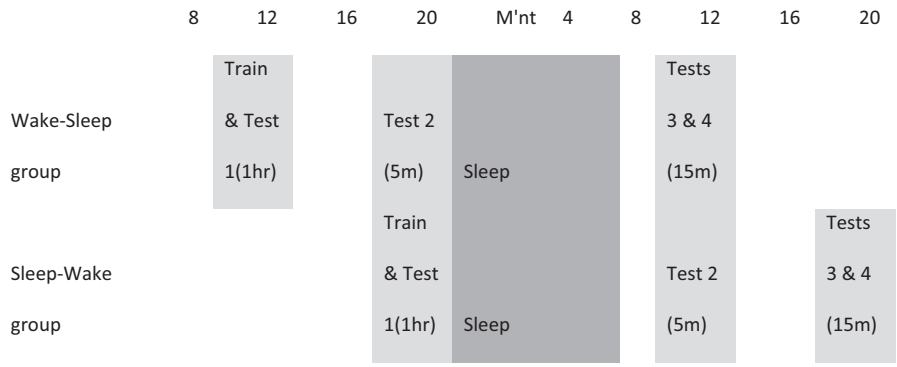

Figure 2 *Testing schedule for Wake-Sleep and Sleep-Wake groups.*

10:12 hours between morning and evening testing (range: 08:30 to 11:45 hours), and 13:30 hours between evening and morning testing (range: 11:55 to 15:15 hours). Between-groups ANOVAs showed significant differences in interval length between the three groups (sleep interval: $F(2, 72) = 7.20$, $p = .001$, $\eta_p^2 = .17$; wake interval: $F(2, 72) = 4.93$, $p = .01$, $\eta_p^2 = .12$) driven by children with DS having a 43-minute longer sleep interval and 36-minute shorter wake interval relative to the TD group. 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 minimize disruption to normal routines and bedtimes.

Children were individually tested, 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 minimize the interference effects that may occur from wake 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 just 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.

Results

Data were analysed using IBM Statistical Package for Social Sciences V.22 and screened for outliers using Cook's distances. Outlying scores are common in developmental disorders due to the variability between children, and removal of outliers (2 TD, 3 DS, 3 WS) did not change the significance of findings here; thus, children with outlying scores were included in the analyses (see Thomas, Annaz, Ansari, Scerif, Jarrold *et al.*, 2009). Outlying scores tended to be for children who performed particularly well on the task.

First, we assessed that the DS and WS groups were well matched at baseline using an ANOVA to compare scores at Test 1 between the three groups. Animal Names data were then analysed using repeated measures ANOVAs. The between-subjects independent variables were the three Groups (TD, DS, WS) and two Conditions (Sleep-Wake, Wake-Sleep). Within-subjects dependent variables were scores on the task at each Session (Tests 1, 2, 3, 4). Post-hoc tests were conducted using the Bonferroni correction and for repeated measures ANOVAs, multivariate statistics are reported. Tests 1, 2 and 3 were investigated in one repeated measures ANOVA to study the interaction between sleep and wake. Interactions were then further investigated with repeated measures ANOVAs for each Group and Condition. Test 4 was assessed in a separate ANOVA to compare with performance at Test 3.

In order to assess whether baseline performance was related to sleep-dependent learning, partial correlations were used for each Group to control for age and correlate score at Test 1 with sleep-related change in score (calculated as score after sleep minus score before sleep). In each Group a median split was used to divide participants into high and low performers based on scores at Test 1. A variable was computed to code whether there was an improvement, reduction, or no change in scores following sleep. Chi-square was then used to assess whether performance at baseline was related to sleep-dependent change in scores. Further, we used partial correlations to investigate whether there was a relationship between non-verbal mental age and sleep-related change in score after controlling for chronological age.

Baseline performance on the Animal Names task

ANOVA showed a significant difference between the TD, DS and WS groups at Test 1 ($F(2, 72) = 15.35$, $p < .001$, $\eta_p^2 = .30$), driven by the TD group scoring significantly

higher than both the DS ($p < .001$) and WS groups ($p < .001$). There was no significant difference in scores between the DS and WS groups ($p = 1.00$)

Assessing performance changes between Tests 1, 2 and 3

The repeated measures between-subjects ANOVA showed a significant main effect of Group ($F(2, 69) = 18.49$, $p < .001$, $\eta_p^2 = .35$), where the TD group had significantly higher scores than both the DS and WS groups ($p < .001$ for each), who did not significantly differ from one another ($p = 1.00$).

There was also a significant main effect of Session (Wilks' lambda = .81, $F(2, 68) = 8.25$, $p = .001$, $\eta_p^2 = .20$) whereby scores increased between Tests 1 and 2 ($p = .002$) but not between Tests 2 and 3 ($p = 1.00$). When split into the three groups, this main effect of Session was evident for the TD and WS groups but not the DS group (TD: Wilks' lambd = .57, $F(2, 30) = 11.30$, $p < .001$, $\eta_p^2 = .42$; DS: Wilks' lambda = .90, $F(2, 17) = .98$, $p = .40$, $\eta_p^2 = .10$; WS: Wilks' lambda = .36, $F(2, 19) = 16.94$, $p < .001$, $\eta_p^2 = .64$). Overall, both the TD and WS groups significantly improved on the task between Tests 1 and 2 ($p < .05$), but not between Tests 2 and 3.

As expected, the effect of Condition was not significant ($F(1, 69) = .07$, $p = .79$, $\eta_p^2 = .001$), indicating comparable scores between the Sleep-Wake and Wake-Sleep conditions. Scores are presented in Table 2 and illustrated in Figure 3.

There was a significant interaction effect between Group and Session (Wilks' lambda = .74, $F(4, 136) = 5.72$, $p < .001$, $\eta_p^2 = .14$) and between Condition and Session (Wilks' lambda = .86, $F(2, 68) = 5.79$, $p = .005$, $\eta_p^2 = .15$), meaning that pattern of scores at each Session differed between the three Groups and between the two Conditions.

The Group by Condition by Session interaction was not significant (Wilks' lambda = .91, $F(4, 136) = 1.59$, $p = .18$, $\eta_p^2 = .05$), meaning that, overall, the pattern of scores between tests for each Group did not depend on the Condition.

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

For the TD group, the interaction between Session and Condition approached significance (Wilks' lambda = .82, $F(2, 30) = 3.20$, $p = .06$, $\eta_p^2 = .18$). This interaction was significant for the DS group (Wilks' lambda = .60, $F(2, 17) = 5.76$, $p = .01$, $\eta_p^2 = .40$) but not for the WS group (Wilks' lambda = .88, $F(2, 19) = 1.30$, $p = .30$, $\eta_p^2 = .12$). This means that for the DS group the pattern of scores at each Session was dependent on Condition; and there was a trend for this effect in the TD group.

Repeated measures ANOVAs were then conducted to assess performance changes between each Session for each Group and Condition. The TD group in both Conditions showed a significant improvement on the task following the sleep retention interval but no significant change after wake. Children with DS showed no signif-

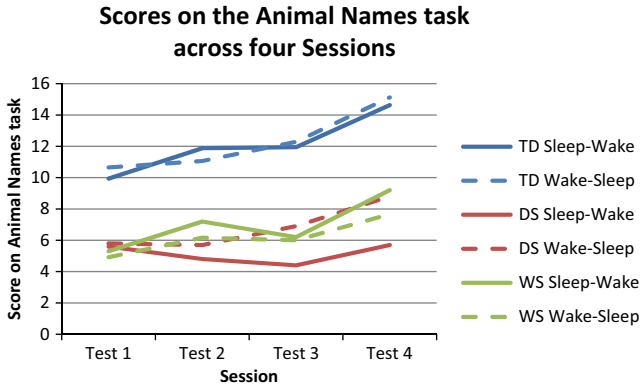

Figure 3 *Mean scores across four Tests on the Animal Names task for each Group (TD, DS, WS) and Condition (Sleep-Wake, Wake-Sleep). Maximum possible score of 20.*

Table 2 *Mean score (SD) at each session (Tests 1, 2, 3, 4) by Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep) on the Animal Names task (maximum possible score of 20)*

Condition/group	*n*	Test 1	Test 2	Test 3	Test 4
Sleep-wake		PM	AM	PM	PM
TD	16	9.94 (4.58)	11.88 (4.98)	11.94 (4.96)	14.63 (4.49)
DS	10	5.60 (3.03)	4.80 (3.19)	4.40 (2.72)	5.70 (3.89)
WS	10	5.30 (4.27)	7.20 (5.25)	6.20 (5.29)	9.20 (5.41)
Wake-sleep		AM	PM	AM	AM
TD	17	10.65 (4.40)	11.06 (3.40)	12.29 (3.67)	15.12 (3.33)
DS	10	5.80 (3.19)	5.70 (3.97)	6.90 (4.56)	8.80 (4.59)
WS	12	4.92 (2.87)	6.17 (2.72)	6.00 (3.38)	7.67 (4.05)

icant change in scores after wake or sleep, although there was a non-significant trend (p = .07) for children with DS in the Wake-Sleep Condition to improve on the task following sleep. Children with WS significantly improved on the task following their first retention interval, i.e. after sleep for the Sleep-Wake condition and after wake for the Wake-Sleep condition. Table 3 shows the change in score following each retention interval with repeated measures ANOVA results.

Assessing performance changes between Tests 3 and 4

To assess whether children's performance improved at the final test and that they had not already reached their maximum ability, a repeated measures ANOVA with between-subjects factors Group and Condition was conducted to compare score at Test 4 with score at Test 3. This showed a significant main effect of Session (Wilks' lambda = .51, $F(2, 69) = 67.67$, $p < .001$, $\eta_p^2 = .50$) caused by an overall increase in scores between Tests 3 and 4. Between-subjects comparisons showed a significant main effect of Group ($F(1, 69) = 24.60$, $p < .001$, $\eta_p^2 = .42$), where the TD group had significantly higher scores than both the DS and WS groups ($p < .001$ for each), who did not significantly differ from one another ($p = 1.00$). The effect of Condition was not significant ($F(1, 69) = .67$, $p = .42$, $\eta_p^2 = .01$), indicating comparable scores between the Sleep-Wake and Wake-Sleep conditions. Interactions between Group and Session, Condition and Session, and Group, Condition and Session were all non-significant (all p values > .05) indicating no differences in the pattern of scores between groups or conditions.

These interactions were investigated in further detail by conducting the repeated measures ANOVA for each Group with the between-subjects factor of Condition. This showed that all groups significantly improved on the Animal Names task at Test 4 (TD: Wilks' lambda = .38, $F(1, 31) = 51.09$, $p < .001$, $\eta_p^2 = .62$; DS: Wilks' lambda = .63, $F(1, 18) = 10.59$, $p = .004$, $\eta_p^2 = .37$; WS: Wilks' lambda = .51, $F(1, 20) = 19.37$, $p < .001$, $\eta_p^2 = .49$). There was no significant interaction between Condition and Session for any group (all p values > .05), meaning that for each Group the pattern of change in scores was comparable between Conditions.

Repeated measures ANOVAs were then conducted to assess performance changes between Tests 3 and 4 for each Group and Condition. TD children and children with WS in both Conditions and children with DS in the Wake-Sleep condition significantly improved on the task at Test 4 (see Table 3).

Relationship between baseline performance, mental age and sleep-dependent learning

Partial correlations controlling for age showed that there was no significant relationship between performance at Test 1 and change in score following sleep, for any group (TD: r = .12, p = .52; DS: r = .22, p = .38; WS: r = .39, p = .08).

Table 3 *Changes in score and repeated-measures ANOVA results for each Group (TD, DS, WS) and Condition (Sleep-wake, Wake-Sleep) on the Animal Names task*

Group	Condition	n	Interval	Change in score (95% CI)	F	p	η_p^2
TD	Sleep-Wake	16	**Sleep**	**1.94 (1.22–2.65)**	33.45	<.001	.69
			Wake	.06 (−.43–.56)	.07	.79	.01
			Test 4	**2.69 (1.48–3.90)**	22.39	<.001	.60
	Wake-Sleep	17	**Sleep**	**1.23 (.25–2.22)**	7.03	.02	.31
			Wake	.41 (−1.01–83)	.38	.55	.02
			Test 4	**2.83 (1.71–3.93)**	29.12	<.001	.65
DS	Sleep-Wake	10	Sleep	−.80 (−1.80–.20)	3.27	.10	.27
			Wake	−.40 (−.90–.10)	3.27	.10	.27
			Test 4	1.30 (−.13–2.73)	4.21	.07	.32
	Wake-Sleep	10	Sleep	1.20 (−.10–2.50)	4.38	.07	.33
			Wake	−.10 (1.59–1.39)	.02	.88	.00
			Test 4	**1.90 (.199–3.60)**	6.38	.03	.42
WS	Sleep-Wake	10	**Sleep**	**1.90 (1.04–2.76)**	25.19	.001	.74
			Wake	−1.00 (−2.01–.01)	5.00	.052	.36
			Test 4	**3.00 (1.12–4.88)**	13.07	.01	.59
	Wake-Sleep	12	Sleep	−.17 (−1.17–.84)	.13	.72	.01
			Wake	**1.25 (.43–2.07)**	11.30	.01	.51
			Test 4	**1.67 (.18–3.16)**	6.04	.03	.36

Note: Significant differences in **bold**. CI = Confidence Interval

Table 4 *Number of children whose performance on the Animal Names task improved, reduced or did not change following sleep. Split by Group (TD, DS, WS) and high and low performance at Test 1*

		Improvement	Reduction	No change	Total
TD	High performance	11	1	5	17
	Low performance	8	6	2	16
	Total	19	7	7	33
DS	High performance	7	4	1	12
	Low performance	3	3	2	8
	Total	10	7	3	20
WS	High performance	7	4	1	12
	Low performance	4	6	0	10
	Total	11	10	1	22

Chi-square showed that, whilst there was a consistent pattern across the three groups for high performers being more likely to improve on the task following sleep, these differences were not significant (TD: χ^2 (2, 33) = 5.31, p = .07, phi = .40; DS: χ^2 (2, 20) = 1.33, p = .51, phi = .26; WS: χ^2 (2, 22) = 2.05, p = .36, phi = .31) (see Table 4).

Partial correlations controlling for age showed that in the TD group there was a significant positive relationship between non-verbal mental age (based on RCPM raw score) and overnight performance gains on the Animal Names task. No significant relationship was found in the DS or WS groups (TD: r = .38, p = .03; DS: r = −.24, p = .33; WS: r = .20, p = .38). Correlations where chronological age was not controlled for yielded similar results.

Discussion

Sleep is an active state that aids the consolidation of newly acquired memories (Ashworth *et al*., 2014; Karni, Tanne, Rubenstein & Askenasy, 1994; Walker & Stickgold, 2004, 2006). Children with DS and WS experience significant problems with both sleep and learning, yet we know of only one previous study (Dimitriou *et al*., 2013) that has investigated sleep-dependent learning in children with WS, and none that have studied this phenomenon in DS. The present study used the newly developed Animal Names task to assess sleep-dependent learning of declarative information in 33 TD children, 20 children with DS and 22 children with WS. This is the first direct cross-syndrome comparison of sleep-dependent learning in neurodevelopmental disorders. All three groups were well-matched for age and sex, and the DS and WS groups were comparable in terms of non-verbal mental age and baseline performance on the Animal Names task.

As hypothesized, our data confirm previous reports of sleep-related consolidation of word pairs in TD children (Backhaus *et al*., 2008; Wilhelm *et al*., 2008), with performance scores increasing significantly following sleep compared to wake in the TD group, regardless of whether initial training took place in the morning or evening. That scores improved following sleep, rather than remaining stable, suggests an active role of sleep in the reinforcement of the memory traces for the Animal Names task. In addition, there was no decline in performance over the course of the day, so improved performance following sleep cannot simply be attributed to the fact that children were less tired than in the evening. The present study was carefully counterbalanced to control for circadian effects on learning and children were tested as close to the sleep period as possible; however, further control for time-of-day effects could be applied by employing a group of children who are first retested 24 hours after training (Kuriyama *et al*., 2004).

In contrast with TD children, and consistent with our hypothesis, children with DS did not show any significant change in memory performance between each session on the Animal Names task. Thus, learning did not appear to depend on sleep. Nevertheless, there was a weak trend (p = .07) for the Wake-Sleep group to improve after sleep, but not after wake, which was not evident in the Sleep-Wake group. In fact, performance of the Sleep-Wake group showed a non-significant decline in performance across Sessions. Hence, further research should examine whether these children may benefit from learning cognitively demanding tasks in the morning as opposed to the evening. School-age TD children tend to prefer morning rather than evening for intellectual and physical activities (Kim, Dueker, Hasher & Goldstein, 2002). The same may be true for individuals with DS but their distinct pattern of learning in the current study suggests that tiredness or accumulated sleep pressure throughout the day may have more impact on the learning of children with DS than it does on children with WS or TD children.

The Animal Names task was adapted from word-pairs and non-word learning tasks in order to be more appealing and engaging for children as well as being mindful of the specific needs of children with neurodevelopmental disorders. Only one TD child performed already at ceiling and only two children with DS were unable to complete the task, so it can be assumed to be of appropriate difficulty for the age range targeted, i.e. children aged 6 to 12, including those with developmental delay. Verbal memory and expressive language are

particular problems for individuals with DS (Hick, Botting & Conti-Ramsden, 2005; Ypsilanti & Grouios, 2008). Future studies of declarative sleep-dependent learning in individuals with DS could use tasks adapted to place fewer demands on these problem areas. The 2D object location task used by Wilhelm *et al*. (2008) with TD children may be suitable as a non-verbal declarative task for those with neurodevelopmental disorders. Alternatively, Jarrold, Thorn and Stephens (2009) used an Alien Names task to assess short-term verbal memory in children with DS, but reduced the demands on expressive language by providing multiple choice answers of similar sounding names. A task that enabled children with DS to perform at their full potential might therefore allow sleep-dependent gains to become more readily apparent.

In contrast, children with WS remembered more animal names at Test 2 than at Test 1, regardless of whether sleep or wake occurred in the retention interval. In addition, for the WS Sleep-Wake group, a decline in performance during wake between Tests 2 and 3 approached significance. This pattern of findings is interesting and difficult to explain since it did not appear to be related to sleep or wake, as predicted; nor was it related to the time of day (e.g. better performance in the morning). Further studies are needed to establish why the declarative memory of children with WS improved between one session and the next and, indeed, whether this is a reliable finding. No children were reported to take a nap on the study day, so it cannot be assumed that consolidation occurred during daytime sleep. It is possible that memory consolidation in children with WS is time-dependent rather than sleep-dependent. Daytime consolidation has been demonstrated in TD children, although only for implicit procedural learning, not for declarative tasks (Fischer, Wilhelm & Born, 2007; Wilhelm *et al*., 2008). Alternatively, having had a break from learning, children with WS performed better on the task at the beginning of the second session when they were more refreshed than they had been at the end of the first session. The findings partially support the only other known study (Dimitriou *et al*., 2013) which also did not find evidence of sleep-dependent learning in WS; however, in contrast, children in that study also did not improve between Tests 1 and 2, as they did in the present study. This could be due to differences in consolidation of different types of memory, i.e. the procedural finger tapping task reported by Dimitriou *et al*. (2013) relative to the declarative Animal Names, and warrants further investigation.

It has been evidenced in TD children that sleep-dependent learning on a procedural task requires a certain pre-sleep level of skill (Drosopoulos *et al*., 2007; Tucker & Fishbein, 2008; Wilhelm *et al*., 2012). In the current study, the relationship between sleep-dependent change in scores and baseline performance was in the expected direction for each group. This trend approached significance ($p = .08$) for the WS group but relationships were not significant for any group. In the TD group there was a trend towards high performers at baseline being more likely to improve on the task following sleep, relative to reducing their score or no change. It is likely that with larger groups these effects would have been significant. Nevertheless, this trend may help to explain why the TD children, who performed well on the task at baseline, were able to benefit from sleep whilst children with DS and WS may not have reached the prerequisite level. Further research should investigate whether more intense training sessions and a higher pre-sleep level of performance for children with DS and WS would encourage sleep-dependent memory consolidation. Conversely, children with developmental delay may consolidate memories differently from TD children, and their lack of sleep-related learning gains could constitute yet another contribution to their learning difficulties.

In addition, there was a correlation in TD children between higher non-verbal mental age and increased sleep-dependent learning on the Animal Names task, even after controlling for chronological age. This suggests that children who had the most learning potential (as evidenced by higher mental age) were more likely to benefit from sleep for memory consolidation, possibly due to increased learning-related changes in sleep architecture (Smith *et al*., 2004). It is possible that sleep is generally more effective for high-performing individuals, or that individuals are high performers because a greater degree of cognitive enhancement occurs during sleep relative to low-performing individuals (Smith *et al*., 2004). This potentially bi-directional relationship should be investigated in more detail.

It should be noted that DS and WS are complex disorders with a varied pattern of cognitive strengths and weaknesses. Therefore it is likely that cognitive performance is also influenced by confounding factors that were not accounted for in the present study; for example, motivation to perform well on the task. In addition, it is possible that, due to reduced cognitive capabilities and regular cognitive overload, sleep-dependent learning in intellectual disabilities occurs only for the most salient and important information, so was not evident for the more arbitrary Animal Names task.

All groups except the DS Sleep-Wake group showed improvement on the Animal Names task at Test 4, showing that children did have the cognitive capacity for increased learning when they were told the names one more time. That the DS Sleep-Wake group did not significantly improve ($p = .07$) could reflect the fact that

this task was late in the day when children may be tired and not concentrate as well as they might in the morning. Conversely, the DS Wake-Sleep group did significantly improve performance at Test 4, again suggesting that learning occurs best during the morning for these children.

Educators could use the findings of our study regarding sleep-dependent memory consolidation to utilize children's night-time sleep to their educational advantage; for example, by testing them on their homework the following morning or revisiting the previous day's work to reinforce any sleep-related gains. In contrast, children with DS and WS may use different means for consolidating newly learnt material. With this in mind, individual syndrome-specific education strategies should be developed to allow these children to achieve their potential. The 'morning advantage' could be exploited in the classroom to benefit children with DS by teaching them more challenging or important information earlier in the day whilst children with WS could be given shorter lessons with frequent breaks to ensure that they are refreshed and able to perform at their best, as well as a time delay between learning phases to allow for time-dependent memory consolidation. These types of educational strategies might lead to significant improvements in children's learning, improving educational attainment for children with intellectual disabilities. Whilst these are important and novel findings with implications for education, they should be interpreted in light of the sample size, methodological limitations and the need for replication. In addition, the 6 to 12 years age range of participants in the current study is a period associated with considerable changes in cognitive ability and sleep architecture, which may have added noise to the findings. Nevertheless, the groups were well matched for chronological age as well as gender. Further research should be completed to overcome these limitations and to determine the best strategies for children with DS and WS to benefit from sleep for learning, which could be training them to a prerequisite level before sleep.

In TD children, the level of sleep-dependent learning does not appear to be dependent on sleep quality or duration (Ashworth *et al*., 2014); in fact, even a short nap is sufficient to promote declarative sleep-dependent gains (Lahl, Wispel, Willigens & Pietrowsky, 2008). Rather, declarative memory consolidation appears to be dependent on finer aspects of sleep architecture, in particular, the proportion of NREM sleep (Backhaus *et al*., 2008; Kurdziel, Duclos & Spencer, 2013). Very few studies have investigated sleep architecture and learning in TD children and no such research exists in DS and WS. Differences in sleep architecture have been demonstrated in these groups, with reduced REM and increased stages I and II in DS (Diomedi *et al*., 1999; Miano, Bruni, Elia, Scifo, Smerieri *et al*., 2008) and increased SWS in WS (Gombos *et al*., 2011; Mason *et al*., 2011). These differences could contribute to variances in sleep-dependent learning. One might expect that an increase in SWS in the WS group would aid consolidation of declarative information (Born & Wilhelm, 2012; Gais & Born, 2004). This was not reflected in the current data; however, an increase in SWS usually indicates fatigue and 'catch-up sleep', so it may be that children with WS are chronically tired due to other sleep problems and/or increased cognitive overload that accumulates throughout the day. Further research in TD children and children with neurodevelopmental disorders is needed to determine the precise aspects of sleep architecture that are involved in memory consolidation. This would further establish optimum methods for enhancing memory consolidation.

A limitation of the current study was that the retention interval for the sleep period was somewhat longer than the wake retention period and that this difference was significantly more pronounced in the DS group relative to TD. This was necessary to minimize disruption to routine, and unavoidable due to bedtimes and school start times. Testing children before school was usually not possible due to families' busy morning routines. Nevertheless, efforts were made to avoid interference from other tasks by asking children to avoid cognitively demanding activities during the sleep retention interval, and by testing them as close to bedtime and as early in the morning as feasible, and always before lessons began.

In light of the findings of the present study, it is clear that there is a complex interaction between sleep and learning for children with DS and WS as well as for TD children, which must be investigated further. Parents, educationists, clinicians and researchers need to understand the importance of sleep for children's learning and educational attainment. Healthy sleep habits and management of sleep problems should be imperative, as well as educational strategies that feature children's night-time sleep as an aid to learning.

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