**Obstructive sleep apnoea contributes to executive function impairment in young children with Down syndrome**

**Running header: OSA predicts EF impairment in DS**

Anna Joyce1, Heather Elphick2, Michael Farquhar3, Paul Gringras3, Hazel Evans4, Romola S Bucks5, Jana Kreppner6, Ruth Kingshott2, Jane Martin7, Janine Reynolds2, Carla Rush3, Johanna Gavlak4, Catherine M Hill4,8

***Corresponding author.***

Dr Anna Joyce, Coventry University, Priory Street, Coventry, CV2 3JT

Email: [anna.joyce@coventry.ac.uk](mailto:anna.joyce@coventry.ac.uk)

1 Centre for Innovative Research Across the Lifecourse, Coventry University   
2 Department of Paediatric Respiratory Medicine, Sheffield Children’s NHS Foundation Trust

3 Evelina London Children’s Hospital, Guys & St Thomas’s NHS Trust

4 Southampton Children’s Hospital, Southampton University NHS Trust

5 School of Psychological Science, University of Western Australia

6. School of Psychology, University of Southampton

7 Southampton Biomedical Research Unit, Southampton General Hospital

8 School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton

***Acknowledgements***

We would like to thank members of the UK Down Syndrome Medical Interest group, paediatric colleagues and the Down Syndrome Association for their help in identifying children who were eligible to participate. Special thanks are due to Jane Martin (Southampton), Janine Reynolds (Sheffield) and Anna Joyce and Carla Rush (London) for leading recruitment at each site and to Dr Richard Tomlinson and the team at Exeter for acting as a satellite recruitment site. Thanks are also due to the Southampton NIHR Wellcome Trust Clinical Research Facility for hosting the study at the Southampton site. Most importantly, we thank the families for their enthusiasm to participate in this study. This study was generously supported by Action Medical Research and the Garfield Weston Foundation [grant reference 2040].

# **Abstract**

Objective/Background: Children with Down syndrome (DS) commonly experience difficulties with executive function (EF). They are also vulnerable to obstructive sleep apnoea (OSA). OSA is associated with EF deficits in typically developing children. A recent study reported an association between OSA and cognitive deficits in 38 school-aged children with DS. We experimentally investigated EF behaviours in young children with DS, and their association with OSA.

Participants and Methods: Children with DS were recruited to take part in a larger study of OSA (N=202). Parents of 80 children (50 male) aged 36 to 71 months (*M* = 56.90, *SD* = 10.19 months) completed the Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P). Of these 80 children, 69 were also successfully studied overnight with domiciliary cardiorespiratory polygraphy to diagnose OSA.

Results: Obstructive apnoea/hypopnoea index was in the normal range (0-1.49/h) for 28 children but indicated OSA (≥1.5/h) in 41 children. Consistent with previous research, we found a large effect for children experiencing particular weaknesses in working memory, planning and organising, whilst emotional control was a relative strength. OSA was associated with poorer working memory (β=.23, R2=.05, p=.025), emotional control (β=.20, R2=.04, p=.047) and shifting (β=.24, R2=.06, p=.023). Conclusions: Findings suggest that known EF difficulties in DS are already evident at this young age. Children with DS already have limited cognitive reserve and can ill afford additional EF deficit associated with OSA. OSA is amenable to treatment and should be actively treated in these children to promote optimal cognitive development.

**Key words:** Down syndrome; executive function; obstructive sleep apnoea; sleep

Down syndrome (DS) is the commonest sporadic chromosomal anomaly, affecting around 1 in 892 live births in Europe (Loane et al., 2012). It results in moderate to severe intellectual disability and a characteristic pattern of cognitive strengths and weaknesses including poor expressive language skills, executive functions, and auditory short term memory, but relatively good visuospatial skills (Chapman & Hesketh, 2000; Roizen & Patterson, 2003). Sleep problems, such as difficulties initiating and maintaining sleep, restlessness, bedtime resistance, anxiety and daytime sleepiness are common in DS (Angriman, Caravale, Novelli, Ferri, & Bruni, 2015; Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2013; Carter, McCaughey, Annaz, & Hill, 2009). Importantly, up to 80% of these children may suffer from obstructive sleep apnoea (OSA); an occlusion of the upper airway leading to intermittent hypoxia and fragmented sleep (Austeng et al., 2014; de Miguel-Diez, Villa-Asensi, & Alvarez-Sala, 2003; Hill et al., 2016). Risk factors for OSA in DS include obesity, a small upper airway and midface, macroglossia and generalised hypotonia (Churchill, Kieckhefer, Landis, & Ward, 2012). In contrast, enlarged tonsils and/or adenoids pose the highest risk for OSA in typically developing children (Ray & Bower, 2005).

In typically developing children OSA is associated with impairments of executive function (EF) (O'Brien et al., 2004). These higher order cognitive processes are neurally mediated by the prefrontal cortex and allow a flexible and organised approach to complex problem solving. Domains of EF include planning, problem solving, working memory, attention, self-regulation and inhibition. EFs begin to develop during the preschool years and are predictive of later academic abilities, lifelong success, health, wealth and quality of life (Blair & Razza, 2007; R. Bull, Espy, & Wiebe, 2008; Diamond, 2013).

Observations in childhood OSA, along with data from animal models of intermittent hypoxia, suggest localisation of neural dysfunction in this condition to the prefrontal cortex (Beebe & Gozal, 2002). During sleep, in contrast to other brain structures, the prefrontal cortex shows reduced activity and is functionally disconnected from areas with which it usually interacts during wake. This may reflect an enhanced need to ‘recalibrate’ during sleep without input from other brain regions (Beebe & Gozal, 2002). If this restorative function is disrupted by the cellular and biochemical stressors of sleep disturbance and intermittent hypoxia characteristic of OSA, impairment of EF may arise.

Due to the relatively late maturation of the prefrontal cortex throughout childhood and adolescence (Sisk & Foster, 2004), untreated OSA in early childhood could restrict long-term cognitive potential through alteration of prefrontal cortex neuronal integrity. This is particularly relevant in children with DS who, independent of OSA, have impaired frontal lobe development (Nadel, 2003; Smigielska-Kuzia et al., 2011; Wisniewski, 1990). Indeed, individuals with DS experience difficulties with EF tasks across the lifespan to a greater extent than would be predicted given their mental age and in comparison to individuals with other forms of intellectual disability, possibly due to their relatively small volume prefrontal cortex (Nadel, 2003). Difficulties are most apparent where tasks are verbally mediated, for example, auditory is poorer than visuospatial working memory (Grieco, Pulsifer, Seligsohn, Skotko, & Schwartz, 2015). Previous parent-report studies have consistently shown that children with DS have particular deficits in working memory, planning and organising, relative to other domains and compared to mental age-matched typically developing children (Daunhauer et al., 2014; Edgin et al., 2015; Lee et al., 2011). Investigating EF abilities according to children’s mental age allows comparison of EF skills relative to general cognitive ability, rather than chronological age which, in DS, is characterised by a high degree of individual variability in intellectual ability.

The extent to which OSA contributes to EF difficulties in DS has received little attention in the research literature. A notable, recent study of 38 children with DS aged 7-12 years reported that the 19 children with OSA (defined by an apnoea/hypopnoea index >1.5/h) showed a large effect for poorer verbal IQ and cognitive flexibility than those without OSA (Breslin et al., 2014). Associations between parentally reported features of OSA and EF performance have been reported in adolescents and young adults with DS (Chen, Spanò, & Edgin, 2013), and between parent reports of restless sleep and parent/teacher concerns of EF difficulties in school aged children with DS (Esbensen & Hoffman, 2018). There are no published data to the authors’ knowledge that report the effects of OSA on EF behaviours in younger children with DS.

Based on data in typically developing children and this limited research in DS, we predicted that 1) young children with DS would experience significant impairments in mental age-scored EF behaviours relative to normed scores and 2) Poorer EF behaviours would be associated with the presence of OSA.

# **Methods**

## **Participants**

Children with DS aged six months to sixth birthday were recruited through three children’s hospitals in the UK: Evelina London, Southampton and Sheffield, as part of a larger study investigating prevalence of OSA (N=202) (Hill et al., 2016). Children were excluded if they had undergone a cardiorespiratory study in the preceding three months, to avoid family burden or if they received home oxygen therapy or non-invasive ventilation. Children were eligible for the present analyses if they were aged >36 months (n=96).

The study entitled “Screening for obstructive sleep apnoea in children with Down syndrome” was approved by the UK National Research ethics committee (reference number: 13/SC/0106) and was adopted by the National Institute of Health Research portfolio (ID: 14250). All parents provided written informed consent for their child to take part in the study.

## **Materials**

### **Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P).** The BRIEF-P is a 63-item parent-report questionnaire that assesses the behavioural manifestations of EF in the everyday context across five domains: Inhibit, Shift, Emotional Control, Working Memory and Plan/Organise. These scales combine to yield three broader indices and an overall score: Inhibitory Self Control Index, Flexibility Index, Emergent Metacognition Index and Global Executive Composite. See Box 1 for a definition of each scale and index. Finally, the BRIEF-P also indicates the extent to which respondents answered questions in an inconsistent or unusually negative manner. Higher scores indicate greater deficit and T-scores above 65, based on aged norms of 460 children where the mean is 50 and SD is 10, may be clinically relevant. In line with previous research (Lee et al., 2011), T-scores on each BRIEF-P scale and index were calculated per the manual based on mental age rather than chronological age to group children into BRIEF-P age categories (<47 months, >48months).

The BRIEF-P is validated in children aged 2 years to 5 years 11 months across a wide range of social and demographic contexts. It is suitable for use in children with a range of developmental disabilities (Gioia, Espy, & Isquith, 2003), and has previously been used in children with DS (Daunhauer et al., 2014; Lee et al., 2011).

**Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III); Block Design.** The block design is a non-verbal visual-spatial task requiring the child to recreate an abstract stimulus design from a set of coloured blocks. It yields a scaled score with a mean of 10 and SD of 3 which we used to estimate mental age for the purpose of scoring the BRIEF-P. All children performing at floor level (n=33) were grouped into the lower BRIEF-P age category.

Block design was selected due to low language demands, being quick to administer, and because performance in children with DS is consistent with their general cognitive ability (Yang, Conners, & Merrill, 2014).

**Cardiorespiratory polygraphy.** OSA was monitored using the body-worn Somnotouch device (Somnomedics, Germany) comprising abdominal and thoracic effort, nasal air flow, snore sensor, pulse oximetry, actigraphy and body position monitoring. Parents were shown how to use the equipment and were encouraged to attempt a domiciliary study. They were provided with step-by-step photographic and written instructions and a telephone number in case of difficulties. Where domiciliary studies failed, or if the parent had a strong preference, then the study was conducted with identical equipment in a hospital sleep laboratory.

Cardiorespiratory polygraphy sleep studies were scored as per American Academy of Sleep Medicine scoring criteria (Berry et al., 2012) by an experienced sleep technologist (RK), with every 10th study double-scored by a second experienced technologist (JG). Studies were scored in 30 second epochs for sleep and wake, using a combination of parental sleep log to interpret sleep onset and offset; the in-device X, Y, Z accelerometer; changes in variables such as heart rate and respiratory rate; and what had occurred in surrounding epochs. Epochs with at least 15 seconds of increased activity were classified as estimated wake. Obstructive apnoea was scored when nasal airflow decreased by >90% compared to pre-event baseline for two or more breaths with continued inspiratory effort; and hypopnoea was scored when airflow decreased by >30% accompanied by at least three percent oxyhaemoglobin desaturation with continued inspiratory effort. Recordings with fewer than four hours of artefact free data were discarded (Urschitz, Brockmann, Schlaud, & Poets, 2010) and parents were given the opportunity to repeat the study. Further details of scoring criteria and quality standards have been previously published (Hill et al., 2016). For consistency with published research on cognition and OSA in DS (Breslin et al., 2014) we use a threshold of obstructive apnoea/hypopnoea index (OAHI; the number of apnoeas and hypopnoeas per hour) of >1.5 to define OSA.

Whilst the SOMNOtouch device provides accurate cardiorespiratory measures, it has yet to be formally validated against gold standard polysomnography in young children. However, preliminary data in two children (aged 7 and 9 years) suggested good levels of agreement with polysomnography (Hill et al 2016).

## **Methodology**

Children attended one of the three centres with a parent/guardian where they completed the Block Design task. Parents were provided with the sleep monitoring equipment and a BRIEF-P. Sleep studies were usually carried out on the night after parent training. Equipment and the questionnaire were returned the following day by courier. Further details on the methods are reported in Hill et al. (2016).

## **Analyses**

Data were analysed using IBM Statistical Package for Social Sciences (SPSS) v24. They were inspected for outliers using Cook’s distances; none was found.

To assess the EF abilities of our sample relative to standardised scores, one-sample *t* tests were used to compare mental age T-scores on each subscale to the normative mean of 50. To assess the pattern of strengths and weaknesses within the sample, within groups ANOVAs were used to compare scores on each of the five subscales and, separately, the three indices to one another. The Bonferroni correction was used in ANOVAs for multiple comparisons and reported *p* values are adjusted accordingly.

Finally, to assess whether OSA predicted poorer EF behaviours, multivariate regression models were calculated in Mplus v7.4 with 10,000 bootstrapped samples to reduce random sampling errors and produce more accurate and reliable results. Three separate models were run, controlling multiple comparisons within each model. OSA group was the predictor and dependent measures were 1) T-scores on each scale, 2) T-scores on each index, and 3) Global Executive Composite. Data were skewed towards normal/mild OSA; thus, we used the clinical cut-off of OAHI ≤1.49 (OSA absent, *n*=28) and OAHI ≥1.5 (OSA present, *n*=41) as a categorical variable to define OSA group, which normalised the data.

# **Results**

## **Participants**

Of 96 eligible children, data were missing for 16 whose parents did not complete the BRIEF-P questionnaire. Non-completers were 10 months younger than completers (t(94)= -3.53, p=.001); there were no sex differences between completers and non-completers. The final sample consisted of 80 children (50 male) aged 36 to 71 months (*M* = 56.90, *SD* = 10.19 months); 33 from Southampton, 24 from London and 23 from Sheffield. All children had trisomy 21 due to non-dysjunction, other than 1 child with mosaicism (aged 53 months) and 5 children with translocation (age range 55-71 months). No child had a history of epilepsy. ANOVA and Chi-Square respectively showed no age or sex differences between centres, and no age difference between males and females (all *p* values >.05).

## Data for five participants (four male) on the BRIEF-P were later removed as they scored in the unacceptable range for inconsistency, suggesting that these parent reports may be unreliable. Thus, reliable BRIEF-P data are reported for 75 children. Missing response items in some questionnaires meant that scores could not be calculated for up to four participants on some scales. Sleep data include only children whose parents satisfactorily completed the BRIEF-P. Data were missing for six of these children who had unsuccessful cardiorespiratory studies, usually due to equipment being removed before four hours of artefact-free recording were achieved, or the child not tolerating sensors; thus yielding 69 children with both BRIEF-P and cardiorespiratory data. There were no significant age or sex differences between children with successful and unsuccessful studies.

## **BRIEF-P**

Following mental age-based scoring, one sample *t* tests showed significantly poorer EFs on every measure for children with DS relative to the mean of 50 in a typically developing reference group (Table 1 and Figure 1).

==========

Table 1 and Figure 1 here

==========

A within groups ANOVA to compare scores on each scale identified significant differences between scales (*F*(2.75,192.47)=55.26, *p*<.001, ƞp2=.44). Pairwise comparisons showed that, relative to all other scales, children performed most poorly on Working Memory (all *p* values <.001), followed by Plan/Organize (all *p* values <.005). In contrast, Emotional Control was an area of relative strength in comparison to Inhibit (*p*=.04), Working Memory (*p*<.001), and Plan/Organize (*p*<.001).

Further investigation using ANOVA to compare indices was also significant (*F*(1.50,104.84)=86.52, *p*<.001, ƞp2=.55). Pairwise comparisons revealed that Emergent Metacognition Index (which comprises the Working Memory and Plan/Organize scales) was significantly poorer than both Inhibitory Self Control Index (*p*<.001) and Flexibility Index (*p*<.001) which did not differ significantly from one another although there was a trend for Inhibitory Self Control Index being poorer than Flexibility Index (*p*=.06).

## **Cardiorespiratory polygraphy**

Cardiorespiratory polygraphy results for the larger study are published (Hill et al., 2016). Mean OAHI (*n*=69) was 5.05/h (*SD*=13.09) and ranged from 0.00 to 81.40/h). OAHI was found to be in the normal range (0-1.49/h) for 28 children but indicated mild OSA (1.5-4.99/h) for 32 children, moderate OSA (5-9.99/h) for three children and severe OSA (≥10/h) for 6 children.

## **Association between EF behaviours and OSA**

Children with OSA (OAHI≥1.5/h) were older (mean=59.63 months, SE=1.51) than children without OSA (mean=54.32 months, SE=1.96) (*t*(67)=-2.18, *p*=.033). Chi square showed no significant sex differences between children with (n=41; 24 male) and without (n=28; 17 male) OSA.

Children with OSA experienced greater difficulties with Shift, Emotional Control and Working Memory relative to children without OSA, with OSA explaining between 4% and 6% of the variance in scores. This indicates that OSA was associated with deficits in transitioning smoothly between activities or attentional focus, difficulty modulating emotional responses, and poorer ability to hold information in mind whilst working on a response. See Table 2 for comparison of T-scores for children with and without OSA and multivariate regression results.

Further investigation showed that children with OSA experienced greater difficulties on all indices as well as Global Executive Composite, suggesting that OSA contributes to difficulties with self-regulating behaviour and emotions, the ability to modify or change behaviour according to different environmental demands, and active problem solving, as well as an overall effect on EF (Table 2). OSA explained 4-5% of the variance in index scores.

**Discussion**

This is the first published study to report the extent to which OSA predicts parental report of mental age-scored EF behaviours in very young children with DS. We showed that children with DS experience considerable weaknesses in EF ability, and that the presence of OSA was associated with performance deficits on three scales (Shift, Emotional Control and Working Memory) and all three indices as well as GEC.

We expected OSA to be associated with increased EF difficulties. This hypothesis was supported for Shifting, Emotional Control and Working Memory scales, all three indices and the Global Executive Composite. Since Working Memory was also an area of weakness for children with DS, it is noteworthy that it is associated with OAHI, and it is likely that treating OSA could be a possible intervention for improving working memory, as well as other EFs in children with DS. Nevertheless, *R*2values were small (ranging from .04 to .06), so although associations were significant, OAHI was only able to explain a small amount of the variance in scores (4-6%). Future research should determine other precise factors that influence EF and whether these interact with OSA status, for example co-occurring medical conditions or socioenvironmental factors such as nutrition or parent education. This would provide evidence to support multidisciplinary interventions to improve EF in children with DS.

As per our first hypothesis, children showed weaknesses on all EF scales relative to normed scores. Consistent with previous reports in children with DS, ranging in age from 2 to 11 years (Daunhauer et al., 2014; Edgin et al., 2015; Lee et al., 2011), our sample had the greatest deficits in Working Memory and Plan/Organize, relative to other sub-scales and to norms for mental age-matched typically developing children. The consistency of our findings in this young age group suggest a stability of these relative EF behavioural traits throughout childhood development. The pre-school years are a critical period for the maturation of EF to enable school readiness. Our findings suggest specific cognitive domains that could be targeted with early interventions to enable children with DS to reach their academic potential. Importantly, we note that Emotional Control is a relative strength for these children, which should be recognised as the research literature predominantly focuses on weaknesses.

**Implications**

The current study provides evidence that domiciliary cardiorespiratory studies are a feasible approach to examine sleep disordered breathing in young children with DS, who are typically restless sleepers and can be difficult to study (Fernandez et al., 2017; Kingshott et al., 2018).

OSA is common in children with DS (Austeng et al., 2014; de Miguel-Diez et al., 2003; Hill et al., 2016); yet sleep problems are often under-recognised and -reported by parents, or assumed to be simply a feature of DS (Shott et al., 2006); thus, they often persist without adequate treatment. Currently, screening is recommended for all children with DS by 4 years of age (M. J. Bull & Committee on Genetics, 2011). Adenotonsillectomy successfully treats OSA in up to 83% of cases in typically developing children (Brietzke & Gallagher, 2006; M. Friedman, Wilson, Lin, & Chang, 2009), but only up to 50% of cases in children with DS, owing to multiple co-occurring factors affecting airway obstruction including midface hypoplasia, obesity, macroglossia and general hypotonia. Children with significant residual post-operative OSA may benefit from weight loss or treatment with continuous or biphasic positive airway pressure ventilation (CPAP/BiPAP) (Simpson, Oyekan, Ehsan, & Ingram, 2018).

The prevalence of OSA in our sample was similar to previous reports (Austeng et al., 2014; de Miguel-Diez et al., 2003) and we used a sampling approach designed to minimise selection bias; thus, the sample is likely to reflect the general DS population.

Our findings that certain EF behaviours are associated with sleep disordered breathing lend weight to the importance of early screening and treatment for OSA, which could see downstream improvements in children’s cognitive abilities, including EF. Parents and practitioners need to be aware of the prevalence of OSA in DS, its resistance to treatment, and its associated features. In typically developing children cognitive outcomes, including EF, improve significantly following treatment of OSA (B. C. Friedman et al., 2003; Marcus et al., 2013); further research is needed to assess whether the same is true for children with DS.

**Limitations**

Whilst preliminary data suggest good levels of agreement with polysomnography (Hill et al 2016), the SOMNOtouch device has yet to be formally validated against gold standard polysomnography in young children. Although it does provide accurate cardiorespiratory measures, validation would increase confidence in results.

We used parent report of EF behaviours, as objective EF testing in young children with intellectual disabilities is challenging and prone to poor compliance, motivation and difficulty determining the child’s true level of ability. Parents can provide a wealth of information on everyday EF behaviours; thus, the BRIEF-P, as a robust measure validated in children with developmental disorders, including DS (Edgin et al., 2015; Gioia et al., 2003), was considered the most appropriate measure for this young group. Nonetheless, future studies would benefit from the use of objective measures alongside parent report, as scores on the BRIEF-P may not always map onto performance-based measures (McAuley, Chen, Goos, Schachar, & Crosbie, 2010).

Future studies should also include robust measures of mental age. Our use of the WPPSI-III Block Design was sufficient to group children according to BRIEF-P age categories, however, we could not determine mental age for 33 children scoring at floor level.

**Summary**

To our knowledge, the current study is the first to investigate the extent to which OSA predicts EF behaviours in young children with DS. It provides a novel and useful observation of everyday EF behaviours in young children with DS and importantly indicates that EF behaviours are associated with OSA; a common problem in children with DS. Our findings that Working Memory and Plan/Organize are compromised even in this young age group, and that some difficulties are associated with OSA, suggest that identification and treatment of OSA may limit EF impairments (Beebe & Gozal, 2002) in these children.

**References**

Angriman, M., Caravale, B., Novelli, L., Ferri, R., & Bruni, O. (2015). Sleep in children with neurodevelopmental disabilities. *Neuropediatrics, 46*(3), 199-210. doi:10.1055/s-0035-1550151

Ashworth, A., Hill, C. M., Karmiloff-Smith, A., & Dimitriou, D. (2013). Cross syndrome comparison of sleep problems in children with Down syndrome and Williams syndrome. *Res Dev Disabil, 34*(5), 1572-1580.

Austeng, M. E., Overland, B., Kvaerner, K. J., Andersson, E. M., Axelsson, S., Abdelnoor, M., & Akre, H. (2014). Obstructive sleep apnea in younger school children with Down syndrome. *International Journal of Pediatric Otorhinolaryngology, 78*(7), 1026-1029.

Beebe, D. W., & Gozal, D. (2002). Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *Journal of Sleep Research, 11*(1), 1-16.

Berry, R. B., Budhiraja, R., Gottlieb, D. J., Gozal, D., Iber, C., Kapur, V. K., . . . Tangredi, M. M. (2012). Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *Journal of Clinical Sleep Medicine, 8*(5), 597-619. doi:10.5664/jcsm.2172

Blair, C., & Razza, R. P. (2007). Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. *Child Development, 78*(2), 647-663. doi:10.1111/j.1467-8624.2007.01019.x

Breslin, J., Spano, G., Bootzin, R., Anand, P., Nadel, L., & Edgin, J. (2014). Obstructive sleep apnea syndrome and cognition in Down syndrome. *Dev Med Child Neurol, 56*(7), 657-664.

Brietzke, S. E., & Gallagher, D. (2006). The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. *Otolaryngology Head and Neck Surgery, 134*(6), 979-984. doi:10.1016/j.otohns.2006.02.033

Bull, M. J., & Committee on Genetics. (2011). Health supervision for children with Down syndrome. *Pediatrics, 128*(2), 393-406. doi:10.1542/peds.2011-1605

Bull, R., Espy, K. A., & Wiebe, S. A. (2008). Short-term memory, working memory, and executive functioning in preschoolers: longitudinal predictors of mathematical achievement at age 7 years. *Dev Neuropsychol, 33*(3), 205-228. doi:10.1080/87565640801982312

Carter, M., McCaughey, E., Annaz, D., & Hill, C. M. (2009). Sleep problems in a Down syndrome population. *Archives of Disease in Childhood, 94*(4), 308-310. doi:10.1136/adc.2008.146845

Chapman, R. S., & Hesketh, L. J. (2000). Behavioral phenotype of individuals with Down syndrome. *Mental Retardation and Developmental Disabilities Research Reviews, 6*(2), 84-95. doi:10.1002/1098-2779(2000)6:2<84::aid-mrdd2>3.0.co;2-p

Chen, C. C., Spanò, G., & Edgin, J. O. (2013). The impact of sleep disruption on executive function in Down syndrome. *Res Dev Disabil, 34*(6), 2033-2039.

Churchill, S. S., Kieckhefer, G. M., Landis, C. A., & Ward, T. M. (2012). Sleep measurement and monitoring in children with Down syndrome: a review of the literature, 1960-2010. *Sleep Medicine Reviews, 16*(5), 477-488.

Daunhauer, L. A., Fidler, D. J., Hahn, L., Will, E., Lee, N. R., & Hepburn, S. (2014). Profiles of everyday executive functioning in young children with down syndrome. *Am J Intellect Dev Disabil, 119*(4), 303-318. doi:10.1352/1944-7558-119.4.303

de Miguel-Diez, J., Villa-Asensi, J. R., & Alvarez-Sala, J. L. (2003). Prevalence of sleep-disordered breathing in children with Down syndrome: polygraphic findings in 108 children. *Sleep, 26*(8), 1006-1009.

Diamond, A. (2013). Executive Functions. *Annu Rev Psychol, 64*, 135–168. doi:10.1146/annurev-psych-113011-143750

Edgin, J. O., Tooley, U., Demara, B., Nyhuis, C., Anand, P., & Spano, G. (2015). Sleep Disturbance and Expressive Language Development in Preschool-Age Children With Down Syndrome. *Child Dev, 86*(6), 1984-1998. doi:10.1111/cdev.12443

Esbensen, A. J., & Hoffman, E. K. (2018). Impact of sleep on executive functioning in school-age children with Down syndrome. *Journal of Intellectual Disability Research, 62*(6), 569-580. doi:10.1111/jir.12496

Fernandez, F., Nyhuis, C. C., Anand, P., Demara, B. I., Ruby, N. F., Spano, G., . . . Edgin, J. O. (2017). Young children with Down syndrome show normal development of circadian rhythms, but poor sleep efficiency: a cross-sectional study across the first 60 months of life. *Sleep Med, 33*, 134-144. doi:10.1016/j.sleep.2016.12.026

Friedman, B. C., Hendeles-Amitai, A., Kozminsky, E., Leiberman, A., Friger, M., Tarasiuk, A., & Tal, A. (2003). Adenotonsillectomy improves neurocognitive function in children with obstructive sleep apnea syndrome. *Sleep, 26*(8), 999-1005.

Friedman, M., Wilson, M., Lin, H. C., & Chang, H. W. (2009). Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngology Head and Neck Surgery, 140*(6), 800-808. doi:10.1016/j.otohns.2009.01.043

Gioia, G. A., Espy, K. A., & Isquith, P. K. (2003). *Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P)*. Lutz, FL: Psychological Assessment Resources.

Grieco, J., Pulsifer, M., Seligsohn, K., Skotko, B., & Schwartz, A. (2015). Down syndrome: Cognitive and behavioral functioning across the lifespan. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 169*(2), 135-149. doi:10.1002/ajmg.c.31439

Hill, C. M., Evans, H. J., Elphick, H., Farquhar, M., Pickering, R. M., Kingshott, R., . . . Gringras, P. (2016). Prevalence and predictors of obstructive sleep apnea in young children with Down syndrome. *Sleep Medicine, 27-28*, 99-106. doi:10.1016/j.sleep.2016.10.001

Kingshott, R. N., Gahleitner, F., Elphick, H. E., Gringras, P., Farquhar, M., Pickering, R. M., . . . Hill, C. M. (2018). Cardiorespiratory sleep studies at home: experience in research and clinical cohorts. *Archives of Disease in Childhood*. doi:10.1136/archdischild-2018-315676

Lee, N. R., Fidler, D. J., Blakeley-Smith, A., Daunhauer, L., Robinson, C., & Hepburn, S. L. (2011). Caregiver report of executive functioning in a population-based sample of young children with Down syndrome. *American Journal of Intellectual and Developmental Disabilities, 116*(4), 290-304. doi:10.1352/1944-7558-116.4.290

Loane, M., Morris, J. K., Addor, M.-C., Arriola, L., Budd, J., Doray, B., . . . Dolk, H. (2012). Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. *European Journal of Human Genetics, 21*(1), 27-33. doi:doi:10.1038/ejhg.2012.94

Marcus, C. L., Moore, R. H., Rosen, C. L., Giordani, B., Garetz, S. L., Taylor, H. G., . . . Redline, S. (2013). A Randomized Trial of Adenotonsillectomy for Childhood Sleep Apnea. *The New England Journal of Medicine, 368*, 2366-2376. doi:10.1056/NEJMoa1215881

McAuley, T., Chen, S., Goos, L., Schachar, R., & Crosbie, J. (2010). Is the behavior rating inventory of executive function more strongly associated with measures of impairment or executive function? *Journal of the International Neuropsychological Society, 16*(3), 495-505. doi:10.1017/s1355617710000093

Nadel, L. (2003). Down's syndrome: A genetic disorder in biobehavioral perspective. *Genes, Brain and Behavior, 2*(3), 156-166. doi:10.1034/j.1601-183X.2003.00026.x

O'Brien, L. M., Mervis, C. B., Holbrook, C. R., Bruner, J. L., Smith, N. H., McNally, N., . . . Gozal, D. (2004). Neurobehavioral correlates of sleep-disordered breathing in children. *Journal of Sleep Research, 13*(2), 165-172. doi:10.1111/j.1365-2869.2004.00395.x

Ray, R. M., & Bower, C. M. (2005). Pediatric obstructive sleep apnea: the year in review. *: Current Opinion in Otolaryngology & Head and Neck Surgery, 13*, 360-365. doi:10.1097/01.moo.0000186076.53986.71

Roizen, N. J., & Patterson, D. (2003). Down's syndrome. *Lancet, 361*(9365), 1281-1289.

Shott, S. R., Amin, R., Chini, B., Heubi, C., Hotze, S., & Akers, R. (2006). Obstructive sleep apnea: Should all children with Down syndrome be tested? *Archives of Otolaryngology - Head and Neck Surgery, 132*(4), 432-436.

Simpson, R., Oyekan, A. A., Ehsan, Z., & Ingram, D. G. (2018). Obstructive sleep apnea in patients with Down syndrome: current perspectives. *Nature and Science of Sleep, 10*, 287-293. doi:10.2147/nss.s154723

Sisk, C. L., & Foster, D. L. (2004). The neural basis of puberty and adolescence. *Nature neuroscience, 7*(10), 1040-1047. doi:doi:10.1038/nn1326

Smigielska-Kuzia, J., Bockowski, L., Sobaniec, W., Sendrowski, K., Olchowik, B., Cholewa, M., . . . Lebkowska, U. (2011). A volumetric magnetic resonance imaging study of brain structures in children with Down syndrome. *Neurologia i neurochirurgia polska, 45*(4), 363-369.

Urschitz, M. S., Brockmann, P. E., Schlaud, M., & Poets, C. F. (2010). Population prevalence of obstructive sleep apnoea in a community of German third graders. *The European Respiratory Journal, 36*(3), 556-568.

Wisniewski, K. E. (1990). Down syndrome children often have brain with maturation delay, retardation of growth, and cortical dysgenesis. *American journal of medical genetics. Supplement, 7*, 274-281.

Yang, Y., Conners, F. A., & Merrill, E. C. (2014). Visuo-spatial ability in individuals with Down syndrome: Is it really a strength? *ResearchinDevelopmentalDisabilities, 35*, 1473-1500. doi:10.1016/j.ridd.2014.04.002

Box 1.

*Definition of each scale and index of the BRIEF-P*

|  |  |
| --- | --- |
| **Scale** | **Definition** |
| Inhibit | Ability to control behaviour and impulses appropriately. |
| Shift | Flexibly and smoothly transitioning between activities, situations or problems. |
| Emotional Control (EC) | Appropriately modulating emotional responses according to context. |
| Working Memory (WM) | Holding information in mind for completing an activity. |
| Plan/Organise (PO) | Ability to anticipate future events or consequences and guide behaviour appropriately. |
| **Index** |  |
| Inhibitory Self Control Index (ISCI) | Sum Inhibit and EC. Ability to modulate actions, responses, emotions, and behaviour via appropriate inhibitory control. |
| Flexibility Index (FI) | Sum Shift and EC. Ability to move flexibly and appropriately among actions, responses, emotions, and behaviour. |
| Emergent Metacognition Index (EMI) | Sum WM and PO. Becoming an active and effective problem-solver by sustaining ideas and activities in working memory whilst planning and organising problem-solving approaches. |
| Global Executive Composite (GEC) | Sum of all five scales. Provides an overarching summary measure. |

Table 1.

*Mean and SD for T-scores on the BRIEF-P scales and t test results for comparison to the normative sample*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | n | Mean | Std. Error | Range | *t* |
| Scale |  |  |  |  |  |
| Inhibit | 74 | 63.65 | 1.30 | 41 - 90 | 10.52\* |
| Shift | 75 | 60.47 | 1.36 | 38 - 86 | 7.71\* |
| EC | 75 | 58.89 | 1.67 | 35 - 93 | 5.31\* |
| WM | 72 | 77.18 | 1.42 | 52 - 102 | 19.17\* |
| PO | 75 | 67.81 | 1.53 | 35 - 97 | 11.64\* |
| Index |  |  |  |  |  |
| ISCI | 74 | 63.39 | 1.46 | 37 - 94 | 9.16\* |
| FI | 75 | 60.89 | 1.55 | 35 - 94 | 7.01\* |
| EMI | 72 | 75.36 | 1.55 | 46 - 103 | 16.39\* |
| GEC | 71 | 71.08 | 1.58 | 41 - 103 | 13.38\* |

Note: Higher scores indicate increased dysfunction. Data were missing for some subscales, so total n may be slightly reduced. \**p*<.001. EC, Emotional Control; WM, Working Memory; PO, Plan/Organize; ISCI, Inhibitory Self Control Index; FI, Flexibility Index; EMI, Emergent Metacognition Index; GEC, Global Executive Composite.

Table 2.

*Mean (SD) for T-scores on the BRIEF-P scales and results of multivariate regression models*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | n | OAHI <1.5 | OAHI >1.5 | All | β | *R*2 | *p* |
| Scale |  |  |  |  |  |  |  |
| Inhibit | 27 / 41 | 62.30 (10.13) | 66.00 (11.19) | 64.53 (11.04) | .16 | .03 | .077 |
| Shift | 28 / 41 | 57.11 (12.11) | 62.61 (10.25) | 60.38 (11.29) | .24 | .06 | .023 |
| EC | 28 / 41 | 55.79 (14.62) | 61.68 (14.36) | 59.29 (14.65) | .20 | .04 | .047 |
| WM | 26 / 40 | 75.38 (11.02) | 80.30 (11.75) | 78.36 (11.63) | .23 | .05 | .025 |
| PO | 28 / 41 | 66.64 (9.54) | 70.22 (15.05) | 68.77 (13.13) | .14 | .02 | .112 |
| Index |  |  |  |  |  |  |  |
| ISCI | 27 / 41 | 61.19 (12.31) | 66.17 (12.41) | 64.19 (12.52) | .20 | .04 | .044 |
| FI | 28 / 41 | 57.36 (13.91) | 63.59 (12.47) | 61.06 (13.33) | .23 | .05 | .027 |
| EMI | 26 / 40 | 73.96 (10.60) | 78.25 (13.90) | 76.56 (12.79) | .19 | .04 | .044 |
| GEC | 25 / 40 | 68.80 (12.55) | 74.15 (12.96) | 72.09 (12.97) | .20 | .04 | .048 |

Note: n = OAHI <1.5 / OAHI >1.5. Data were missing for some subscales, so total n may be slightly reduced. Higher scores indicate increased dysfunction. EC, Emotional Control; WM, Working Memory; PO, Plan/Organize; ISCI, Inhibitory Self Control Index; FI, Flexibility Index; EMI, Emergent Metacognition Index; GEC, Global Executive Composite.

*Figure 1.* Mean and standard error scores on each scale and index of the BRIEF-P, relative to the normative score.

SE, standard error; EC, Emotional Control; WM, Working Memory; PO, Plan/Organize; ISCI, Inhibitory Self Control Index (sum Inhibit and EC); FI, Flexibility Index (sum Shift and EC); EMI, Emergent Metacognition Index (sum WM and PO); GEC, Global Executive Composite (sum Inhibit; Shift; EC; WM; PO).