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The impact of sleep disruption on executive function in Down syndrome

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ABSTRACT

The high prevalence of sleep disorders, particularly obstructive sleep apnea, is well established in children with Down syndrome. However, only a few studies have focused on older children and young adults in this population. Given the presence of sleep disorders and the early emergence of Alzheimer's disease, more work is needed to examine the relationship between sleep and cognition in Down syndrome. Twenty-nine adolescents and young adults with Down syndrome participated in the present study. Parents reported on their sleep difficulties using a well-validated measure of sleep problems in intellectual disabilities. Based on theoretical models linking obstructive sleep apnea to prefrontal cortex dysfunction, we tested components of executive functions that have been shown to be impaired in previous studies of Down syndrome. First, results indicate that participants with Down syndrome with higher body mass index also had increased caregiver reports of sleep apnea symptoms. Individuals with high ratings of sleep disruption also showed greater difficulties with executive function. These results suggest that sleep disruption may place this set of functions at risk in young adults. Future work should examine if this risk may result in earlier onset of dementia or steeper decline with Alzheimer's disease. Further, additional studies are needed to investigate the effect of exercise interventions and weight reduction on sleep disorders in this population.

1. Introduction

Accumulated studies have indicated a high prevalence of sleep disorders in individuals with Down syndrome (DS). For example, Waldman, Hasan, and Perlman (2009) reported that obstructive sleep apnea (OSA) occurs in at least one-half of this population. In addition, bedtime resistance, sleep anxiety, night waking, parasomnias, daytime sleepiness and sleep-disordered breathing (SDB) are commonly reported sleep disorders and behaviors amongst children and adolescents with DS (Breslin, Edgin, Bootzin, Goodwin, & Nadel, 2011; Carter, McCaughey, Annaz, & Hill, 2009). Breslin et al. (2011) further indicated that these patterns of sleep disruption might vary with age. While reported levels of sleep anxiety decreased across childhood and into adulthood, across this same age-range parent reports of SDB did not vary. In Breslin et al., the large majority of participants were endorsed as having symptoms of SDB, and these were consistently elevated across age.

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Therefore, age may be an important factor in determining the pattern of sleep problems and their functional impact, including the relation between poor sleep and cognition. While a number of studies have examined patterns of sleep disturbance in children with DS, studies in adults have been far fewer. In fact, to our knowledge, only one study has examined sleep disorders and behaviors in adults with DS (Trois et al., 2009). Adults with DS are at high risk for increasing sleep disturbance and Alzheimer's disease (AD), a condition that can be exacerbated by sleep problems. Therefore, more work is needed to determine whether or not sleep problems and cognitive deficits may be linked in older adolescents and adults with DS.

This high prevalence of sleep disorders in individuals with DS is due to anatomical abnormalities, such as midfacial and mandibular hypoplasia, tonsils and adenoidal encroachments, and reduced respiratory tract (Fink, Madaus, & Walker, 1975). Dyken, Lin-Dyken, Poulton, Zimmerman, and Sedars (2003) reported that the occurrence of SDB is associated with increased body mass index (BMI) in children with DS. Various studies have indicated that adults with DS were more likely to be overweight (BMI $\geq$ 25) when compared to other types of intellectual disabilities and the general population, with up to 70% of this group falling in this range (Melville, Cooper, McGrother, Thorp, & Collacott, 2005; Prasher, 1995). Trois et al. (2009) found that 88% of adults with DS (n = 16) had clinically diagnosed OSA, showing a positive correlation between BMI and the apnea hypopnea index. Thus, it is possible that the symptoms of SDB may originate as young as infancy in DS and persist or increase into their adult years, partly as a consequence of increasing obesity.

In addition to the added risk for sleep disorders into adulthood due to obesity, this population deals with an increased risk for AD as they age. In fact, individuals with DS almost universally show AD-related neuropathology by age 40 years (Wisniewski, Dalton, McLachlan, Wen, & Wisniewski, 1985). Exact age of onset for the functional decline associated with AD neuropathology is currently unknown. However, some studies suggest very early accumulation of amyloid-β (Aβ), with staining methods finding its presence in some children (i.e., one child at the age of 8 years) (Leverenz & Raskind, 1998). Sleep disordered breathing has been linked to increased rates of decline and levels of neuropathology in non-DS groups (Kang et al., 2009; Yaffe et al., 2011). Therefore, the concurrence of risk for sleep disturbance and early AD in DS is of concern. A first step to understanding any potential links between these two conditions is to further examine how patterns of sleep disturbance may impact cognition across the transition into adulthood in DS.

In the typical population, the association between SDB (e.g., snoring, OSA) and excessive daytime sleepiness, decreased mood and impaired cognitive function has been widely discussed (Labbate, Pollack, Otto, Langenauer, & Rosenbaum, 1994; Owens, Opipari, Nobile, & Spirito, 1998). One of the most researched and consistent associations is the link between OSA and poor performance on tests of executive functions (EF), regulated by the prefrontal cortex (PFC) (Kheirandish & Gozal, 2006; Mathieu et al., 2008). As reviewed by Beebe and Gozal (2002), patients with OSA display more frequent executive dysfunction (i.e., impaired working memory span, poor verbal fluency, and inhibition). From these findings Beebe and Gozal (2002) proposed a multidimensional model to understand the impact of sleep disruption on EF. In this model they proposed that OSA leads to hypoxic events and arousals that specifically disrupt prefrontal brain function through alteration of the restorative features of sleep as well as cellular homeostasis. They went beyond the links between poor sleep and transient alterations in daytime attention and processing speed to suggest that OSA may permanently alter the function of this region, thus impacting prefrontal function across the long-term.

Drawing on established frameworks to define the nature of the frontal functions impacted by OSA, Beebe and Gozal (2002) presented evidence suggesting that patients with OSA show deficits in inhibition, set-shifting, working memory, self-regulation of affect and arousal, analysis/synthesis and contextual memory. Each of these cognitive processes falls under the umbrella of "executive functions". Those with DS also show consistent impairments in this set of functions. For instance, studies of school age children and young adults show EF is specifically impaired in this population, with greater deficits found on measures of attention shifting and working memory than on tasks tapping inhibitory control (Edgin et al., 2010). Aging adults have also shown deficits on a number of EF tasks, including tests of verbal fluency and inhibition (Ball et al., 2006). Therefore, individuals with DS show disturbances in EF and sleep, but how are these two sets of difficulties linked? To our knowledge, no study has previously examined the relationship between sleep quality and executive functions in this population.

Taken together, the first objective of the current study was to examine the relation among different factors of sleep disorders/behaviors and executive dysfunction in an older sample with DS, including adolescents and young adults. To measure sleep we utilized a sleep questionnaire specifically designed and validated for this population, the Sleep Questionnaire by Simonds and Parraga (1982). We related sleep to performance on EF tasks shown to be impaired in past investigations, including choice reaction time, verbal fluency, and a measure of inhibition. In line with the predictions of Beebe and Gozal (2002), we expected that elevated caregiver ratings in sleep disorders/behaviors, particularly ratings of OSA, would be related to executive deficits. Furthermore, in line with the past literature, we expected that adults with DS with high BMI would have higher ratings of OSA.

2. Materials and measurement

2.1. Participants

Twenty-nine adolescents and young adults with DS (21 males, 8 females, aged 14–31 years) with no history of sensory impairment or physical disabilities participated in this study (refer to Table 1 for participant characteristics). While 30

Table 1
Participants' clinical characteristics and sleep behaviors.

Measures	Lower OSA ratings ($n = 13$)	Higher OSA ratings ($n = 16$)	F/χ^2	p
Clinical characteristics				
Mean (SD) age in years	20.26 (5.01)	22.44 (5.72)	1.16	0.29
Mean (SD) mental age in years	6.05 (1.17)	6.10 (2.25)	1.40	0.22
Height (cm)	148.25 (10.78)	148.24 (9.59)	0.00	0.99
Weight (kg)	66.96 (21.30)	79.47 (24.99)	2.05	0.16
% Male	61.5	81.2	1.40	0.24
Mean (SD) body mass index	28.08 (10.00)	36.06 (10.69)	4.23	0.05
Other sleep behaviors				
Disorders of initiating and maintaining sleep	7.15 (2.64)	8.00 (2.37)	0.83	0.37
Other disorders/behaviors occurring during sleep	10.62 (2.18)	11.25 (2.84)	0.44	0.51
Sleep related disorders/behaviors occurring during the day	9.23 (4.68)	10.25 (4.49)	0.36	0.56

participants were tested, a total of 29 individuals were used for analysis because one participant had current continuous positive airway pressure treatment. All subjects still resided at home with their parents. Height, weight and BMI were measured. Participants' mental age was tested using the Peabody Picture Vocabulary test (3rd ed.; PPVT-III). Participants were drawn from a group enrolled in a larger study of the benefits of physical activity on cognition. Many of the participants regularly participated in Special Olympics and represent a healthy portion of the population with DS.

Vision was tested using a standard eye chart (i.e., Snellen) and using a modified version that consists of letter E's pointing in different directions for DS participants who could not recognize letters. In this test the participant was asked to say or point to the directions that the E's were pointing. Hearing was tested using an audiometer (the Maico Ma 25). All participants had normal or at least 20/100 vision and normal or corrected-to-normal hearing and no known neurological disorders. All participants could complete the assessments.

2.2. Measures

2.2.1. Sleep questionnaire by Simonds and Parraga (1982)

The Sleep Questionnaire was a 7-point Likert-type scale, developed by Simonds and Parraga (SQ–SP; 1982) and modified by Stores, Stores, and Buckley (1996) to explore sleep problems in children with DS and other ID. Based on these studies, the test–retest reliability for the total SQ–SP score ranged from, $r = 0.83–1.00$. Four types of sleep factors were derived from SQ–SP, including (1) disorders of initiating and maintaining sleep, (2) features associated with OSA, (3) disorders/behaviors occurring during sleep, and (4) sleep related disorders/behaviors occurring during the day. The first factor included items such as bedtime resistance, the second rated snoring or gasping for breath, the third included ratings such as nightmares or sleep walking, and the fourth factor included questions regarding daytime sleepiness, naps, or daytime overactivity. Disorders of initiating and maintaining sleep, features associated with OSA, and sleep related disorders/behaviors occurring during the day each consisted of six items with a possible range from 6 to 42. Disorders/behaviors occurring during sleep consisted of eight items with a possible range from 8 to 56. Higher scores represented poorer sleep behavior.

2.2.2. Cognitive function tests

2.2.2.1. Choice Reaction Time Test. Participants were instructed to put their right index fingers on the response button to the display of a blue light and their left index fingers on the other response button to a white light. Participants were asked to push a button as quickly as possible following a stimulus (i.e., either blue or white light). Before testing, five practice trials were given to ensure the understanding of instructions and then 20 testing trials were conducted. The logarithm of the average time (ms) of the 20 testing trials was used as the variable of interest. This task measures processing speed and alertness. Similar measures have been shown to be impaired in relation to daytime sleepiness.

2.2.2.2. Verbal Fluency Test. For this test the participant is asked to generate exemplars of four categories, including two semantic categories (i.e., names of animals and names of food or drink) and two phonetic categories (i.e., words beginning with the letter S and words beginning with the letter F). Participants were requested to list as many as words possible in 60 s. The total sum of words generated was used as the variable of interest in this study. In previous studies, word production on both categories was significantly reduced in individuals with DS compared with their typical peers (Nash & Snowling, 2008).

2.2.2.3. Knock–Tap Test. This test contains two phases. In the first phase, the participants were required to knock with their knuckles on the table when the examiner tapped and vice versa. In the second phase, the participant knocked when the

examiner used the side fist, banged with the side fist when the examiner knocked, and did not move when the examiner tapped. The sum of the correct responses was used as the outcome measure. While this test traditionally measures aspects of inhibitory control (inhibiting the modeled response in phase 1), there is a clear element of rule shifting in phase 2. Recent neuroimaging studies demonstrated that more brain activation was evident in the PFC when similar neuropsychological tests were used to measure inhibition and verbal fluency in the healthy population (Aron, Robbins, & Poldrack, 2004; Costafreda et al., 2006).

2.3. Procedure

All procedures were approved by the human ethics committee at Arizona State University. Upon arrival, parents/caregivers signed consent forms. As for the participants, they read (or were read) and signed assent forms before data collection began. After that, each participant's visual acuity and hearing were tested followed by the PPVT-III assessment. Participants then underwent a series of 3 tests (i.e., Choice Reaction Time Test, Verbal Fluency Test, and Knock–Tap Test), for which the order of administration was counterbalanced across participants. The total experiment lasted about 45 min to 1 h.

2.4. Data analyses

Statistical analyses were performed in SPSS 19.0. For all analyses, the significance level was set at $p < 0.05$. The distributional properties of all variables were examined for skewness and kurtosis and transformed (ln) if necessary. Our examination of the background and sleep variables as related to OSA involved separating the children with higher vs. lower scores through a median split on the ratings from that scale. Then differences in background variables, such as BMI, were examined with ANOVA for continuous outcomes and chi-square for dichotomous variables. The correlations between sleep, BMI, and cognitive outcomes were investigated with the Pearson product-moment correlation coefficient (two-tailed).

3. Results

3.1. Relationship between sleep behavior and background variables

The means and standard divisions for participants' background information (i.e., chronological age (CA), mental age, height, weight and BMI, and sleep problems) based on parent's ratings of OSA severity are presented in Table 1. Participants were equivalent across all background variables, with the exception of BMI, with individuals with higher OSA ratings also having higher BMI ($p = 0.05$). Elevated ratings of OSA did not relate to elevated sleep problems on other scales of the Sleep Questionnaire. In total, 40% ($n = 12$) of participant's caregivers endorsed the features associated OSA (i.e., loud snoring daily or several times a week) and 70% ($n = 21$) of participants were obese based on BMI definition from the Centers for Disease Control and Prevention.

3.2. Relationship between sleep behavior and executive function

Table 2 shows the correlation between each sleep factor and the measures of executive function. The "disorders of initiating and maintaining sleep" factor was negatively correlated with verbal fluency performance ($r = -0.38$, $p = 0.04$). Hence, high ratings of poor sleep on this scale related to fewer words produced. The "features associated with OSA" factor was also significantly negatively correlated with verbal fluency performance ($r = -0.36$, $p = 0.05$) and the Knock–Tap Test ($r = -0.41$, $p = 0.03$). Therefore, subjects with high ratings of OSA features produced fewer words and successfully completed fewer trials on the knock–tap measure (see Fig. 1). Finally, sleep related disorders/behaviors occurring the day was negatively correlated with the knock–tap measure. Given the potential for differences in BMI to directly influence cognition over and beyond sleep disruption, we examined the relation between each of the executive function outcome measures and BMI. There were no direct correlations between BMI and EF performance ($p > 0.15$ or above for all).

Table 2
Pearson correlations between sleep behavior and neuropsychological variables in individuals with DS.

Measure	CRT	Verbal fluency	Knock and tap
Disorders of initiating and maintain sleep	0.32	−0.38*	−0.06
Features associated with OSA	0.22	−0.36*	−0.41*
Disorders/behavior occurring during sleep	0.05	−0.15	0.17
Sleep related disorders/behaviors occurring the day	0.15	−0.32	−0.40*

* p values < 0.05.

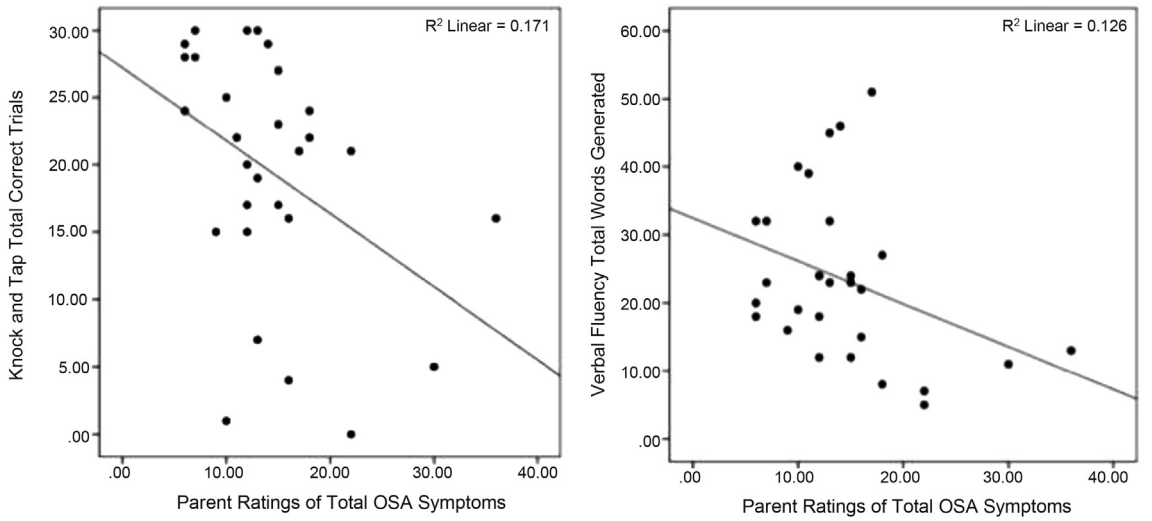

Fig. 1. The relation between OSA ratings and performance on executive measures in individuals with DS.

4. Discussion

This study examined the relation between parent ratings of sleep disruption and executive functions in a relatively healthy cohort of 29 older adolescents and young adults with DS. Consistent with previous studies in the typical population (Alhola & PoloKantola, 2007; Beebe & Gozal, 2002), this study showed the features associated with OSA were significantly associated with poor verbal fluency and inhibition. From our review of the literature, this is the first study to examine correlations between parent ratings of sleep disruption and cognitive deficits in individuals with DS. These findings suggest that it is possible that PFC development is negatively affected by OSA in this population. Future work should move forward from these results to examine the relation between sleep problems in DS and measures of brain structure and function. While ratings of OSA did not directly relate to other sleep problems, such as bedtime resistance or daytime sleepiness, these domains also showed some significant correlations with executive tasks. Therefore, different types of sleep disturbance may show complex patterns of association with differing executive domains. Here we lack the sample size and methods to tease apart these associations fully, but we can say that parent ratings of OSA are an independently important predictor of executive dysfunction in adults with DS.

Furthermore, these findings suggest more research is needed to elucidate the links between poor sleep, cognitive impairment, and decline in adults with DS. These findings show correlations between poor sleep and cognition in young adults with DS, but what impact will their sleep problems have on their development of AD or rate of decline? Previous studies have linked OSA to a steeper rate of AD-related decline in females in the typical population. Moreover, the levels of Aβ accumulation were found to significantly increase during acute sleep deprivation in the human APP transgenic mouse model (Kang et al., 2009). Based on these studies, we hypothesize that the presence of OSA in individuals with DS may result in earlier cognitive decline and could potentially exacerbate Alzheimer's dementia. Given these findings, and our evidence for links between poor sleep and executive deficits in adolescents and young adults, further research is needed to examine sleep disruption in older adults with DS after the age of 50 years, when their risk for cognitive decline is greatest (i.e., 50% of individuals with DS over 50 years will be diagnosed with AD).

Another avenue for future research would be to examine the extent that BMI reduction may reduce the severity of OSA, subsequently allowing for improvement of cognitive skills or better long-term maintenance of cognitive function. Consistent with the findings of Trois et al. (2009), increased BMI related to OSA ratings in the current study, suggesting that obesity might an important cause of OSA. Exercise regimens may have an effect on sleep and associated variables that could be beneficial, although it must be noted that we found no evidence for a direct relation between BMI and cognition, but clear links between BMI and sleep disturbance. To date, exercise has been suggested as an alternative nonpharmacologic treatment for weight loss and to alleviate the symptoms of SDB in the typical population. Peppard and Young (2004) investigated the relation between physical activity habits and SDB in 1104 healthy adults and found that insufficient exercise was associated with an increased severity of SDB. Davis, Tkacz, Gregoski, Boyle, and Lovrekovic (2006) conducted a 13-week aerobic exercise program for overweight children and found that 50% showed improved symptoms of SDB after the program. In the current study, half of the participants maintained moderate-to-vigorous physical activity levels in their daily lives (i.e., 30 min each time, three times per week). This may explain why we found a lower prevalence of OSA as compared to previous studies in children and adults with DS (i.e., 40% endorsed elevated levels vs. 70–80% in other studies) (Breslin et al., 2011; Stores et al., 1996; Trois et al., 2009). However, while our group did engage in regular physical activity on average, a number

of studies have indicated lower physical activity levels in individuals with DS as compared typical peers (Sit, McManus, McKenzie, & Lian, 2007; Wu et al., 2010). Therefore, given these results, future studies are needed to understand the effectiveness of exercise programs on sleep disorders/behaviors in individuals with DS and whether or not these programs can lessen cognitive deficits or even support the maintanence of cognitive functions across aging.

Some study limitations should be noted. Although the Sleep Questionnaire used here has been validated in a large sample of individuals with DS and other intellectual disabilities, parents might not always be fully accurate in their reports of sleep disruption. This is particularly true in adults who may not receive as much monitoring as children. However, each individual in the current study still resided in their parent's home. Given these issues, future studies should employ objective measures of sleep quality (e.g., polysomnography, actigraphy). Specifically, polysomnography would be the best tool to generate more reliable and accurate measures of sleep disruption and sleep disordered breathing in this population, as we know of no study that has validated actigraphy for the detection of OSA in this group to date.

In summary, the findings of the current study show that the features associated with OSA relate to executive deficits in verbal fluency and the knock/tap task (i.e., inhibition) in older adolescents and younger adults with DS. These results suggest more work is needed to fully illuminate the links between sleep disruption and cognitive deficits in this syndrome, including future tests of our hypothesis that sleep disruption may be a very important factor leading to AD-related decline in this syndrome. Finally, given the links between BMI and OSA demonstrated here and elsewhere, exercise interventions should be undertaken. These interventions may help to alleviate the impact of sleep related disorders, possibly providing a chance to make a difference in the long-term cognitive outcome and quality of life of those with DS.

Conflict of interest statement

The authors have no conflicts of interest to declare in reference to this work.

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